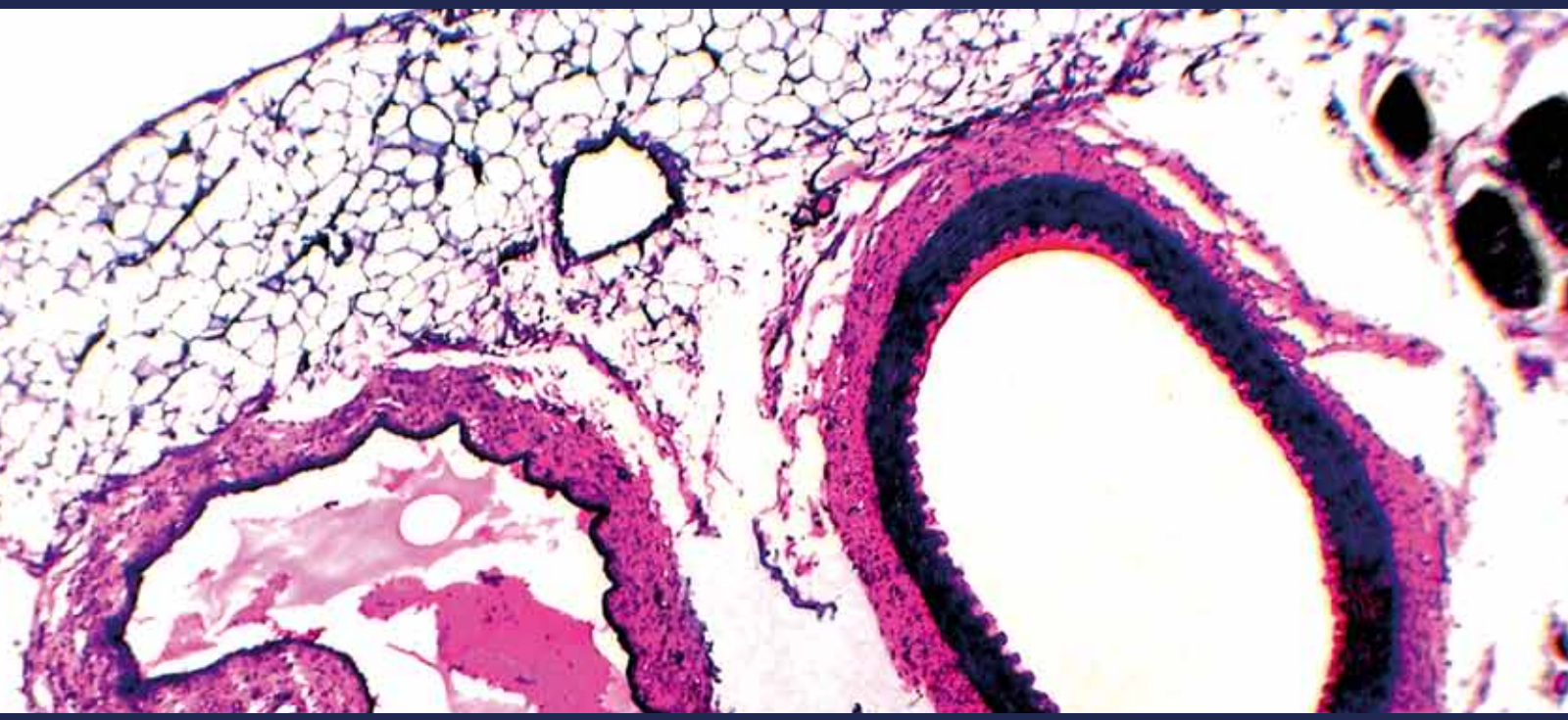
International Journal of Hypertension

Hypertension and Diabetes in Obesity

Guest Editors: Kazuko Masuo, Michael L. Tuck, and Gavin W. Lambert



Hypertension and Diabetes in Obesity

International Journal of Hypertension

Hypertension and Diabetes in Obesity

Guest Editors: Kazuko Masuo, Michael L. Tuck, and Gavin W. Lambert

Editorial Board

Contents

SAGE-Hindawi Access to Research
International Journal of Hypertension
Volume 2011, Article ID 695869, 2 pages
doi:10.4061/2011/695869

Editorial

Hypertension and Diabetes in Obesity

Kazuko Masuo,[1,2] Michael L. Tuck,[3] and Gavin W. Lambert[1,4]

[1] *Human Neurotransmitters Laboratory, Baker IDI Heart & Diabetes Institute, Melbourne, VIC 8008, Australia*
[2] *Nucleus Network Ltd., Baker IDI Heart & Diabetes Institute, Melbourne, VIC 8008, Australia*
[3] *Endocrinology and Metabolic Disease, VA Greater Los Angeles Healthcare System and David Geffen School of Medicine at UCLA, Los Angeles, CA 90073, USA*
[4] *Faculty of Medicine, Nursing and Health Sciences, Monash University, Melbourne, VIC 3800, Australia*

Correspondence should be addressed to Kazuko Masuo, kazuko.masuo@bakeridi.edu.au

Received 30 March 2011; Accepted 30 March 2011

The epidemic-like rise in the prevalence of obesity constitutes an undoubted and serious global health problem. Importantly, hypertension and diabetes are frequently associated with obesity and, together, constitute a significant burden in terms of patients' morbidity and escalating health care costs. When considered in isolation, obesity, hypertension, and diabetes are all associated with increased risk of the development of cardiovascular and renal complications; however, the coexistence of this triumvirate generates a substantial elevation in disease risk. The driving forces linking obesity, hypertension, and diabetes remain to be clarified due, in part, to the complex and multifactorial nature of the conditions that involve combinations of environmental, genetic, life style, and behavioural confounders. Additionally, it is recognized that neuroendocrine mechanisms, including insulin resistance, sympathetic nervous activation, and stimulation of the renin-angiotensin-aldosterone system (RAAS), are also involved [1–4].

This special issue on hypertension and type 2 diabetes related to obesity includes several epidemiological studies focusing on the prevalence of metabolic syndrome, type 2 diabetes, and hypertension. New data emanating from Peru, Ethiopia, Sudan, Egypt, and Nepal documents the prevalence of cardiometabolic disease in these countries as being similar to that reported in westernized countries such as the USA, Canada, Australia, and European countries as well as Japan [5, 6]. Importantly, an emerging body of data, such as that presented by Professor C. Brufani et al., highlights the importance of obesity in children. They reported the contribution of birth weight to central fat depot and insulin sensitivity in metabolic syndrome in obese Italian children. The challenge will be in designing and implementing effective strategies to arrest and reverse this pattern.

The strong linkage between hypertension and type 2 diabetes was reviewed by Professor E. Dean which provides insight into the mechanisms involved. Dr. S. Horita et al. reviewed the contribution of the kidneys, especially renal sodium transport, to the development of insulin resistance and hypertension in obesity. Diabetic patients and obese individuals frequently present with different circadian patterns of blood pressure compared to nondiabetic or nonobese subjects. A nondipping pattern is very common in obese hypertensive patients. In diabetic patients, ambulatory blood pressure monitoring provides a more robust measure in predicting future cardiovascular events than clinic blood pressure. Dr. C. Anigbogu et al. provided evidence that in rats the circadian rhythm of blood pressure and heart rate changes with progression of diabetes. Professor K. Eguchi reviewed recent epidemiological studies in diabetes and obesity using ambulatory blood pressure monitoring. Taken together, these observations demonstrate the importance of ambulatory blood pressure monitoring.

The first line of therapy for the treatment of type 2 diabetes and obesity-related hypertension is weight loss with lifestyle modifications such as diet and exercise. Nonpharmacological treatments were outlined by Dr. J. Pappachan et al. Another article by S. Guy et al. indicated that video gaming provided some benefit in initiating lifestyle modifications that aided in weight loss. Patients with diabetes and hypertension frequently present with atherogenic diseases and dyslipidemia. Dr. E. Morales-Villegas and colleagues

provided a review indicating that statins are very effective in treating dyslipidemia and reducing overall cardiovascular risk.

This special issue covered a wide range of materials with a focus on type 2 diabetes and hypertension. Articles included epidemiology, physiology, and treatments. In summary, this issue demonstrated that (i) abdominal obesity is related to the high prevalence of hypertension and type 2 diabetes regardless of ethnicity, (ii) insulin resistance is a major mechanism linking the onset and development of hypertension and type 2 diabetes, and (iii) weight loss with diet and exercise is an important aspect in treating hypertension in type 2 diabetes and aids in increasing the efficacy of antihypertensive medications. Further investigations on mechanisms and genetics are needed in order to develop appropriate and effective therapeutic regimens in order to prevent and limit obesity-related illnesses such as hypertension and type 2 diabetes. Early intervention is vital, given emerging evidence of end-organ dysfunction in young overweight or obese individuals [7, 8].

Acknowledgments

The editors thank the authors of all submissions and the tireless reviewers for their critical assistance. The editors enjoyed the variety of articles and hope that this special issue is useful for clinical practice and research and hope that the content of this special issue facilitates the reduction of the global burden of obesity and obesity-related illness.

Kazuko Masuo
Michael L. Tuck
Gavin W. Lambert

References

[1] K. Masuo, "Role of beta2- and beta33 adrenoceptor polymorphisms in hypertension and metabolic syndrome," *International Journal of Hypertension*, vol. 2010, Article ID 832821, 2010.

[2] M. D. Esler, N. E. Straznicky, N. Eikelis, K. Masuo, G. Lambert, and E. A. Lambert, "Mechanisms of sympathetic activation in obesity-related hypertension," *Hypertension*, vol. 48, pp. 787–796, 2008.

[3] M. Esler, G. Jennings, and G. Lambert, "Noradrenaline release and the pathophysiology of primary human hypertension," *American Journal of Hypertension*, vol. 2, no. 3, pp. 1405–1465, 1989.

[4] K. Masuo, "Obesity-related hypertension: role of the sympathetic nervous system, insulin, and leptin," *Current Hypertension Reports*, vol. 4, no. 2, pp. 112–118, 2002.

[5] A. H. Mokdad, E. S. Ford, B. A. Bowman et al., "Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001," *Journal of the American Medical Association*, vol. 289, no. 1, pp. 76–79, 2003.

[6] E. L. M. Barr, A. J. Cameron, B. Balkau et al., "HOMA insulin sensitivity index and the risk of all-cause mortality and cardiovascular disease events in the general population: the australian diabetes, obesity and lifestyle study (AusDiab) study," *Diabetologia*, vol. 53, no. 1, pp. 79–88, 2010.

[7] E. Lambert, C. I. Sari, T. Dawood et al., "Sympathetic nervous system activity is associated with obesity-induced subclinical organ damage in young adults," *Hypertension*, vol. 56, no. 3, pp. 351–358, 2010.

[8] K. Masuo, G. W. Lambert, M. D. Esler, H. Rakugi, T. Ogihara, and M. P. Schlaich, "The role of sympathetic nervous activity in renal injury and end-stage renal disease," *Hypertension Research*, vol. 33, no. 6, pp. 521–528, 2010.

SAGE-Hindawi Access to Research
International Journal of Hypertension
Volume 2011, Article ID 931402, 10 pages
doi:10.4061/2011/931402

Research Article

Waist Circumference, Body Mass Index, and Other Measures of Adiposity in Predicting Cardiovascular Disease Risk Factors among Peruvian Adults

K. M. Knowles,[1] L. L. Paiva,[1] S. E. Sanchez,[2] L. Revilla,[3] T. Lopez,[3] M. B. Yasuda,[4] N. D. Yanez,[1] B. Gelaye,[1] and M. A. Williams[1]

[1] *Department of Epidemiology, Multidisciplinary International Research Training Program, School of Public Health, University of Washington, Health Sciences Building F-161E, Seattle, WA 98195, USA*
[2] *Universidad San Martin de Porres and Hospital Dos de Mayo, Parque "Histoira de la Medicina Paruana" s/n, Alt. Cdra. 13 Av. Grau-Cercado, Lima, Peru*
[3] *Direccion General de Epidemiologia, Ministerio de Salud, Capac Yupanqui No. 1400 Jesus Maria, Lima 11, Peru*
[4] *Laboratorio de Patologiia Clinica, Instituto Nacional de Salud del Peru, Capac Yupanqui No. 1400 Jesus Maria, Lima 11, Peru*

Correspondence should be addressed to M. A. Williams, mawilliams84@gmail.com

Received 29 November 2010; Accepted 29 December 2010

Academic Editor: Kazuko Masuo

Objectives. To examine the extent to which measures of adiposity can be used to predict selected components of metabolic syndrome (MetS) and elevated C-reactive protein (CRP). *Methods*. A total of 1,518 Peruvian adults were included in this study. Waist circumference (WC), body mass index (BMI), waist-hip ratio (WHR), waist-height ratio (WHtR), and visceral adiposity index (VAI) were examined. The prevalence of each MetS component was determined according to tertiles of each anthropometric measure. ROC curves were used to evaluate the extent to which measures of adiposity can predict cardiovascular risk. *Results*. All measures of adiposity had the strongest correlation with triglyceride concentrations (TG). For both genders, as adiposity increased, the prevalence of Mets components increased. Compared to individuals with low-BMI and low-WC, men and women with high-BMI and high- WC had higher odds of elevated fasting glucose, blood pressure, TG, and reduced HDL, while only men in this category had higher odds of elevated CRP. Overall, the ROCs showed VAI, WC, and WHtR to be the best predictors for individual MetS components. *Conclusions*. The results of our study showed that measures of adiposity are correlated with cardiovascular risk although no single adiposity measure was identified as the best predictor for MetS.

1. Introduction

Worldwide, cardiovascular disease (CVD) is the primary cause of death; it killed an estimated 17.1 million people in 2004 [1, 2]. Historically, CVD was thought to be a disease endemic to developed countries only [3]; however, new evidence indicates that developing countries are more strongly affected by CVD than their more affluent counterparts [1–3].

The presence of metabolic syndrome (MetS) is a major risk factor for CVD [4]. According to the third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults, MetS is defined as a co-occurrence of specific health states, including elevated triglyceride concentrations (TG), reduced high-density lipoprotein (HDL), elevated blood pressure (BP), elevated fasting glucose (FG), and high waist circumference (WC) [5]. Body mass index (BMI), WC, Waist-to-hip ratio (WHR), waist-height ratio (WHtR) [6], and visceral adiposity index (VAI) [7] have been reported as similarly predictive for the presence of MetS in men and women.

Obesity is defined by the World Health Organization (WHO) as BMI $> 30\,kg/m^2$, and overweight is classified as BMI $> 25\,kg/m^2$ [8]. The established BMI cut-off points were designed for international use. Because of the concern that BMI cut-offs points might not accurately predict health risks

in all populations, the WHO established a commission and charged participants with examining available data about WC and WHR [9]. In light of concerns raised about the ability of BMI alone to predict cardiovascular risk, multiple studies have recently attempted to compare BMI with WC and other anthropometric measures of obesity, such as WHR, WHtR, and VAI, as predictors for CVD risk. In a meta-analysis of abdominal obesity indices comparing BMI, WC, WHR, and WHtR, researchers concluded that WHtR was the best predictor for both hypertension and dyslipidemia for both men and women, while BMI was the least accurate predictor of hypertension [10]. When assessing the accuracy of VAI in comparison to BMI and WC using receiver operating characteristic (ROC) curves, Amato and colleagues found VAI to be independently associated with cardiovascular events, while BMI and WC were not found to be significant discriminators [7].

Between 2000 and 2009 among Peruvians aged 15 or older, 11.5% of men and 12.5% of women were obese [11]. A recent study in Lima found the prevalence of MetS to be 21.6% in men and 29.9% in women [12]. Given that the prevalence of obesity is on the rise, and that CVD is an important cause of morbidity and mortality in Peru, its risk factors and their measurements warrant further study for this population. The purpose of the present study was to investigate the extent to which measures of adiposity (BMI, WC, WHR, WHtR, and VAI) can be used to predict elevated C-reactive protein (CRP) and selected components of MetS: elevated TG, reduced HDL, elevated BP, and elevated FG among Peruvian adults.

2. Materials and Methods

The data used for the present study were gathered as part of the Prevalencia de Factores de Riesgo de Enfermedades No-Transmisibles (prevalence of risk factors for noncommunicable diseases) population-based study, known as the FRENT study. Details of the study setting, sampling, and data collection procedures have been described previously [12, 13]. For the present analysis, we excluded participants taking antidiabetic drugs ($n = 30$), lipid lowering drugs ($n = 33$), or antihypertensive drugs ($n = 81$). The final analyzed sample included 1,518 participants, 952 women (62.7%) and 566 men (37.3%).

Participants were interviewed by trained health professionals using a standardized instrument, previously validated by the Pan American Health Organization (PAHO) and approved by the WHO [14]. Interview questions collected consisted of socio-demographic information, smoking status, alcohol consumption, medical history, and level of physical activity. Participants' height and weight were measured in accordance with PAHO procedures with participants wearing light clothing and no shoes [14]. Waist circumference (cm) was measured around the point halfway between the iliac crest and the sides of the lower ribs; the hip circumference (cm) was measured using the point of maximum girth around the buttocks.

Resting mean systolic and diastolic BP were calculated as an average of two measurements: the first taken after the participant had been seated for five minutes or more, and the second measure taken 30 minutes into the interview. Blood samples were drawn from participants the day after the interview, and an individual had fasted for at least 12 hours. Aliquots of serum samples were used to determine FG, TG, HDL, and LDL concentrations using standard procedures at the Peruvian National Institute of Health Laboratory in Lima, Peru. Serum CRP concentrations were measured by an ultrasensitive competitive immunoassay (Dade Behring, Deerfield, Illinois) at the University of Washington. All laboratory procedures were conducted without knowledge of participants' medical history.

All study participants provided informed consent, and all research protocols were approved by Institutional Review Boards of National Institute of Health (Lima, Peru), Dos de Mayo Hospital (Lima, Peru), and Human Subjects Division of the University of Washington (Seattle, WA, USA).

2.1. Variable Specification. WHR was calculated as waist circumference divided by hip circumference, and WHtR was computed as waist circumference divided by height. VAI was calculated according to the definition established by Amato and colleagues [7], using VAI = 1 as the reference for a nonobese participant with normal TG and HDL concentrations

$$\text{Men:}\quad \text{VAI} = \frac{\text{WC}}{39.68 + (1.88 * \text{BMI})} * \frac{\text{TG}}{1.03} * \frac{1.31}{\text{HDL}},$$
$$\text{Women:}\quad \text{VAI} = \frac{\text{WC}}{36.58 + (1.89 * \text{BMI})} * \frac{\text{TG}}{0.81} * \frac{1.52}{\text{HDL}}. \tag{1}$$

BMI was calculated as weight (kg) divided by height squared (m^2) and categorized using WHO guidelines (lean: $<18.5\,kg/m^2$; normal: 18.5–$24.9\,kg/m^2$; overweight: 25.0–$29.9\,kg/m^2$; obese $\geq 30\,kg/m^2$). In accordance with the NCEP diagnostic criteria, MetS components were defined as (1) elevated BP (mean value of systolic blood pressure ≥ 130 mmHg, mean value of diastolic blood pressure, ≥ 85 mmHg); (2) abdominal obesity (waist circumference >102 cm in men and >88 cm in women); (3) low HDL (<40 mg/dL in men and <50 mg/dL in women); (4) elevated TG (≥ 150 mg/dL); (5) elevated FG (≥ 110 mg/dL) or current drug therapy for diabetes [5].

2.2. Statistical Analyses. Data were analyzed using Statistical Package for the Social Sciences (version 17.0, SPSS Inc., Chicago, IL, USA) software. All analyses were stratified by gender. Pearson Chi square test was used to compare socio-demographic and behavioral characteristics between men and women. Correlation between the four selected MetS components and anthropometric measurements was evaluated using Spearman's rank coefficients. Each anthropometric measurement was divided *a priori* into tertiles and the prevalence of each MetS component was calculated for each tertile. Categories of CRP were defined by the following tertiles: <0.81 mg/L, 0.81–2.53 mg/L, and >2.53 mg/L. Elevated CRP was defined as being in the highest tertile (>2.53 mg/mL) [13]. Logistic regression procedures

Table 1: Socio-demographic characteristics of the study population.

Characteristic	Women $N = 952$ N (%)	Men $N = 566$ N (%)	P-value
Age (years)			.001
≤24	151 (15.9)	131 (23.1)	
25–34	234 (24.6)	146 (25.8)	
35–44	231 (24.3)	109 (19.3)	
45–54	173 (18.2)	84 (14.8)	
55–64	109 (11.4)	52 (9.2)	
≥65	54 (5.7)	44 (7.8)	
Education			.001
≤6 years	165 (17.8)	59 (10.7)	
7–12 years	429 (46.4)	262 (47.5)	
≥12 years	331 (35.8)	230 (41.7)	
Smoking status			<.001
Never smoker	800 (84.0)	315 (55.7)	
Pervious smoker	60 (6.3)	69 (12.2)	
Current smoker	92 (9.7)	182 (32.2)	
Currently employed			<.001
No	530 (55.8)	194 (34.4)	
Yes	419 (44.2)	370 (65.6)	
Alcohol consumption			<.001
Low	572 (60.1)	198 (35.0)	
Moderate	371 (39.0)	330 (58.3)	
Excessive	9 (0.9)	38 (6.7)	
Body mass index (kg/m^2)			.002
Underweight (<18.5)	8 (0.8)	10 (1.8)	
Normal (18.5–24.9)	402 (42.2)	219 (38.7)	
Overweight (25.0–29.9)	339 (35.6)	247 (43.6)	
Obesity (≥30.0)	203 (21.3)	90 (15.9)	
Leisure time physical activity			.002
No	217 (22.8)	168 (29.7)	
Yes, <150 minutes/week	637 (66.9)	328 (58.0)	
Yes, ≥150 minutes/week	98 (10.3)	70 (12.4)	

*All P values were obtained using Pearson Chi Square.

were used to estimate odd ratios (ORs) and 95% confidence intervals (95% CI) of components of MetS and CRP according to combinations of overall (BMI) and central adiposity (WC) measures. For these analyses, participants were grouped *a priori* as follows: low BMI and low WC (the reference group), high BMI and low WC, low BMI and high WC, and high BMI and high WC. Because there were few subjects in the low BMI and high WC category, those with low BMI and high WC were grouped with high BMI and low WC. Potential-confounding variables were selected for assessment *a priori* on the basis of their hypothesized relationship with adiposity measures and cardiometabolic risk. The presence of confounding was empirically assessed by entering potential covariates into a logistic regression model one at a time and by comparing the adjusted and unadjusted ORs. Final logistic regression models included covariates that altered unadjusted ORs by at least 10% [15]. For all analyses, significance was set at a P value of less than .05. Finally, receiver operating characteristic (ROC) curves with area under the curve (AUC) were used to evaluate which measure of adiposity (BMI, WC, WHR, WHtR, VAI) most accurately predicted the different components of MetS.

3. Results

Characteristics of study participants are summarized in Table 1. The mean age of study participants was 39.3 years (38.3 years for men and 39.9 years for women). Overall, men tended to be younger, more educated, and more likely to be employed. Men reported smoking and consuming

Table 2: Spearman's rank correlation coefficients for anthropometric measurements and metabolic syndrome components.

	BMI (kg/m^2)	WC (cm)	WHR	WHtR	VAI
		Men			
Fasting plasma glucose (mg/dL)	0.330	0.292	0.205	0.304	0.222
Triglyceride (mg/dL)	0.462	0.461	0.335	0.439	0.948
HDL (mg/dL)	−0.291	−0.286	−0.188	−0.247	−0.664
Systolic blood pressure (mmHg)	0.273	0.301	0.255	0.291	0.188
Diastolic blood pressure (mmHg)	0.331	0.330	0.298	0.316	0.247
		Women			
Fasting plasma Glucose (mg/dL)	0.306	0.301	0.107	0.301	0.250
Triglyceride (mg/dL)	0.437	0.455	0.226	0.451	0.933
HDL (mg/dL)	−0.220	−0.209	−0.194	−0.213	−0.618
Systolic blood pressure (mmHg)	0.296	0.323	0.180	0.304	0.271
Diastolic blood pressure (mmHg)	0.265	0.265	0.164	0.262	0.227

The P values for all Spearman's rank correlations listed are less than or equal to.001.

alcohol more frequently than women. On the basis of BMI values, men tended to be overweight (43.6% versus 35.6% of women), but women were more commonly obese (21.3% versus 15.9%, resp.).

Spearman's rank correlation coefficients were used to evaluate associations between anthropometric measurements and components MetS (Table 2). The strongest correlation was between VAI with triglyceride concentrations (men: $r = 0.948$, women: $r = 0.933$), followed by VAI with HDL concentrations (men: $r = -0.664$, women: $r = -0.618$); however, this was expected as TG and HDL are used to calculate VAI. For all measures of adiposity, triglyceride concentrations had the strongest positive correlation for men: BMI ($r = 0.462$), WC (0.461), WHtR ($r = 0.439$), and WHR ($r = 0.335$) and for women: WC ($r = 0.455$), WHtR ($r = 0.451$), BMI ($r = 0.437$), and WHR ($r = 0.226$). Of the measures of adiposity studied, BMI was most positively correlated with FG for both men ($r = 0.330$) and women ($r = 0.306$). Other than VAI, BMI was most strongly negatively correlated with reduced HDL.

Table 3 shows for both genders that the prevalence of elevated FG, BP, TG, and reduced HDL increased progressively as tertiles of each of the measures of adiposity studied increased. Table 4 shows the risk of MetS components in relation to central adiposity measures for men and women, adjusting for age, education, smoking, leisure time physical activity, and alcohol consumption. Compared to the low BMI & low WC (reference group), men with high BMI or high WC had 3.40 higher odds of having elevated TG (95% CI: 2.21–5.23), while men having both high BMI and high WC had an even higher adjusted odds ratio (AOR) (AOR: 3.89 95% CI: 2.15–7.04). For women, these AORs were 1.72 (95% CI: 1.02–2.91) and 4.64 (95% CI: 3.05–7.06), respectively. Men having either high BMI or high WC had 2.04 increased odds of reduced HDL (95% CI: 1.38–3.02), while men having high BMI and high WC had even higher odds for reduced HDL (AOR: 3.97 95% CI: 2.20–7.18). For women, these AORs were 1.29 (95% CI: 0.89–1.88) and 2.71 (95% CI: 1.95–3.75), respectively. Men having either high BMI or high WC had 1.85 higher odds for elevated BP (95% CI: 1.18–2.88), and men in the high BMI & high WC category had even higher odds (AOR: 2.93, 95% CI: 1.61–5.32). For women in the same anthropometric measures categories, these AORs were 1.45 (95% CI: 0.82–2.58) and 2.09 (95% CI: 1.32–3.32), respectively. Men having just one of the adiposity measurements of high BMI or high WC had 1.66 higher odds (95% CI: 0.86–3.23) of having elevated FG, while men having both high BMI and high WC had 2.32 higher odds of having elevated FG (95% CI: 1.03–5.19). For women with high BMI or high WC, the AOR was 1.14 (95% CI: 0.53–2.43), and for women with both high BMI and high WC, the AOR was 2.92 (95% CI: 1.65–5.16). Men having high BMI or high WC had 1.61 higher odds of having elevated CRP (95% CI: 1.08–2.41), and these odds increased for men having both high BMI and high WC (AOR: 1.86 95% CI: 1.05–3.31). For women, this association was not significant: 1.23 (95% CI: 0.83–1.83) for those in the high BMI or high WC category, and among high BMI & high WC category: 1.15 (95% CI: 0.82–1.60).

Figures 1 and 2 show the level how adiposity measures predict each of the MetS components studied. As expected due to inclusion in the formula, VAI was the best predictor for elevated TG (area under curve [AUC] = 0.98) among men and women (AUC = 0.97), and reduced HDL for men (AUC = 0.82) and women (AUC = 0.80). VAI and BMI were the best predictors for FG for men (AUC = 0.67 and 0.67, resp.), while for women, WC and WHtR were the best predictors (AUC: 0.72 and 0.72, resp.). For elevated triglycerides, WC was the best predictor (AUC: 0.73) for men while for women, WHR was the best (AUC: 0.65). For elevated BP, WC was the best predictor (AUC: 0.66) for men while for women, WHtR was the best (AUC = 0.70). For reduced HDL, BMI was the strongest predictor for both men (AUC: 0.66) and women (AUC = 0.62).

4. Discussion

To our knowledge, no research has previously been published assessing the multiple adiposity measures in predicting MetS among Peruvian adults. This study has demonstrated

Table 3: Prevalence of metabolic syndrome components in relation to varying degree of adiposity as assessed using different anthropometric measures.

Measurement of obesity		Metabolic syndrome components			
		Elevated FG	High TG	Low HDL	Elevated BP
		%	%	%	%
Among Men		$N = 64$	$N = 209$	$N = 252$	$N = 154$
Body mass index	$Tertile_1$ (<24.2)	17.2	15.8	21.4	22.1
(kg/m^2)	$Tertile_2$ (23.3–27.6)	28.1	33.0	36.5	27.9
	$Tertile_3$ (>27.6)	54.7	51.2	42.1	50.0
Waist circumference	$Tertile_1$ (<88.0)	17.2	13.0	24.7	20.7
(cm)	$Tertile_2$ (88.0–97.0)	35.9	38.0	33.9	29.9
	$Tertile_3$ (≥97.0)	46.9	49.0	41.4	49.4
Waist-to-hip ratio	$Tertile_1$ (<0.91)	23.4	17.9	27.5	23.5
	$Tertile_2$ (0.91–0.96)	31.3	35.7	33.9	30.7
	$Tertile_3$ (>0.96)	45.3	46.4	38.6	45.8
Waist-to-height ratio	$Tertile_1$ (<0.52)	17.2	13.0	20.3	20.8
	$Tertile_2$ (0.52–0.58)	29.7	37.5	39.4	27.9
	$Tertile_3$ (≥0.58)	53.1	49.5	40.2	51.3
VAI	$Tertile_1$ (<2.85)	17.2	0.0	11.2	23.4
	$Tertile_2$ (2.85–5.47)	29.7	15.4	29.9	35.7
	$Tertile_3$ (≥5.47)	53.1	84.6	59.0	40.9
Among women		$N = 110$	$N = 253$	$N = 575$	$N = 187$
Body mass index	$Tertile_1$ (<24.1)	16.4	15.0	26.6	19.8
(kg/m^2)	$Tertile_2$ (24.1–28.0)	23.6	28.5	33.0	29.9
	$Tertile_3$ (>28.0)	60.0	56.5	40.3	50.3
Waist circumference	$Tertile_1$ (<83.0)	12.7	10.3	29.3	14.4
(cm)	$Tertile_2$ (83.0–93.0)	28.2	35.6	32.9	30.5
	$Tertile_3$ (≥93.0)	59.1	54.2	37.8	55.1
Waist-to-hip ratio	$Tertile_1$ (<0.87)	20.0	20.2	28.9	20.9
	$Tertile_2$ (0.87–0.92)	32.7	30.8	33.6	36.4
	$Tertile_3$ (>0.92)	47.3	49.0	37.5	42.8
Waist-to-height ratio	$Tertile_1$ (<0.54)	11.8	12.3	27.0	15.5
	$Tertile_2$ (0.54–0.61)	26.4	30.8	34.1	26.7
	$Tertile_3$ (≥0.61)	61.8	56.9	38.9	57.8
VAI	$Tertile_1$ (<3.00)	12.7	0.0	17.9	15.0
	$Tertile_2$ (3.00–5.59)	21.8	7.9	32.1	29.9
	$Tertile_3$ (≥5.59)	65.5	92.1	50.0	55.1

FG: fasting plasma glucose; TG: triglyceride; HDL: high density lipoprotein-cholesterol; BP: blood pressure; VAI: visceral adiposity index.

the association between adiposity measures and MetS components. First, all adiposity measures were statistically significantly correlated with all MetS components studied. The prevalence of these factors increased gradually with increasing tertiles for each adiposity measure. Second, men and women with high overall and central adiposity values (i.e., high BMI & high WC) consistently had higher odds of having cardiometabolic risk factors when compared with their leaner counterparts. Notably, elevated CRP was associated with high BMI and/or high WC for men. However, no such association was observed among women. This is in agreement with previous studies that reported a gender difference CVD risk in relation to CRP levels [13]. WC was the best measure of adiposity to predict elevated BP in men. On the other hand, WC was most predictive of elevated FG in women.

Our observations are generally consistent with some, though not all, prior studies. Medina-Lezama et al. reported that WC was a better and accurate measure of CVD risk among Andean adults [16]. Similarly, other investigators reported that WC was a better predictor of CVD risk factors (better than BMI) among non-Hispanic black, Mexican American, and non-Hispanic white participants of the third National Health and Nutrition Examination Survey [17]. Additionally, Menke and colleagues noted that WC was a better predictor of hypertension, diabetes, low HDL cholesterol, elevated triglycerides, and insulin resistance than BMI [18]. Our findings and those of others [16–18] are somewhat

Table 4: Risk of metabolic syndrome components in relation to visceral adiposity.

	Low BMI & Low WC	High BMI or High WC**		High BMI and High WC	
	OR (CI)	OR (CI)	*P* value (SE)	OR (CI)	*P* value (SE)
			Among Women		
Elevated triglyceride	1.00 (Reference)	2.44 (1.50–3.98)	0.000 (0.249)	6.47 (4.37–9.58)	0.000 (0.200)
Adjusted*	1.00 (Reference)	1.72 (1.02–2.91)	0.042 (0.268)	4.64 (3.05–7.06)	0.000 (0.214)
Reduced HDL	1.00 (Reference)	1.28 (0.89–1.83)	0.184 (0.183)	2.64 (1.96–3.56)	0.000 (0.152)
Adjusted*	1.00 (Reference)	1.29 (0.89–1.88)	0.178 (0.191)	2.71 (1.95–3.75)	0.000 (0.167)
Elevated BP	1.00 (Reference)	1.99 (1.20–3.30)	0.007 (0.258)	3.40 (2.27–5.08)	0.000 (0.205)
Adjusted*	1.00 (Reference)	1.45 (0.82–2.58)	0.206 (0.294)	2.09 (1.32–3.32)	0.002 (0.236)
Elevated fasting glucose	1.00 (Reference)	1.70 (0.83–3.45)	0.144 (0.362)	4.34 (2.54–7.41)	0.000 (0.273)
Adjusted*	1.00 (Reference)	1.14 (0.53–2.43)	0.744 (0.389)	2.92 (1.65–5.16)	0.000 (0.291)
Elevated CRP	1.00 (Reference)	1.46 (1.00–2.14)	0.049 (0.193)	1.29 (0.95–1.76)	0.102 (0.157)
Adjusted*	1.00 (Reference)	1.23 (0.83–1.83)	0.310 (0.203)	1.15 (0.82–1.60)	0.429 (0.171)
			Among Men		
Elevated Triglyceride	1.00 (Reference)	3.81 (2.53–5.75)	0.000 (0.209)	5.65 (3.20–9.96)	0.000 (0.289)
Adjusted*	1.00 (Reference)	3.40 (2.21–5.23)	0.000 (0.220)	3.89 (2.15–7.04)	0.000 (0.303)
Reduced HDL	1.00 (Reference)	2.21 (1.53–3.20)	0.000 (0.189)	4.33 (2.48–7.57)	0.000 (0.284)
Adjusted*	1.00 (Reference)	2.04 (1.38–3.02)	0.000 (0.199)	3.97 (2.20–7.18)	0.000 (0.302)
Elevated BP	1.00 (Reference)	1.98 (1.29–3.04)	0.002 (0.218)	3.67 (2.08–6.49)	0.000 (0.291)
Adjusted*	1.00 (Reference)	1.85 (1.18–2.88)	0.007 (0.227)	2.93 (1.61–5.32)	0.000 (0.305)
Elevated fasting glucose	1.00 (Reference)	2.10 (1.11–3.96)	0.022 (0.324)	3.61 (1.67–7.81)	0.001 (0.394)
Adjusted*	1.00 (Reference)	1.66 (0.86–3.23)	0.135 (0.339)	2.32 (1.03–5.19)	0.041 (0.412)
Elevated CRP	1.00 (Reference)	1.66 (1.13–2.43)	0.010 (0.195)	2.04 (1.18–3.52)	0.010 (0.278)
Adjusted*	1.00 (Reference)	1.61 (1.08–2.41)	0.019 (0.204)	1.86 (1.05–3.31)	0.034 (0.293)

* Adjusted for age, education, smoking, leisure time physical activity, and alcohol consumption.
** Low BMI and High WC combined with High BMI and Low WC.

inconsistent with other reports. For instance, Wildman and colleagues reported that WC and BMI were equally predictive of CVD risk [19]. Moreover, results from a 2007 meta-analysis [20] suggested that measures of overall obesity (BMI) and measures of central obesity (WHR and WC) performed equally well in predicting incident type 2 diabetes. Other investigators, however, have reported that WHtR is the best predictor of CVD risk and other cardiometabolic risk factors (including hypertension and dyslipidemia) than other anthropometric measurements [19–26]. In a meta-analysis of indices of abdominal obesity, Lee et al. reported that BMI was the poorest discriminator, whilst WHtR was the best discriminator for hypertension, diabetes, and dyslipidemia for both men and women [10]. Herrera and colleagues also reported that WHtR was the most accurate measure of coronary heart disease risk, followed by WC, and BMI, in their study [22]. Finally, some have suggested that WHR, because it takes body fat distribution into account by showing abdominal and peripheral adiposity, may be the ideal measurement of adiposity [27]. However, we found WHR to have the weakest correlation and lowest AUC values of the adiposity measures for all MetS components, with the exception of elevated BP in men. VAI appeared to be the best predictor of elevated TG and low HDL in our study. However, it is important to note that triglyceride and HDL concentrations are included in the calculation of VAI values. Our observation of higher odds of cardiometabolic risks among men and women with combined high overall adiposity and central adiposity (i.e., high BM and WC values) is biologically plausible, as intra-abdominal fat is known to be highly associated with all components of MetS [28].

As noted by Paniagua et al. [26], heterogeneity in study findings across studies that have assessed cardiometabolic risk factors in relation to indices of adiposity may be attributable to differences in race/ethnicity, age, and gender distributions of participants across study populations. A number of investigators have reported differences in the predictive value of obesity indicators according to ethnicity [29, 30]. Vazquez et al. noted that central obesity was a stronger predictor of incident type 2 diabetes than were measures of total body fat [20]. However, measures of overall obesity were better predictor of type 2 diabetes in US and European Caucasian [31]. Though no anthropometric measurement was consistently the best predictor for MetS among the present population of Peruvian adults, we noted that VAI, WC, and WHtR to be the best predictors for individual MetS components.

Strengths of our study include the extensive CVD risk-factor data available for study participants and the unique opportunity to assess these risk factors in a population-based sample representative of adult residents of Lima and Callao, Peru. Limitations of our study include the cross-sectional design which did not allow us to assess the temporality of the relation between the adiposity measures and metabolic

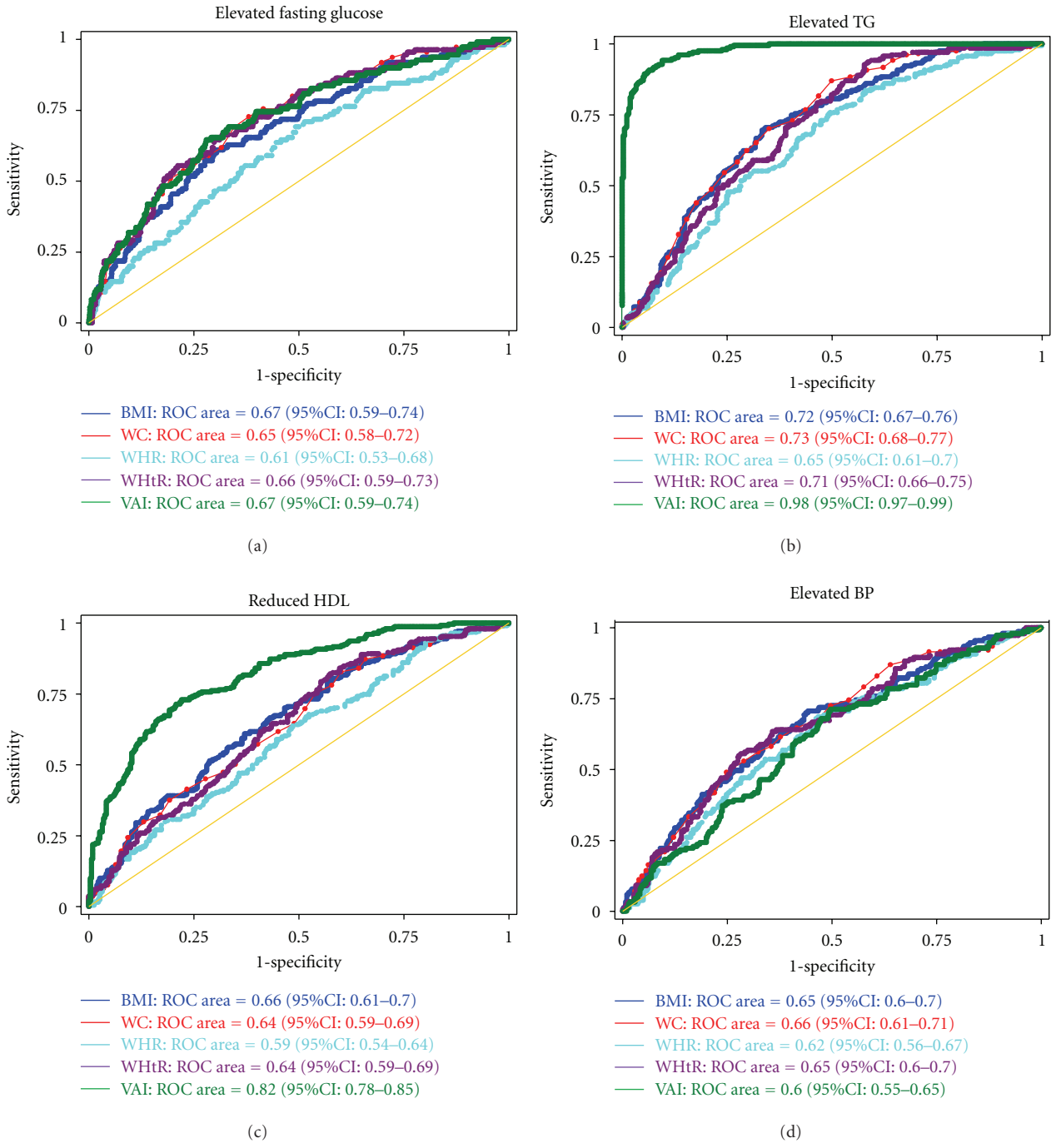


Figure 1: Receiver operating characteristic (ROC) curves with area under curve (AUC) and 95% confidence intervals of body mass index (BMI), waist circumference (WC), waist-to-hip ratio (WHR) and waist-to-height ratio (WHtR) for predicting cardiovascular disease risk factors among Peruvian men.

syndrome components. Some nonsystematic error in reporting of smoking history, physical activity, and other covariates may have occurred. Additionally, despite adjustment for multiple confounders, residual confounding by unmeasured or imprecisely measured covariates may persist. Finally, concordance of our study results with previous reports from geographically, racially, and ethnically diverse populations, in part, attenuates these concerns.

Although the best adiposity measurement for predicting CVD remains controversial, in our study most measures of adiposity were correlated with the cardiometabolic factors of interest. The results of our study underscore the importance of using simple, broadly applicable measures of adiposity such as WC and WHtR in community-based epidemiologic studies. These relatively inexpensive and easily obtained measures are useful for assessing cardiovascular

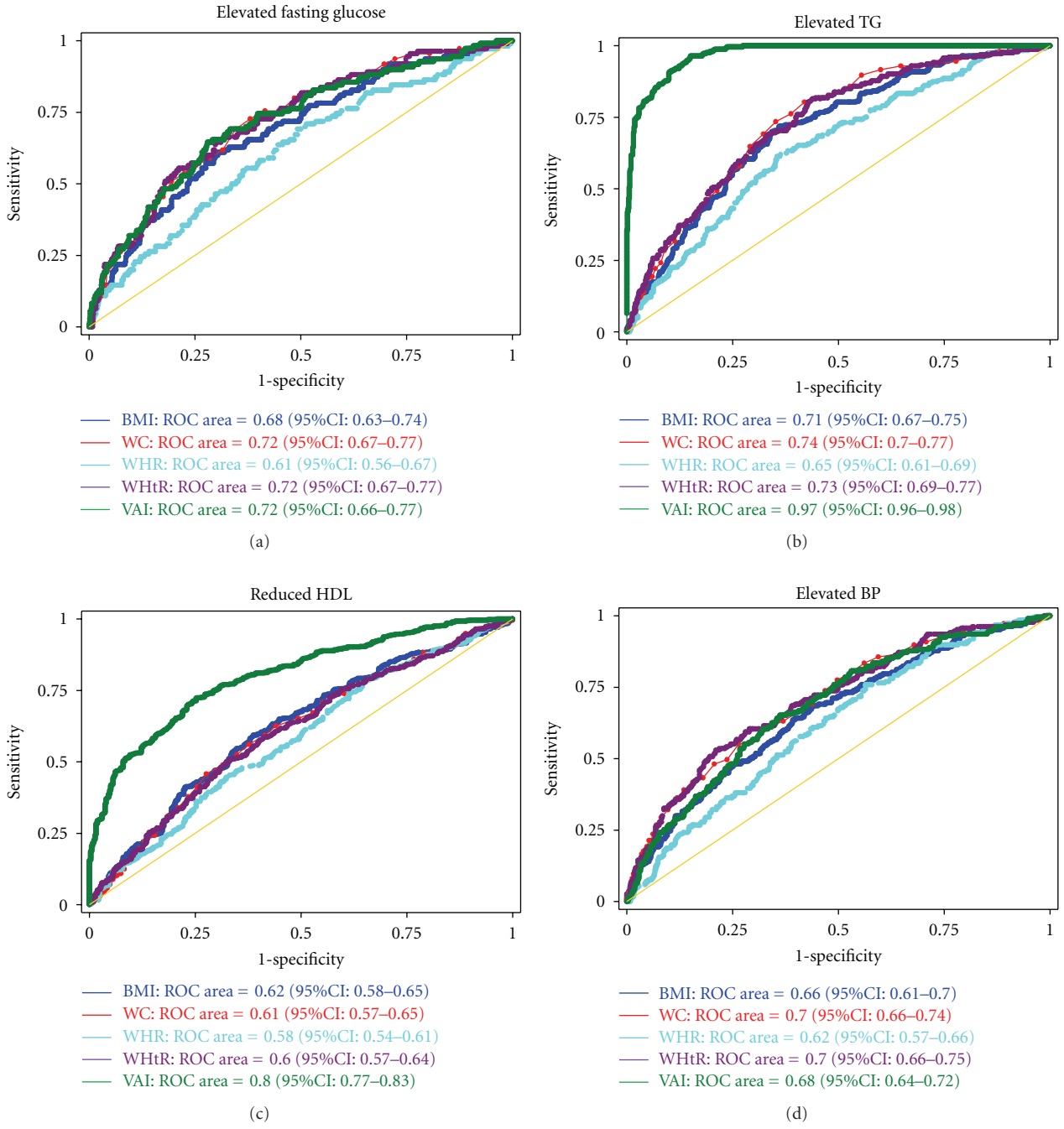


Figure 2: Receiver operating characteristic (ROC) curves with area under curve (AUC) and 95% confidence intervals of body mass index (BMI), waist circumference (WC), waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR) for predicting cardiovascular disease risk factors among Peruvian Women.

disease risk in nonclinical settings. Though the various measurements each have advantages and disadvantages, it is evident that, to date, no single measurement can be identified as the optimal choice for CVD prediction on its own. To this effect, the United States National Institutes of Health (NIH) now recommends the use of WC in conjunction with BMI as a complementary indicator of health risk among normal and overweigh subjects [32]. The overall results of our study showed that measures of adiposity are correlated with cardiovascular risk among Peruvian adults. Investigators in Latin America have called for a country-specific epidemiological data to help bring public health policy changes for surveillance, prevention, and intervention [33]. The high prevalence of MetS, obesity, and observed associations of cardiometabolic risks with adiposity measures reported in this study calls for increased efforts aimed towards clinical preventive services to identify and control the existing metabolic abnormalities among

patients. Additionally, development and implementation of public health programs that promote healthful behaviors including increased physical activity, eating balanced diets, and avoidance of adult weight gain are needed to help reduce the burden of noncommunicable diseases among Peruvian adults.

Conflict of Interests

The authors declare that they have no conflict of interests.

Authors' Contributions

L. Revilla, TTC, M. B. Yasuda, and S. E. Sanchez participated in the design of the study and carried out data collection. K. M. Knowles and L. L. Paiva participated in statistical analysis, interpretation of results, and drafting the paper. S. E. Sanchez and N. D. Yanez led the analysis, supervised research trainees, and participated in interpretation of results and in drafting the paper. B. Gelaye and M. A. Williams conceived and participated in data analysis, interpretation of results, and providing critical review of the paper. All authors read and approved the final paper. K. M. Knowles and L. L. Paiva contributed equally to this work.

Acknowledgments

The FRENT study was supported by General Direction of Epidemiology Bureau (Direccion Nacional de Epidemiologia) and the Peruvian National Institute of Health, Lima, Peru. The present analysis was completed while Ms Kaylee Knowles and Ms Laura Paiva were research training fellows with the Multidisciplinary International Research Training (MIRT) Program of the School of Public Health, University of Washington. The MIRT Program is supported by an Award from the National Institutes of Health, National Center on Minority Health and Health Disparities (no. T37-MD001449).

References

[1] WHO, *The Global Burden of Disease 2004 Update*, WHO, Geneva, Switzerland, 2004.

[2] WHO, "World Health Report. Prevention Chronic Disease: A vital Investment," Geneva, Switzerland, 2008, http://www.who.int/chp/chronic_disease_report/contents/part1.pdf.

[3] M. Ezzati, S. Vander Hoorn, C. M. M. Lawes et al., "Rethinking the "diseases of affluence" paradigm: global patterns of nutritional risks in relation to economic development," *PLoS Medicine*, vol. 2, no. 5, article e133, 2005.

[4] E. S. Ford, "Risks for all-cause mortality, cardiovascular disease, and diabetes associated with the metabolic syndrome: a summary of the evidence," *Diabetes Care*, vol. 28, no. 7, pp. 1769–1778, 2005.

[5] S. M. Grundy, D. Becker, L. T. Clark et al., "Detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III)," *Circulation*, vol. 106, no. 25, pp. 3143–3421, 2002.

[6] A. Bosy-Westphal, C. Geisler, S. Onur et al., "Value of body fat mass vs anthropometric obesity indices in the assessment of metabolic risk factors," *International Journal of Obesity*, vol. 30, no. 3, pp. 475–483, 2006.

[7] M. C. Amato, C. Giordano, M. Galia et al., "Visceral adiposity index: a reliable indicator of visceral fat function associated with cardiometabolic risk," *Diabetes Care*, vol. 33, no. 4, pp. 920–922, 2010.

[8] WHO, *Obesity: Preventing and Managing the Global Epidemic*, Geneva, Switzerland, 2000.

[9] C. Nishida, G. T. Ko, and S. Kumanyika, "Body fat distribution and noncommunicable diseases in populations: overview of the 2008 WHO Expert Consultation on Waist Circumference and Waist-Hip Ratio," *European Journal of Clinical Nutrition*, vol. 64, no. 1, pp. 2–5, 2010.

[10] C. M.Y. Lee, R. R. Huxley, R. P. Wildman, and M. Woodward, "Indices of abdominal obesity are better discriminators of cardiovascular risk factors than BMI: a meta-analysis," *Journal of Clinical Epidemiology*, vol. 61, no. 7, pp. 646–653, 2008.

[11] WHO, *World Health Statistics*, WHO, Geneva, Switzerland, 2010.

[12] B. Gelaye, L. Revilla, T. Lopez, S. Sanchez, and M. A. Williams, "Prevalence of metabolic syndrome and its relationship with leisure time physical activity among Peruvian adults," *European Journal of Clinical Investigation*, vol. 39, no. 10, pp. 891–898, 2009.

[13] B. Gelaye, L. Revilla, T. Lopez et al., "Association between insulin resistance and c-reactive protein among Peruvian adults," *Diabetology and Metabolic Syndrome*, vol. 2, no. 1, article 30, 2010.

[14] PAHO: PAN AMERICAN HEALTH ORGANIZATION, "Countrywide Integrated Noncommunicable Diseases Intervention (CINDI) Programme," September 2010, http://www.paho.org/english/ad/dpc/nc/hcncindi.pdf.

[15] K. J. Rothman and S. Greenland, *Modern Epidemiology*, Lippincott-Raven, Philadelphia, Pa, USA, 1998.

[16] J. Medina-Lezama, C. A. Pastorius, H. Zea-Diaz et al., "Optimal definitions for abdominal obesity and the metabolic syndrome in Andean Hispanics: the PREVENCION study," *Diabetes Care*, vol. 33, no. 6, pp. 1385–1388, 2010.

[17] S. Zhu, S. B. Heymsfield, H. Toyoshima, Z. Wang, A. Pietrobelli, and S. Heshka, "Race-ethnicity-specific waist circumference cutoffs for identifying cardiovascular disease risk factors," *American Journal of Clinical Nutrition*, vol. 81, no. 2, pp. 409–415, 2005.

[18] A. Menke, P. Muntner, R. P. Wildman, K. Reynolds, and HE. Jiang, "Measures of adiposity and cardiovascular disease risk factors," *Obesity*, vol. 15, no. 3, pp. 785–795, 2007.

[19] R. P. Wildman, D. Gu, K. Reynolds, X. Duan, X. Wu, and J. He, "Are waist circumference and body mass index independently associated with cardiovascular disease risk in Chinese adults?" *American Journal of Clinical Nutrition*, vol. 82, no. 6, pp. 1195–1202, 2005.

[20] G. Vazquez, S. Duval, D. R. Jacobs, and K. Silventoinen, "Comparison of body mass index, waist circumference, and waist/hip ratio in predicting incident diabetes: a meta-analysis," *Epidemiologic Reviews*, vol. 29, no. 1, pp. 115–128, 2007.

[21] W. Aekplakorn, V. Pakpeankitwatana, C. M. Y. Lee et al., "Abdominal obesity and coronary heart disease in Thai men," *Obesity*, vol. 15, no. 4, pp. 1036–1042, 2007.

[22] V. M. Herrera, J. P. Casas, J. J. Miranda et al., "Interethnic differences in the accuracy of anthropometric indicators of obesity in screening for high risk of coronary heart disease," *International Journal of Obesity*, vol. 33, no. 5, pp. 568–576, 2009.

[23] S. Y. Ho, T. H. Lam, and E. D. Janus, "Waist to stature ratio is more strongly associated with cardiovascular risk factors than other simple anthropometric indices," *Annals of Epidemiology*, vol. 13, no. 10, pp. 683–691, 2003.

[24] W.-Y. Lin, L.-T. Lee, C.-Y. Chen et al., "Optimal cut-off values for obesity: using simple anthropometric indices to predict cardiovascular risk factors in Taiwan," *International Journal of Obesity*, vol. 26, no. 9, pp. 1232–1238, 2002.

[25] M. A. Sayeed, H. Mahtab, Z. A. Latif et al., "Waist-to-height ratio is a better obesity index than body mass index and waist-to-hip ratio for predicting diabetes, hypertension and lipidemia," *Bangladesh Medical Research Council Bulletin*, vol. 29, no. 1, pp. 1–10, 2003.

[26] L. Paniagua, V. Lohsoonthorn, S. Lertmaharit, W. Jiamjarasrangsi, and M. A. Williams, "Comparison of waist circumference, body mass index, percent body fat and other measure of adiposity in identifying cardiovascular disease risks among Thai adults," *Obesity Research & Clinical Practice*, vol. 2, no. 3, pp. 215–223, 2008.

[27] D. Canoy, "Distribution of body fat and risk of coronary heart disease in men and women," *Current Opinion in Cardiology*, vol. 23, no. 6, pp. 591–598, 2008.

[28] D. B. Carr, K. M. Utzschneider, R. L. Hull et al., "Intra-abdominal fat is a major determinant of the National Cholesterol Education Program Adult Treatment Panel III criteria for the metabolic syndrome," *Diabetes*, vol. 53, no. 8, pp. 2087–2094, 2004.

[29] P. Deurenberg, M. Yap, and W. A. Van Staveren, "Body mass index and percent body fat: a meta analysis among different ethnic groups," *International Journal of Obesity*, vol. 22, no. 12, pp. 1164–1171, 1998.

[30] B. B. Duncan, L. E. Chambless, M. I. Schmidt et al., "Correlates of body fat distribution: variation across categories of race, sex, and body mass in the atherosclerosis risk in communities study," *Annals of Epidemiology*, vol. 5, no. 3, pp. 192–200, 1995.

[31] J. M. Chan, E. B. Rimm, G. A. Colditz, M. J. Stampfer, and W. C. Willett, "Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men," *Diabetes Care*, vol. 17, no. 9, pp. 961–969, 1994.

[32] NIH, *The Practical Guide to the Identification, Evaluation and Treatment of Overweight and Obesity in Adults*, National Institutes of Health, Bethesda, Md, USA, 2000.

[33] H. Schargrodsky, R. Hernández-Hernández, B. M. Champagne et al., "CARMELA: assessment of cardiovascular risk in seven Latin American cities," *American Journal of Medicine*, vol. 121, no. 1, pp. 58–65, 2008.

SAGE-Hindawi Access to Research
International Journal of Hypertension
Volume 2011, Article ID 629492, 5 pages
doi:10.4061/2011/629492

Research Article

High Rate of Obesity-Associated Hypertension among Primary Schoolchildren in Sudan

Zeena Salman,[1] Gregory D. Kirk,[2] and Mark D. DeBoer[1]

[1] *Department of Pediatrics, University of Virginia School of Medicine, P.O. Box 800386, Charlottesville, VA 22908, USA*
[2] *Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205, USA*

Correspondence should be addressed to Mark D. DeBoer, deboer@virginia.edu

Received 14 October 2010; Accepted 1 December 2010

Academic Editor: Kazuko Masuo

Cardiovascular disease (CVD) frequently has roots in childhood, including following childhood-onset hypertension. Incidence of CVD has increased in developing countries in East Africa during recent urbanization. Effects of these shifts on childhood hypertension are unclear. Our objectives were to (1) Determine the prevalence of hypertension among primary schoolchildren in Khartoum, Sudan; (2) Determine whether hypertension in this setting is associated with obesity. We performed a cross sectional study of 6-12y children from two schools randomly selected in Khartoum, Sudan. Height, weight, BMI, BP and family history of hypertension were assessed. Age-, height- and gender-specific BP curves were used to determine pre-hypertension (90–95%) and hypertension (>95%). Of 304 children, 45 (14.8%) were overweight; 32 (10.5%) were obese; 15 (4.9%) were pre-hypertensive and 15 (4.9%) were hypertensive. Obesity but not family history of hypertension was associated with current hypertension. In multiple logistic regression, adjusting for family history, children who were obese had a relative-risk of 14.7 (CI 2.45-88.2) for systolic hypertension compared to normal-weight children. We conclude that overweight and obesity are highly prevalent among primary schoolchildren in urban Sudan and are strongly associated with hypertension. That obesity-associated cardiovascular sequelae exist in the developing world at young ages may be a harbinger of future CVD in sub-Saharan Africa.

1. Introduction

The prevalence of childhood obesity has been increasing at unsettling rates across the globe [1]. In addition to striking the developed world, this pattern has also been noted in developing countries undergoing rapid epidemiological transitions, including those in East Africa [2]. In Sudan, a study of children in secondary school in the capital Khartoum found that rates of overweight and obesity were 28.5% and 5.6%, respectively [3]. Rates of obesity for younger schoolchildren in East Africa remain unclear, though obesity at younger ages may carry greater importance because younger children possess improved potential for early intervention [4].

Hypertension, a notable sequela of obesity, was already common in sub-Saharan Africa [5] but has been reported to be worsening in prevalence in recent years [6]. Hypertension often goes underdiagnosed in children, in part because its accurate diagnosis requires the use of standardized growth charts specific for age, gender, and height, with hypertension defined as a systolic and/or diastolic blood pressure > 95th percentile and pre-hypertension defined as systolic and/or diastolic blood pressure 90–95th percentile. Underdiagnosis of hypertension may be even more common in developing countries, where medical care is limited to symptomatic diseases, and childhood hypertension has been overlooked in lieu of more urgent disease.

Given the importance of childhood hypertension and pre-hypertension in determining adult cardiovascular disease outcomes [7], our goal was to determine the prevalence of hypertension and pre-hypertension among urban school children in Sudan and to determine whether hypertension was associated with obesity in this population. These data serve to alert providers in developing and developed countries to the extent of the current obesity epidemic.

2. Methods

2.1. Study Area. Sudan is in East Africa, bordering Egypt on the north, Ethiopia on the east, Kenya, Uganda, and Congo on the south, and Central African Republic, Chad, and Libya

on the west. Sudan has 2.5 million square kilometers and 37 million inhabitants, of whom 5–7 million live in the capital of Khartoum. Traditionally an impoverished country, Sudan has experienced an economy that has expanded rapidly with oil exportation over the past 10 years, with Khartoum being the epicenter of economic activity.

2.2. Study Design and Subjects. This was a cross-sectional study using a sample of 304 children aging six through twelve years from two schools randomly selected in Khartoum, the capital of Sudan. All students were given a questionnaire to be filled out by their parents, which asked for signed consent for their child to participate in the study, in addition to other demographic and health information. Ethics approval was obtained from the University of Medical Sciences and Technology (Khartoum, Sudan) Research Ethics Board.

2.3. Data Collection. Questionnaires sent to parents inquired regarding the child's age, gender, and health conditions, both previous and current. The questionnaire also asked whether there was a medical diagnosis of hypertension, diabetes, or heart disease among blood-related family members and which family members were affected. The child was classified as having a positive family history only if disease was present in a first-degree relative.

2.4. Measurements. Measurements taken for each student were body weight, height, and blood pressure. Measurements were taken by trained volunteers in a consistent, standardized manner. Body weight was measured to the nearest tenth of a kilogram on a calibrated digital scale, with the child's shoes removed. Height was measured with the child standing with shoes removed, measured in centimeters to the nearest millimeter. Blood pressure was measured twice, once manually and once digitally, using an appropriate cuff size, based on arm circumference, and the mean was taken and used for analysis.

Body mass index (BMI), defined as body weight in kilograms divided by the square of height in meters (kg/m^2), was used as the measure of obesity in this study. BMI is an accepted measure of obesity in clinical practice, and its use in children has been supported internationally by the International Obesity Task Force (IOTF), which agreed that it provides a reasonable index of adiposity [8] and in that it is a simple and inexpensive measure. It provides reliable estimations, with the exceptions of extremes of age, height, and musculature [9].

BMI was categorized according to the Centers for Disease Control and Prevention (CDC) age- and sex-specific growth charts [10]. The following categories were used: underweight <5th percentile; normal weight, 5th to 85th percentile; overweight, 85th to 95th percentile; obese, >95th percentile.

Blood pressure was categorized according to BP tables from the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents [11], using age and height percentiles, with normotension defined as a BP under the 90th percentile, prehypertension 90th to 95th percentile, and hypertension greater than 95th percentile or an absolute systolic BP (SBP) of ≥120 mm Hg or diastolic BP (DBP) of ≥80 mm Hg. Children were also classified as hypertensive if they were taking antihypertensive medication or had been diagnosed with hypertension previously.

2.5. Statistical Analysis. Descriptive statistics were calculated for gender, family history, and BMI and BP categories. Analyses were performed using the chi-squared test for association, and multinomial logistic regression to investigate the odds of systolic and diastolic prehypertension and hypertension with overweight or obesity, controlling for family history of hypertension. Analyses were conducted using STATA 10.0 (2008 StataCorp LP, College Station, TX).

3. Results

Complete data on height, weight, BP, and family history were available for the entire sample ($n = 304$). The average age of participants was 7.8 years, with a median age of 9 years (range 6–12 years). All were of Sudanese nationality, and the gender distribution was 236 female (77.6%) and 68 male (22.4%).

The number of children who were overweight was 45 (14.8%), and 32 were obese (10.5%). Females had a nonsignificant trend toward higher rates than males of overweight (14.0% versus 11.8%) and obesity (11.0% versus 5.9%, $P > .05$). These frequencies are examined further by age and gender in Table 1.

Prehypertension was detected in 15 (4.9%) participants and additional 15 (4.9%) had hypertension, all on the basis of BP measurement, as none were taking antihypertensives or had a previous diagnosis of hypertension. The rate of elevated BP (prehypertension and hypertension combined) in males and females was 13.2% versus 8.9%. A family history of hypertension was reported for 64 (21.1%) of the participants overall, including 20.1% of children with a normal blood pressure, 20.0% of those with pre-hypertension, and 40.0% of hypertensive children (Table 2). Though there is a higher rate of family history with hypertension compared to normal BP or prehypertension, this difference was not significant by chi-square test ($P > .05$).

Regarding the association between BMI and BP, 31.2% of obese children had hypertension, versus 17.8% of overweight children and 5.3% of normal BMI children. These results were found to be highly statistically significant by Pearson chi-squared test ($P < .001$). Further classification of prehypertension and hypertension into systolic and diastolic is stratified by BP category in Table 3 for descriptive purposes.

Results of multinomial logistic regression analysis are shown in Table 4. The results are given as the relative risk of being in a certain BP category by weight category compared to children with a normal BMI, adjusting for gender and family history. After adjustment for these factors, Sudanese children who were obese had a relative risk of systolic hypertension of 14.7 compared to their normal-weight counterparts ($P < .01$).

Table 1: Age and gender by BMI status.

Characteristic	Normal BMI *n* (%)	Overweight *n* (%)	Obese *n* (%)
Gender			
Male	56 (82.4)	8 (11.8)	4 (5.9)
Female	177 (75.0)	33 (14.0)	26 (11.0)
Age			
6 yrs	34 (82.9)	7 (17.1)	0 (0.0)
7 yrs	40 (80.0)	5 (10.0)	5 (10.0)
8 yrs	42 (77.8)	6 (11.1)	6 (11.1)
9 yrs	54 (75.0)	10 (13.9)	8 (11.1)
10 yrs	19 (63.3)	5 (16.7)	6 (20.0)
11 yrs	19 (73.1)	5 (19.2)	2 (7.7)
12 yrs	25 (80.6)	3 (9.7)	3 (9.7)

Table 2: Gender and family history of hypertension by blood pressure category.

Characteristic	Normotensive *n* (%)	Prehypertension *n* (%)	Hypertension *n* (%)
Gender			
Male	59 (86.8)	2 (2.9)	7 (10.3)
Female	215 (91.1)	13 (5.5)	8 (3.4)
Family History			
Positive	55 (85.9)	3 (4.7)	6 (9.4)
Negative	219 (91.3)	12 (5.0)	9 (3.7)

Table 3: Blood pressure classification according to BMI category.

	Normal BP	Systolic Pre-HT	Diastolic Pre-HT	Systolic HT	Diastolic HT
BMI					
Normal	215 (94.7)	4 (1.8)	5 (2.2)	3 (1.3)	0 (0.0)
Overweight	37 (82.2)	1 (2.2)	2 (4.4)	1 (2.2)	4 (8.9)
Obese	22 (69.0)	2 (6.3)	1 (3.1)	3 (9.4)	4 (12.5)

Table 4: Relative risk of hypertension by BMI category (adjusted for gender and family history).

Blood pressure	Relative risk*	Confidence interval
In overweight children:		
Systolic pre-hypertension	1.44	0.15–13.34
Diastolic pre-hypertension	0.94	0.11–8.03
Systolic hypertension	2.23	0.22–22.86
Diastolic hypertension	1.24	0.14–11.23
In obese children:		
Systolic pre-hypertension	5.65	0.92–34.85
Diastolic pre-hypertension	1.39	0.15–13.13
Systolic hypertension	**14.69**	**2.45–88.2**
Diastolic hypertension	3.61	0.58–22.52

* Compared to risk of normal BP.

4. Discussion

We found a high rate of overweight and obesity among 6–12-year-old primary schoolchildren in urban Sudan, with 14.8% of the children overweight and 10.5% obese. Despite moderate rates of hypertension reported previously among children in sub-Saharan Africa—up to 11% in rural children, suggesting an underlying genetic predisposition [12]—we found that obesity and not family history was the factor most strongly associated with hypertension in our sample. Obese children carried a relative risk of 14.7 for systolic hypertension after adjustment for family history, while family history of hypertension was not significantly associated. That obesity was so highly correlated with hypertension in a part of the world more commonly linked to undernutrition underscores the pervasiveness of the obesity epidemic and its sequelae throughout the world.

Rates of hypertension in sub-Saharan Africa have been noted to be increasing among adults [5, 6, 13] concurrent with rising rates of obesity in urban areas [2]. Prior studies to demonstrate these effects among children in East Africa have been lacking, however. The appearance of early cardiovascular sequelae of obesity at these young ages suggests that urban areas in the developing world may begin to face increasing health concerns in children related to the obesity epidemic.

As in other sub-Saharan African nations, these high rates of obesity in Sudan are felt to be due to the epidemiological transition that has come with Westernization [2]. Increased television viewing and internet surfing have contributed to a more recent sedentary lifestyle. While food availability has improved, dietary habits have shifted away from traditional agricultural choices to an increase in processed foods as seen in Western countries. The appearance of obesity-associated hypertension in children may signal that developing countries are likely to face similar difficulties as developed countries in overcoming lifestyle choices.

Similar reports of obesity have been reported from other less-developed nations outside of Africa. A study of schoolchildren in Beijing, China, reported that approximately 20% of children were overweight or obese [14]. In Karachi, Pakistan, an almost identical prevalence of 25% of children had a high BMI, with 6% of children overweight and 19% obese [15]. In Iran, 8.8% were overweight, and 4.5% were obese [16]. Rates of hypertension in other populations are less clear, although increasing BMI has been consistently associated with increased blood pressure throughout childhood [17–19].

This study had several strengths and weaknesses. The total number of children involved was relatively small (304 subjects), particularly with respect to boys (68 subjects). We collected complete data, including family history of hypertension on all participants. In contrast to many studies of blood pressure in African children that did not determine rates of hypertension based on normal ranges for height, age, and gender [20], we determined blood pressure status for each of our participants, dividing children into normotensive, pre-hypertensive, and hypertensive categories.

In common with other studies [20, 21], we used the average of blood pressure measurements at a single time

point for each subject, acknowledging that measuring blood pressure on separate occasions is necessary for the diagnosis of hypertension on a clinical basis [11]. It is possible that the prevalence of hypertension in our sample would be lower were three measurements used to determine hypertension [22].

In addition, we used BMI as the sole measure of obesity. Other measurements estimating adiposity (waist circumference, bioelectrical impedance, and MRI) are more specific to the amount of fat mass. Nevertheless, for population-based studies BMI correlates well with these other measures and remains widely used as a definition of obesity in hypertension research [23–25].

5. Conclusion

In conclusion, primary schoolchildren in urban Sudan exhibited a high degree of overweight and obesity, and hypertension among these children was more closely linked to obesity than to family history. That obesity-associated cardiovascular sequelae exist in the developing world at such young ages is a harbinger of worsened cardiovascular outcomes in sub-Saharan Africa in the future. To overcome these trends, children in urban settings in Africa are likely to require similar dietary and activity lifestyle adjustments as needed by their counterparts in developed nations.

Funding

M. D. DeBoer received funding NIH HD060739-01.

References

[1] A. M. G. Cali and S. Caprio, "Obesity in children and adolescents," *Journal of Clinical Endocrinology and Metabolism*, vol. 93, no. 11, pp. s31–s36, 2008.

[2] R. Belue, T. A. Okoror, J. Iwelunmor et al., "An overview of cardiovascular risk factor burden in sub-Saharan African countries: a socio-cultural perspective," *Global Health*, vol. 5, p. 10, 2009.

[3] O. A. Salih and E. AbdelAziz, " Underweight, overweight and obesity among Sudanese secondary school children of Khartoum State," *Ahfad Journal*, pp. 38–46, 2007.

[4] M. Dehghan, N. Akhtar-Danesh, and A. T. Merchant, "Childhood obesity, prevalence and prevention," *Nutrition Journal*, vol. 4, 2005.

[5] J. Addo, L. Smeeth, and D. A. Leon, "Hypertension in sub-Saharan Africa: a systematic review," *Hypertension*, vol. 50, no. 6, pp. 1012–1018, 2007.

[6] Y. K. Seedat, "Recommendations for hypertension in sub-Saharan Africa," *Cardiovascular Journal of South Africa*, vol. 15, no. 4, pp. 157–158, 2004.

[7] H. C. McGill, C. A. McMahan, and S. S. Gidding, "Are pediatricians responsible for prevention of adult cardiovascular disease?" *Nature Clinical Practice Cardiovascular Medicine*, vol. 6, no. 1, pp. 10–11, 2009.

[8] S. E. Barlow and W. H. Dietz, "Obesity evaluation and treatment: expert Committee recommendations. The Maternal and Child Health Bureau, Health Resources and Services Administration and the Department of Health and Human Services," *Pediatrics*, vol. 102, no. 3, p. E29, 1998.

[9] D. S. Freedman and B. Sherry, "The validity of BMI as an indicator of body fatness and risk among children," *Pediatrics*, vol. 124, no. 1, pp. S23–S34, 2009.

[10] C. L. Ogden, "Defining overweight in children using growth charts," *Maryland Medicine*, vol. 5, no. 3, pp. 19–21, 2004.

[11] B. Falkner, S. R. Daniels, J. T. Flynn et al., "The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents," *Pediatrics*, vol. 114, no. 2, pp. 555–576, 2004.

[12] K. D. Monyeki, H. C. G. Kemper, and P. J. Makgae, "The association of fat patterning with blood pressure in rural South African children: the Ellisras Longitudinal Growth and Health Study," *International Journal of Epidemiology*, vol. 35, no. 1, pp. 114–120, 2006.

[13] H. H. Vorster, "The emergence of cardiovascular disease during urbanisation of Africans," *Public Health Nutrition*, vol. 5, no. 1 A, pp. 239–243, 2002.

[14] J. Mi, H. Cheng, D. Q. Hou, J. L. Duan, H. H. Teng, and Y. F. Wang, "Prevalence of overweight and obesity among children and adolescents in Beijing in 2004," *Zhonghua Liu Xing Bing Xue Za Zhi*, vol. 27, no. 6, pp. 469–474, 2006.

[15] S. Aziz, W. Noorulain, U. E. R. Zaidi, K. Hossain, and I. A. Siddiqui, "Prevalence of overweight and obesity among children and adolescents of affluent schools in Karachi," *Journal of the Pakistan Medical Association*, vol. 59, no. 1, pp. 35–38, 2009.

[16] R. Kelishadi, G. Ardalan, R. Gheiratmand et al., "Thinness, overweight and obesity in a national sample of Iranian children and adolescents: CASPIAN Study," *Child: Care, Health and Development*, vol. 34, no. 1, pp. 44–54, 2008.

[17] R. M. Lauer, L. A. Barness, R. Clark et al., "National Cholesterol Education Program (NCEP): highlights of the report of the expert panel on blood cholesterol levels in children and adolescents," *Pediatrics*, vol. 89, no. 3, pp. 495–501, 1992.

[18] R. V. Luepker, D. R. Jacobs, R. J. Prineas, and A. R. Sinaiko, "Secular trends of blood pressure and body size in a multiethnic adolescent population: 1986 to 1996," *Journal of Pediatrics*, vol. 134, no. 6, pp. 668–674, 1999.

[19] J. T. Flynn, "Pediatric hypertension: recent trends and accomplishments, future challenges," *American Journal of Hypertension*, vol. 21, no. 6, pp. 605–612, 2008.

[20] C. Agyemang, W. K. Redekop, E. Owusu-Dabo, and M. A. Bruijnzeels, "Blood pressure patterns in rural, semi-urban and urban children in the Ashanti region of Ghana, West Africa," *BMC Public Health*, vol. 5, article 114, 2005.

[21] W. E. Moore, J. E. Eichner, E. M. Cohn, D. M. Thompson, C. E. Kobza, and K. E. Abbott, "Blood pressure screening of school children in a multiracial school district: the healthy kids project," *American Journal of Hypertension*, vol. 22, no. 4, pp. 351–356, 2009.

[22] A. Chiolero, F. Cachat, M. Burnier, F. Paccaud, and P. Bovet, "Prevalence of hypertension in schoolchildren based on repeated measurements and association with overweight," *Journal of Hypertension*, vol. 25, no. 11, pp. 2209–2217, 2007.

[23] S. R. Daniels, P. R. Khoury, and J. A. Morrison, "The utility of body mass index as a measure of body fatness in children and adolescents: differences by race and gender," *Pediatrics*, vol. 99, no. 6, pp. 804–807, 1997.

[24] K. L. McNiece, T. S. Poffenbarger, J. L. Turner, K. D. Franco, J. M. Sorof, and R. J. Portman, "Prevalence of hypertension and pre-hypertension among adolescents," *Journal of Pediatrics*, vol. 150, no. 6, article e1, pp. 640–644, 2007.

[25] J. M. Sorof, D. Lai, J. Turner, T. Poffenbarger, and R. J. Portman, "Overweight, ethnicity, and the prevalence of hypertension in school-aged children," *Pediatrics*, vol. 113, no. 3 I, pp. 475–482, 2004.

SAGE-Hindawi Access to Research
International Journal of Hypertension
Volume 2011, Article ID 193719, 8 pages
doi:10.4061/2011/193719

Research Article

Prevalence of Metabolic Syndrome among Working Adults in Ethiopia

A. Tran,[1] B. Gelaye,[1] B. Girma,[2] S. Lemma,[2] Y. Berhane,[2] T. Bekele,[3] A. Khali,[3] and M. A. Williams[1]

[1] *Multidisciplinary International Research Training Program, Department of Epidemiology, University of Washington School of Public Health, Seattle, WA 98195, USA*
[2] *Addis Continental Institute of Public Health, Addis Ababa, Ethiopia*
[3] *International Clinical Laboratories, Addis Ababa, Ethiopia*

Correspondence should be addressed to B. Gelaye, mirt@uw.edu

Received 27 January 2011; Accepted 27 March 2011

Academic Editor: Kazuko Masuo

Objective. To evaluate the prevalence of metabolic syndrome (MetS) according to the International Diabetes Federation (IDF) and Adult Treatment Panel (ATP) III criteria among working East African adults. *Design*. This cross-sectional study of 1,935 individuals (1,171 men and 764 women) was conducted among working adults in Addis Ababa, Ethiopia. The study was conducted in accordance with the STEPwise approach of the World Health Organization. *Results*. According to ATP III and IDF definitions, the overall prevalence of MetS was 12.5% and 17.9%, respectively. Using ATP III criteria, the prevalence of MetS was 10.0% in men and 16.2% in women. Application of the IDF criteria resulted in a MetS prevalence of 14.0% in men and 24.0% in women. The most common MetS components among women were reduced high-density lipoprotein-cholesterol (HDL-C) (23.2%) and abdominal obesity (19.6%); whilst reduced HDL-C concentrations (23.4%) and high blood pressure (21.8%) were most common among men. *Conclusion*. MetS and its individual components are prevalent among an apparently healthy working population in Ethiopia. These findings indicate the need for evidence-based health promotion and disease prevention programs; and more robust efforts directed towards the screening, diagnosis and management of MetS and its components among Ethiopian adults.

1. Introduction

The global prevalence of chronic noncommunicable diseases (NCDs) is on the rise, with the majority of the growth occurring among populations in developing countries [1]. In sub-Saharan Africa, NCDs are projected to surpass infectious diseases by 2030 [2, 3]. Metabolic syndrome (MetS) is a constellation of risk factors of cardiovascular disease (CVD) such as diabetes and impaired glucose regulation, central obesity, hypertension, and dyslipidemia [4]. Consumption of calorie-dense foods, sedentary lifestyle, tobacco consumption, and use of antiretroviral medications are risk factors for MetS [5–10]. Limited available evidence suggests an increasing prevalence of MetS among populations in sub-Saharan African countries over the past decade [11].

Information concerning the prevalence and risk factors of MetS among sub-Saharan Africa is sparse, as most studies have been conducted in North America, Europe, and Asia [12–17]. To the best of our knowledge, no study has systematically evaluated the prevalence of MetS among Ethiopians.

Currently, there are four widely used definitions for MetS, and there appears to be no consensus about the application of any one diagnostic criteria [18]. We evaluated the prevalence of MetS using the National Cholesterol Education Program Adult Treatment Panel III (ATP III) [19] and the International Diabetes Federation (IDF) [20], two of the most widely used definitions of MetS. Both definitions consider blood glucose impairment (hyperglycemia), excess abdominal/body fat (increased waist and/or obesity), dyslipidemia (low HDL-cholesterol and/or high triglycerides), and elevated blood pressure to be core criteria of MetS [11]. While similar, the definitions have different criteria and cut-off values and may yield differing outcomes [21].

2. Materials and Methods

2.1. Design and Participants. This study was conducted in Addis Ababa, the capital city of Ethiopia during the months of December 2009 and January 2010. Study subjects were current permanent employees of the Commercial Bank of Ethiopia (CBE) and teachers in government schools of Addis Ababa. Workplaces were selected based on their relatively high stability of workforce and willingness to participate in the study. A multistage, probabilistic stratified sampling strategy was used to identify and recruit participants. Probability proportional to size (PPS) sampling procedures were used to select CBE branch offices and schools. All employees of the selected workplaces were invited to participate in the study. Excluding subjects with missing anthropometric information ($n = 22$), pregnant women ($n = 21$), and individuals without laboratory measures ($n = 227$), the final sample size included 1,935 (1,171 men and 764 women) participants.

This study was conducted in accordance with the STEPwise approach of the World Health Organization (WHO) for NCD surveillance in developing countries [22]. The approach has three levels: (1) questionnaire to gather demographic and behavioral information, (2) simple physical measurements, and (3) biochemical tests.

2.2. Data Collection and Variable Specification. Participants were interviewed by trained interviewers using the WHO STEPS-structured questionnaire. In accordance with the STEPS manual, questions related to alcohol and substance use were tailored to reflect the local context of Ethiopia [22]. A few additional questions were added to supplement the questionnaire and to reflect the local context of Ethiopia. The questionnaire was first written in English, translated into Amharic by experts, and translated back into English by a panel of professionals who speak both languages. The questionnaire was pretested before the initiation of the study and contained information regarding sociodemographic characteristics, tobacco and alcohol use, nutritional status, and physical activity. A five-day training of the contents of the STEPS questionnaire, data collection techniques, and ethical conduct of human research was provided to research interviewers prior to the commencement on the study.

Physical/anthropometric examinations and blood sample collections were carried out by trained research nurses. Blood pressure (BP) was measured using a digital measuring device (Microlife BP A50, Microlife AG, Switzerland) with participants sitting after resting for at least five minutes. Three BP measurements were taken with at least three-minute intervals between consecutive measurements. The mean systolic and diastolic BP from the second and third measurements were analyzed [22]. The weights of the participants were measured using a solar-powered scale (Model 871, Seca, Germany). Height and weight were measured with participants wearing light clothing. Waist circumference was taken at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest (hip bone) [22]. Hip circumference was taken around the maximum circumference of the buttocks [22].

Blood samples were collected after a 12-hour overnight fasting. Samples of 12 mL of blood were obtained from each participant employing standard infection prevention procedures. The collected aliquots of blood serum were used to determine participants' fasting glucose concentrations and lipid profiles. Serum triglycerides (TGs), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and fasting serum glucose (FG) were measured at the International Clinical Laboratory (ICL) in Addis Ababa, Ethiopia. ICL is one of the best equipped laboratories in Ethiopia with internationally accredited standard operating procedures. TG concentrations were determined by standardised enzymatic procedures using glycerol phosphate oxidase assay. HDL-C was measured using Ultra-HDL assay which is a homogeneous method for directly measuring HDL-C concentrations in serum plasma without the need for off-line pretreatment or centrifugation steps. Participants' FG was determined using standardized glucose oxidase method. All laboratory assays were completed without knowledge of participants' medical history. Lipid, lipoprotein, and FG concentrations were reported as mg/dL.

Prevalence of MetS was defined according to the IDF and ATP III criteria outlined below.

IDF Definition. In accordance with the IDF criteria, subjects were classified as having MetS if participants had abdominal obesity (defined as waist circumference of ≥94 cm for men and ≥80 cm women) plus two of any of the following risk factors: (1) raised TG level (≥150 mg/dL) or specific treatment for this lipid abnormality; (2) reduced HDL-C (<40 mg/dL in males and <50 mg/dL in females) or specific treatment for this lipid abnormality; (3) raised blood pressure (systolic BP ≥130 or diastolic BP ≥85 mmHg) or treatment of previously diagnosed hypertension; (4) raised FG (≥100 mg/dL) or previously diagnosed with type 2 diabetes.

ATP III Definition. In accordance with the ATP III criteria, subjects were classified as having MetS if participants had three or more of the following risk factors: (1) abdominal obesity (waist circumference >102 cm in males and >88 cm in females); (2) hypertriglyceridemia (TG ≥150 mg/dL); (3) reduced HDL-C (<40 mg/dL in males and <50 mg/dL in females); (4) high BP (≥130/85 mmHg); (5) FG (≥110 mg/dL).

All subjects provided informed consent, and all research protocols were approved by the Institutional Review Boards of Addis Continental Institute of Public Health, Addis Ababa, Ethiopia and the Human Subjects Division at the University of Washington, USA.

2.3. Statistical Analyses. Data were entered into EPI INFO (Version 3.5.1), a public access software made available from the U.S. Centers for Disease Control and Prevention (CDC). Entered data were exported to PASW Statistics (Version 18.0) for statistical analysis. We first explored frequency distributions of sociodemographical, clinical, and

Table 1: Sociodemographic characteristics of the study population.

Characteristic	Men $N = 1,171$ %	Women $N = 764$ %	P value
Age (years)			
≤24	17.5	22.2	<.001
25–34	38.0	31.5	
35–44	16.4	17.2	
45–54	17.5	22.3	
≥55	10.5	6.8	
Education			
≤High school	4.0	6.2	<.001
Technical school	4.1	16.1	
≥ Bachelors	91.9	77.7	
Smoking status			
Never smoker	78.9	99.2	<.001
Pervious smoker	14.0	0.7	
Current smoker	7.1	0.1	
Religion			
Orthodox	79.0	80.6	<.001
Muslim	5.2	2.60	
Protestant	14.7	16.4	
Other	1.1	0.4	
Alcohol consumption in past year			
Less than once a month	65.5	95.4	<.001
1–4 days a week	29.7	3.3	
5-6 days a week	2.8	0.7	
Daily	2.1	0.7	
Khat chewing			
No	86.3	99.3	<.001
Yes	13.7	0.7	
Self-reported health status			
Poor/Fair	35.8	41.8	<.001
Excellent	64.2	58.2	

behavioural characteristics of subjects. Continuous variables were expressed as mean ± standard deviation. For skewed variables, median ± interquartile range was reported. Categorical variables were expressed as number (percentage, %). Chi-square tests were used to evaluate the differences in the distribution of categorical variables for study groups. Student's t-tests were used to evaluate differences in mean for study groups. The prevalence estimates for MetS according to the two definitions were determined separately. Using previously described methods, 95% confidence intervals for prevalence estimates were determined [23]. All reported P values are two tailed, and statistical significance was set at .05 levels.

3. Results

Demographic and lifestyle characteristics of the study population are provided in Table 1. The majority of participants had a college diploma, bachelor's degree, or higher (91.9% men and 77.7% women) and reported to be Orthodox Christians (79.0% men and 80.6% women). Approximately 20.0% of men and less than 1.0% of women reported that they were current or previous smokers; of 4.9% men and 1.5% of women reported almost daily or daily alcohol consumption during the past year. Khat chewing (a natural stimulant with amphetamine-like effects commonly used for social recreation in East African countries) [24] was reported by 13.7% of men and 0.7% of women. Approximately 36.0% of men and 42.0% of women reported having a fair or poor health status.

Table 2 shows the cardiometabolic and clinical characteristics of the study population. Approximately, a quarter of men (24.7%) and women (25.7%) were overweight (BMI 25.0–29.9 kg/m^2). Women were more likely to be obese (10.2%) compared to men (2.1%). Approximately 46.0% of men and 31.0% of women were prehypersensitive (systolic BP 120–130 mmHg or diastolic BP 80–89 mmHg); 15.6% of men and 10.8% of women had stage 1 hypertension (systolic BP 140–159 mmHg or diastolic BP 90–99 mmHg). The mean systolic blood pressure and diastolic blood pressure were higher for men (124.3 mmHg) than for women (116.5 mmHg). Men also had a higher mean waist circumference compared with women. Fasting serum glucose concentrations were similar for both groups. However, mean serum HDL-C and LDL-C concentrations were higher among women as compared with men. Serum triglyceride concentrations were higher, on average, among men as compared with women.

Table 3 shows the prevalence of MetS as defined using the ATP III and IDF diagnostic criteria. Using the ATP III criteria, the prevalence of MetS was 12.5% overall (10.0% among men and 16.2% among women) in the study population. Application of the IDF criteria in this study population yielded a MetS prevalence of 17.9% overall (14.0% of men and 24.0% of women). The prevalence of MetS, irrespective of criteria used, increased markedly with age in both men and women. However, the prevalence was highest between ages 45–54 with 40.5% of men and 53.7% of women having MetS.

The age-adjusted prevalence estimates of each component of MetS according to the ATP III and IDF criteria are summarized in Figure 1. The most common MetS components among women using the ATP III criteria were reduced HDL-C (23.2%) and abdominal obesity (19.6%), whilst reduced HDL-C concentrations (23.4%) and high blood pressure (21.8%) were most common among men. Similar patterns were observed using the IDF criteria. Figure 2 shows the presence of 0, 1, 2, 3, 4, and 5 MetS components among men and women using the ATP III criteria and the presence of 0, 1, 2, 3, and 4 components in addition to central obesity as a requirement among men and women using the IDF definition. While some participants did not meet the MetS criteria of the ATP III and IDF, many had one or two components and may be at risk of developing the syndrome in the future. Using the ATP III criteria, 20.4% of women and 18.6% of men had two MetS components. The IDF criteria also showed a high number of individuals at risk with 46.5% of women and 34.7% of men having central obesity plus one additional component.

Table 2: Cardiometabolic characteristics of study population according to gender.

Characteristic	Gender		P value
	Men $N = 1,171$%	Women $N = 764$%	
Body mass index (kg/m^2)			
Underweight (<18.5)	13.2	11.9	<.001
Normal (18.5–24.9)	59.9	52.2	
Overweight (25.0–29.9)	24.7	25.7	
Obese (≥30.0)	2.1	10.2	
Blood pressure*			
Normotensive	34.4	55.2	<.001
Prehypertension	45.6	30.6	
Stage 1 hypertension	15.6	10.8	
Stage 2 hypertension	4.4	3.5	
	Mean (SD)	Mean (SD)	
Waist circumference	85.6 (11.3)	80.6 (12.9)	<.001
Diastolic blood pressure (mmHg)	80.1 (14.6)	76.3 (10.3)	<.001
Systolic blood pressure (mmHg)	124.3 (16.0)	116.5 (17.0)	<.001
Mean arterial pressure	94.8 (13.4)	89.7 (11.8)	<.001
Fasting glucose (mg/dL)	94.3 (28.7)	93.5 (26.7)	.654
HDL cholesterol (mg/dL)	45.4 (8.4)	50.3 (10.5)	<.001
LDL cholesterol (mg/dL)	115.3 (44.9)	119.8 (34.7)	.908
	Median (IQ)	Median (IQ)	
Triglycerides (mg/dL)†	112.0 (81.0–171.0)	95.0 (72.0–127.0)	.127

† Data are median (interquartile range) since distribution was skewed, and test of significance was based on log-transformed values.
*According to the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, hypertension is classified by the following standards: (1) normotensive (systolic BP < 120 mmHg and diastolic BP < 80 mmHg); (2) prehypertension (systolic BP 120–139 mmHg or diastolic BP 80–89 mmHg); stage 1 hypertension (systolic BP 140–159 mmHg or diastolic BP 90–99 mmHg); stage 2 hypertension (systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg) [25].

Table 3: Prevalence of metabolic syndrome based on different sets of criteria by age group.

		Adult Treatment Panel (ATP) III	
	All	Men ($N = 1171$) % (95% CI)	Women ($N = 764$) % (95% CI)
Overall	12.5 (11.0–14.0)	10.0 (8.3–11.7)	16.2 (13.6–18.8)
Age (years)			
≤24	2.5 (0.9–4.1)	1.7 (0.1–3.5)	3.3 (0.6–6.0)
25–34	7.9 (5.9–9.9)	9.5 (6.8–12.2)	6.5 (3.4–9.6)
35–44	18.4 (14.2–22.6)	21.6 (15.8–27.4)	15.4 (9.2–21.6)
45–54	47.3 (42.2–52.4)	40.5 (33.8–47.2)	53.7 (46.2–61.2)
≥55	23.8 (17.5–30.1)	26.7 (18.8–34.6)	21.1 (9.9–32.3)
		International Diabetes Federation (IDF)	
		Men ($N = 1171$) % (95% CI)	Women ($N = 764$) % (95% CI)
Overall	17.9 (16.2–19.6)	14.0 (12.0–16.0)	24.0 (21.0–27.0)
Age (years)			
≤24	2.6 (1.0–4.2)	1.2 (10.3–20.1)	3.9 (1.0–6.8)
25–34	12.5 (10.0–15.0)	14.7 (11.9–18.5)	10.5 (6.6–14.4)
35–44	20.9 (16.5–25.3)	20.9 (10.1–20.3)	21.0 (14.0–28.0)
45–54	43.3 (38.3–48.3)	38.0 (10.3–20.1)	48.1 (40.6–55.6)
≥55	20.6 (14.6–26.6)	25.2 (8.8–21.6)	16.6 (6.4–26.8)

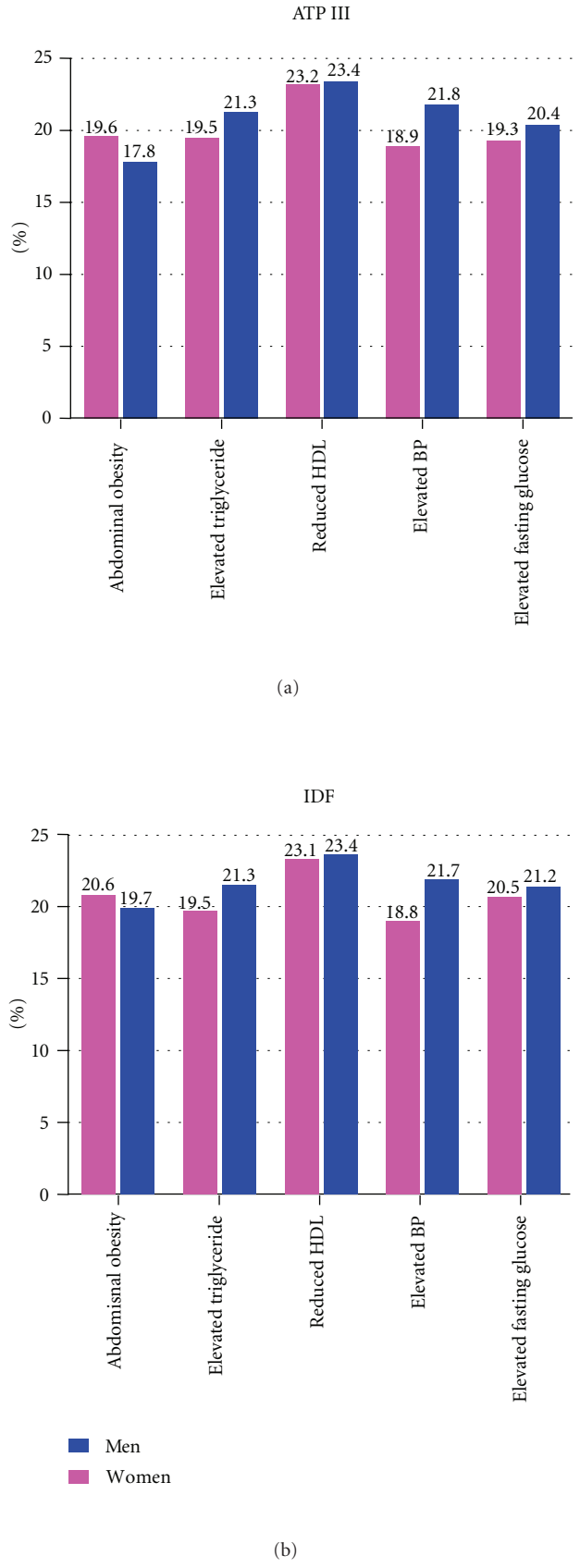


Figure 1: Age-adjusted prevalence of metabolic syndrome components by gender according to ATP III and IDF criteria.

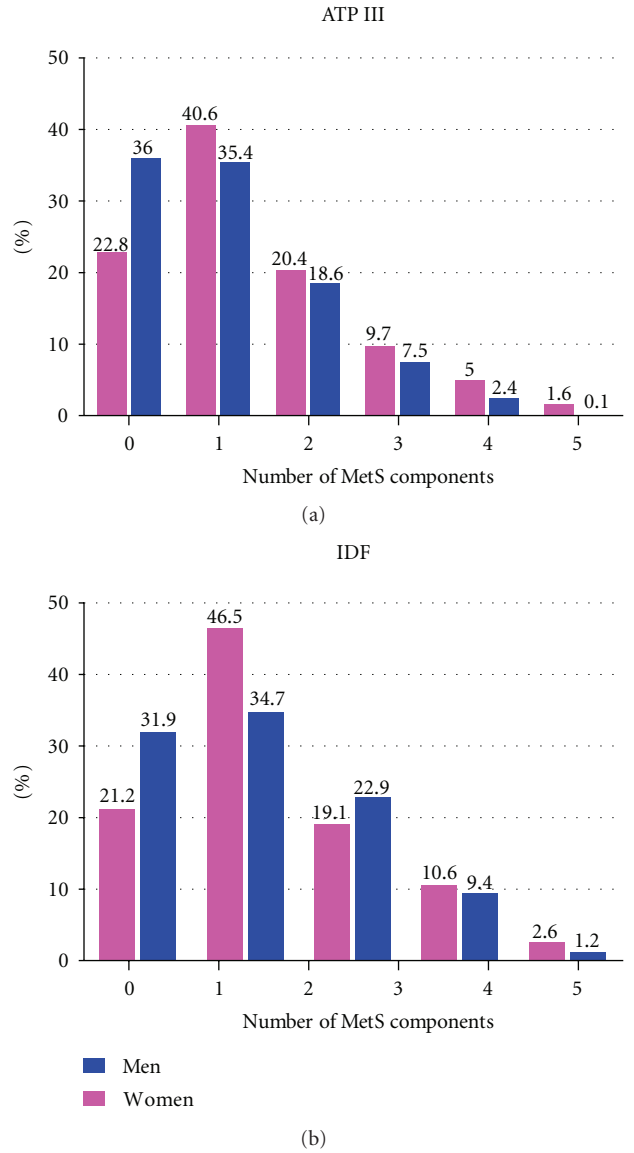


Figure 2: Number of metabolic syndrome components by gender according to ATP III and IDF criteria.

4. Discussion

Findings from this study confirm a high prevalence of MetS among working adults in Addis Ababa, Ethiopia. Using the ATP III criteria, the prevalence of MetS was found to be 12.5%, while the IDF criteria yielded an even higher prevalence of 17.9%. Our results suggest that women are at greater risk for MetS (ATP III 16.2% and IDF 24.0%) than men (ATP III 10.0% and IDF 14.0%). The prevalence of MetS increased markedly with age. MetS was most prevalent among participants in the 45–54 age group (43.3%–47.3%). Lastly, the number of participants with one or two MetS components suggests that certain individuals are potentially at risk of developing the syndrome.

Little information exists concerning the prevalence and epidemiological characteristics of MetS in sub-Saharan

Africa. The first reported MetS study in the region was conducted in the mid-90s in Cameroon [12, 26] which found a 1.5% and 1.3% prevalence of MetS among urban dwelling women and men using IDF criteria [26]; however, the study did not measure HDL-C concentrations. A second study conducted in 2004 by Kelliny et al., in Seychelles, found a high prevalence of MetS where 25%–30% of their study population had the syndrome [11]. A recent study involving adults in semiurban and rural communities in Nigeria found a prevalence of MetS to be 18% [27]. A community-based study conducted in Tanzania in 2009 reported a 38% prevalence of MetS although the study sample size was small [28]. More recently, Adegoke et al. in their study among rural Nigerians reported a 12.1% prevalence of MetS [29]. Our prevalence estimates are higher than what was reported in Cameroon and rural Nigeria [26, 29] but lower than Seychelles and Tanzania [11, 28]. Our study findings were lower than other reports of MetS prevalence of developed countries over the last few years including the USA [15], Portugal [30], and Turkey [31]. However, the results of our study were greater than the prevalence of MetS in some developed countries such as Japan [14] and China [13]. While there is no unanimously accepted definition of MetS, findings from this study resulted in a high prevalence of MetS regardless of the definition (ATP III or IDF) used. Many recent studies have evaluated MetS prevalence using more than one definition including those established by ATP III, IDF, and WHO [11, 29].

Previous studies conducted in sub-Saharan Africa including in Benin and in south-western Nigeria have identified a high prevalence of cardiometabolic risk factors including abdominal obesity (32.0% and 14.7%, resp.) and hypertension (23.0% and 28.0%, resp.) [32, 33]. While there is an accumulating body of evidence on the prevalence of the individual components of MetS among Ethiopians [34–36], to the best of our knowledge, this is the first study to report the prevalence of the syndrome in the country. Tesfaye et al., in their cross-sectional study involving adults in Addis Ababa, Ethiopia, found a high prevalence of hypertension (31.5% among men and 28.9% among women) as a cause for concern [34]. The same study also found a high prevalence of overweight adults and indicated that women were more likely to be overweight than men in their study population [34]. Our findings of high prevalence of MetS and its components are in part due to the epidemiological and nutritional transition that has occurred globally including in sub-Saharan African countries where lifestyle and behavioral changes, both products of modernization and urbanization, have taken place [37–40]. As a result of this epidemiological transition where CVD risk in Africa is increasing [41], preventative measures as well as interventional programs are in demand.

Our study has several strengths including the number of participants which was adequate to make gender- and age-specific comparisons, the inclusion of schools and branch offices in wider geographical areas, the use of standard and calibrated instruments to make measurements, the requirement of reliability tests before data collection, and standardization during training. Limitations of our study include social desirability bias in which participants may withhold information regarding their life-style habits that may not be generally acceptable for working adults (smoking, chewing khat, etc.) [42] which may result in an underestimation of these behaviors. In addition, study findings may not be generalized to the broader Ethiopian population since study subjects consisted of current employed bankers of CBE and teachers in government schools who were fairly well-educated and urban workers.

In conclusion, the prevalence of MetS among our study population was high and ultimately adds to the limited amount of MetS data in sub-Saharan Africa. An increased risk for cardiovascular morbidity and mortality has also been linked to the prevalence of MetS [43]. The findings highlight the need for evidence-based prevention, diagnosis, and management of MetS and its associated factors among working adults in Ethiopia. Individuals with and at risk of MetS ought to focus on weight management and engage in appropriate physical activity levels. Support and promotion of healthy lifestyle behaviors by institutional leaders are also highly desirable. Moreover, future interventions by health policy makers and public health officials ought to focus on the individuals at risk for MetS who have one or two risk factors in order to control any potential burden of the syndrome.

Acknowledgments

This research was completed while Mr. A. Tran was a research training fellow with the Multidisciplinary International Research Training (MIRT) Program of the University of Washington, School of Public Health. The MIRT Program is supported by an award from the National Institutes of Health, National Center on Minority Health and Health Disparities (T37-MD001449). The authors wish to thank Addis Continental Institute of Public Health for providing facilities and logistics support throughout the research process. The authors would also like to thank the Commercial Bank of Ethiopia and Addis Ababa Education Office as well as branch offices and schools for granting access to conduct the study. The International Clinical Laboratories is also gratefully acknowledged for conducting the laboratory analyses.

References

[1] C. J. L. Murray and A. D. Lopez, "Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study," *Lancet*, vol. 349, no. 9064, pp. 1498–1504, 1997.

[2] C. D. Mathers and D. Loncar, "Projections of global mortality and burden of disease from 2002 to 2030," *PLoS Medicine*, vol. 3, no. 11, article e442, 2006.

[3] D. Yach, C. Hawkes, C. L. Gould, and K. J. Hofman, "The global burden of chronic diseases: overcoming impediments to prevention and control," *Journal of the American Medical Association*, vol. 291, no. 21, pp. 2616–2622, 2004.

[4] B. Lu, Y. Yang, X. Song et al., "An evaluation of the International Diabetes Federation definition of metabolic syndrome in Chinese patients older than 30 years and diagnosed with

type 2 diabetes mellitus," *Metabolism*, vol. 55, no. 8, pp. 1088–1096, 2006.

[5] F. Young, J. A. Critchley, L. K. Johnstone, and N. C. Unwin, "A review of co-morbidity between infectious and chronic disease in Sub Saharan Africa: TB and diabetes mellitus, HIV and metabolic syndrome, and the impact of globalization," *Global Health*, vol. 5, article 9, 2009.

[6] M. Hanefeld, A. Ceriello, P. E. H. Schwarz, and S. R. Bornstein, "The metabolic syndrome—a postprandial disease?" *Hormone and Metabolic Research*, vol. 38, no. 7, pp. 435–436, 2006.

[7] Y. Kamari, E. Grossman, M. Oron-Herman et al., "Metabolic stress with a high carbohydrate diet increases adiponectin levels," *Hormone and Metabolic Research*, vol. 39, no. 5, pp. 384–388, 2007.

[8] P. E.H. Schwarz, "Congress report from the American Diabetes Association: 66th Annual Scientific Sessions in Washington, USA," *Experimental and Clinical Endocrinology and Diabetes*, vol. 114, no. 10, pp. 605–610, 2006.

[9] E. Mutimura, N. J. Crowther, A. Stewart, and W. T. Cade, "The human immunodeficiency virus and the cardiometabolic syndrome in the developing world: an African perspective," *Journal of the cardiometabolic syndrome*, vol. 3, no. 2, pp. 106–110, 2008.

[10] World Health Organization, "World Health Report. Prevention Chronic Disease: A vital Investment," 2008, http://www.who.int/chp/chronic_disease_report/contents/part1.pdf.

[11] C. Kelliny, J. William, W. Riesen, F. Paccaud, and P. Bovet, "Metabolic syndrome according to different definitions in a rapidly developing country of the African region," *Cardiovascular Diabetology*, vol. 7, article no. 27, 2008.

[12] A. A. Motala, J. C. Mbanya, and K. L. Ramaiya, "Metabolic syndrome in sub-Saharan Africa," *Ethnicity & disease*, vol. 19, no. 2, pp. S2–S8, 2009.

[13] Y. Feng, X. Hong, Z. Li et al., "Prevalence of metabolic syndrome and its relation to body composition in a Chinese rural population," *Obesity*, vol. 14, no. 11, pp. 2089–2098, 2006.

[14] C. M. Y. Lee, R. R. Huxley, M. Woodward et al., "Comparisons of metabolic syndrome definitions in four populations of the Asia-Pacific region," *Metabolic Syndrome and Related Disorders*, vol. 6, no. 1, pp. 37–46, 2008.

[15] E. S. Ford, "Prevalence of the metabolic syndrome defined by the international diabetes federation among adults in the U.S," *Diabetes Care*, vol. 28, no. 11, pp. 2745–2749, 2005.

[16] K. Shiwaku, A. Nogi, K. Kitajima et al., "Prevalence of the metabolic syndrome using the modified ATP III definitions for workers in Japan, Korea and Mongolia," *Journal of Occupational Health*, vol. 47, no. 2, pp. 126–135, 2005.

[17] E. S. Ford, W. H. Giles, and W. H. Dietz, "Prevalence of the metabolic syndrome among US adults: findings from the Third National Health and Nutrition Examination Survey," *Journal of the American Medical Association*, vol. 287, no. 3, pp. 356–359, 2002.

[18] K. G. M. M. Alberti and P. Z. Zimmet, "Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation," *Diabetic Medicine*, vol. 15, no. 7, pp. 539–553, 1998.

[19] S. M. Grundy, J. I. Cleeman, S. R. Daniels et al., "Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement," *Circulation*, vol. 112, no. 17, pp. 2735–2752, 2005.

[20] K. G. M. M. Alberti, P. Zimmet, and J. Shaw, "The metabolic syndrome—a new worldwide definition," *Lancet*, vol. 366, no. 9491, pp. 1059–1062, 2005.

[21] A. E. Schutte, R. Schutte, H. W. Huisman et al., "Classifying Africans with the metabolic syndrome," *Hormone and Metabolic Research*, vol. 41, no. 2, pp. 79–85, 2009.

[22] World Health Organization, "Chronic diseases and health promotion: Stepwise approach to surveillance (STEPS)," 2010, http://www.who.int/chp/steps/manual/en/index.html.

[23] T. Colton, *Statistics in Medicine*, Little Brown, Boston, Mass, USA, 1974.

[24] W. Getahun, T. Gedif, and F. Tesfaye, "Regular Khat (Catha edulis) chewing is associated with elevated diastolic blood pressure among adults in Butajira, Ethiopia: a comparative study," *BMC Public Health*, p. 390, 2010.

[25] A. V. Chobanian, G. L. Bakris, H. R. Black et al., "Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure," *Hypertension*, vol. 42, no. 6, pp. 1206–1252, 2003.

[26] L. Fezeu, B. Balkau, A. P. Kengne, E. Sobngwi, and J. C. Mbanya, "Metabolic syndrome in a sub-Saharan African setting: central obesity may be the key determinant," *Atherosclerosis*, vol. 193, no. 1, pp. 70–76, 2007.

[27] I. I. Ulasi, C. K. Ijoma, and O. D. Onodugo, "A community-based study of hypertension and cardio-metabolic syndrome in semi-urban and rural communities in Nigeria," *BMC Health Services Research*, vol. 10, article no. 71, 2010.

[28] M. A. Njelekela, R. Mpembeni, A. Muhihi et al., "Gender-related differences in the prevalence of cardiovascular disease risk factors and their correlates in urban Tanzania," *BMC Cardiovascular Disorders*, vol. 9, article 30, 2009.

[29] O. A. Adegoke, R. A. Adedoyin, M. O. Balogun, R. A. Adebayo, L. A. Bisiriyu, and A. A. Salawu, "Prevalence of metabolic syndrome in a rural community in Nigeria," *Metabolic Syndrome and Related Disorders*, vol. 8, no. 1, pp. 59–62, 2010.

[30] A. C. Santos and H. Barros, "Impact of metabolic syndrome definitions on prevalence estimates: a study in a Portuguese community," *Diabetes and Vascular Disease Research*, vol. 4, no. 4, pp. 320–327, 2007.

[31] A. S. Can and T. P. Bersot, "Analysis of agreement among definitions of metabolic syndrome in nondiabetic Turkish adults: a methodological study," *BMC Public Health*, vol. 7, article no. 353, 2007.

[32] R. Sodjinou, V. Agueh, B. Fayomi, and H. Delisle, "Obesity and cardio-metabolic risk factors in urban adults of Benin: relationship with socio-economic status, urbanisation, and lifestyle patterns," *BMC Public Health*, vol. 8, article 84, 2008.

[33] O. O. Oladapo, L. Salako, O. Sodiq, K. Shoyinka, K. Adedapo, and A. O. Falase, "A prevalence of cardiometabolic risk factors among a rural Yoruba south-western Nigerian population: a population-based survey," *Cardiovascular Journal of Africa*, vol. 21, no. 1, pp. 26–31, 2010.

[34] F. Tesfaye, P. Byass, and S. Wall, "Populationbased prevalence of high blood pressure among adults in Addis Ababa: uncovering a silent epidemic," *BMC Cardiovascular Disorders*, vol. 9, article no. 39, 2009.

[35] F. Tesfaye, N. G. Nawi, H. Van Minh et al., "Association between body mass index and blood pressure across three populations in Africa and Asia," *Journal of Human Hypertension*, vol. 21, no. 1, pp. 28–37, 2007.

[36] F. Tesfaye, P. Byass, S. Wall, Y. Berhane, and R. Bonita, "Association of smoking and khat (Catha edulis Forsk) use with high blood pressure among adults in Addis Ababa,

Ethiopia, 2006," *Preventing Chronic Disease*, vol. 5, no. 3, article A89, 2008.

[37] S. Kadiri and B. L. Salako, "Cardiovascular risk factors in middle aged Nigerians," *East African Medical Journal*, vol. 74, no. 5, pp. 303–306, 1997.

[38] R. BeLue, TA Okoror, J Iwelunmor et al., "An overview of cardiovascular risk factor burden in sub-Saharan African countries: a socio-cultural perspective," *Global Health*, vol. 5, article 10, 2009.

[39] L. Fezeu, E. Minkoulou, B. Balkau et al., "Association between socioeconomic status and adiposity in urban Cameroon," *International Journal of Epidemiology*, vol. 35, no. 1, pp. 105–111, 2006.

[40] K. S. Reddy and S. Yusuf, "Emerging epidemic of cardiovascular disease in developing countries," *Circulation*, vol. 97, no. 6, pp. 596–601, 1998.

[41] H. C. Onyegbutulem, P. I. H-Onyegbutulem, M. Reimann, J. Li, S. R. Bornstein, and P. E. Schwarz, "Metabolic syndrome in Africa: an emerging perspective," *Hormone and Metabolic Research*, vol. 41, no. 2, pp. 75–78, 2009.

[42] D. Kebede, A. Alem, G. Mitike et al., "Khat and alcohol use and risky sex behaviour among in-school and out-of-school youth in Ethiopia," *BMC Public Health*, vol. 5, article no. 109, 2005.

[43] BO. Isomaa, P. Almgren, T. Tuomi et al., "Cardiovascular morbidity and mortality associated with the metabolic syndrome," *Diabetes Care*, vol. 24, no. 4, pp. 683–689, 2001.

SAGE-Hindawi Access to Research
International Journal of Hypertension
Volume 2011, Article ID 821971, 9 pages
doi:10.4061/2011/821971

Research Article

Prevalence of Hypertension, Obesity, Diabetes, and Metabolic Syndrome in Nepal

Sanjib Kumar Sharma,[1] Anup Ghimire,[2] Jeyasundar Radhakrishnan,[3] Lekhjung Thapa,[1] Nikesh Raj Shrestha,[1] Navaraj Paudel,[1] Keshar Gurung,[1] Maskey R,[1] Anjali Budathoki,[1] Nirmal Baral,[4] and David Brodie[3]

[1] *Department of Internal Medicine, B. P. Koirala Institute of Health Sciences, Dharan 76500, Nepal*
[2] *Department of Public Health and Community Medicine, B. P. Koirala Institute of Health Sciences, Dharan 76500, Nepal*
[3] *Faculty of Society & Health, Bucks New University, Buckinghamshire HP11 2JZ, UK*
[4] *Department of Biochemistry, B. P. Koirala Institute of Health Sciences, Dharan 76500, Nepal*

Correspondence should be addressed to Sanjib Kumar Sharma, drsanjib@yahoo.com

Received 24 January 2011; Accepted 24 February 2011

Academic Editor: Kazuko Masuo

Background. This study was carried out to establish the prevalence of cardiovascular risks such as hypertension, obesity, and diabetes in Eastern Nepal. This study also establishes the prevalence of metabolic syndrome (MS) and its relationships to these cardiovascular risk factors and lifestyle. *Methods*. 14,425 subjects aged 20–100 (mean 41.4 ± 15.1) were screened with a physical examination and blood tests. Both the International Diabetic Federation (IDF) and National Cholesterol Education Programme's (NCEP) definitions for MS were used and compared. *Results*. 34% of the participants had hypertension, and 6.3% were diabetic. 28% were overweight, and 32% were obese. 22.5% of the participants had metabolic syndrome based on IDF criteria and 20.7% according to the NCEP definition. Prevalence was higher in the less educated, people working at home, and females. There was no significant correlation between the participants' lifestyle factors and the prevalence of MS. *Conclusion*. The high incidence of dyslipidemia and abdominal obesity could be the major contributors to MS in Nepal. Education also appears to be related to the prevalence of MS. This study confirms the need to initiate appropriate treatment options for a condition which is highly prevalent in Eastern Nepal.

1. Introduction

According to the World Health Organization's recent update [1], diabetes, hypertension, and obesity are one of the top five continuing risk factors for cardiovascular deaths in the world. Obesity is increasing substantially and is one of the major contributors of disease prevalence due to its pathophysiological link to other cardiovascular risks such as hypertension and diabetes. It is estimated that, in 2010, 6.4% of adults would have diabetes mellitus affecting 285 million in the world and it will increase to 7.7% by 2030, affecting 439 million adults [2]. Of special note is that there will be a 67% increase in the prevalence of diabetes in developing countries from 2010 to 2030 [2].

Metabolic syndrome (MS) is a constellation of overweight/obesity, hypertension, and disturbances of lipid and carbohydrate metabolism. The definition of MS was debated for a long time to produce a standardized clinical criterion. The World Health Organisation describes MS as the presence of type 2 diabetes or impaired glucose tolerance with any two of the following characteristics: obesity, high levels of triglycerides, low levels of high-density lipoprotein, and hypertension. The International Diabetes Federation (IDF) takes central obesity as a prerequisite for the diagnosis of MS with the association of any two of the other factors, that is, high blood pressure, abnormal blood glucose, high levels of triglycerides, and low levels of high-density lipoprotein. Also, the IDF has derived specific reference values for central obesity for different ethnicities. The National Cholesterol Education Programme (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel, or ATP, III) [3], the National

Heart, Lung and Blood Institute, and the American Heart Association [4] have released a report on the criteria for diagnosing and managing MS. The panel describes MS as the presence of any three of the following: abdominal obesity, dislipidemia (high levels of triglycerides, low HDL), increased blood pressure, and elevated fasting glucose. This definition has been extensively reviewed and accepted by the greatest number of researchers. For the purpose of this paper, the ATP III and IDF's definitions are used and compared.

Each component of MS is a known risk factor for the development of type 2 diabetes, atherosclerosis, and coronary artery disease (CAD). People with MS are 3–10 times more likely to develop cardiovascular disease commensurate with a high risk of morbidity and mortality [5, 6]. Central obesity, one of the components of MS, predicts the occurrence of diabetes and overall cardiovascular risk [7]. The NCEP ATP III [3] states that MS is equal to cigarette smoking as a contributing factor for premature cardiovascular disease.

The prevalence of metabolic syndrome is increasing all over the world with different regions having individual clusters of epidemic risk factors [6, 8], and in particular there is evidence of a high prevalence of MS and diabetes in South Asians [9]. Substantial increase in the prevalence of type 2 diabetes in Asia in recent years has raised serious concerns about cardiovascular consequences for these populations [5, 10]. However, in developing countries, many of these subclinical conditions are not diagnosed until the onset of complications such as myocardial infarction or stroke [11]. It is essential to initiate early detection of these chronic diseases in underdeveloped countries in Asia, such as Nepal, so that preventative action can minimize the consequences.

This study aims to establish the prevalence of hypertension, diabetes, obesity, and metabolic syndrome in the participants of a major health screening programme in Nepal. This study also aims to establish the relationship between the components of MS and lifestyle of the participants.

2. Methods

2.1. Subjects. Nepal is one of the poorest countries of the world at the 136th position of human development index. The total population of Nepal is 27 million. The subjects were the participants of the "Programme for Detection and Management of Chronic Kidney Disease, Hypertension, Diabetes and Cardiovascular Disease," a community-based screening programme in Eastern Nepal [12].

2.2. Research Team and Demographic Data Collection. In this community-based programme a series of community awareness programmes were conducted in a specific locality with the help of local leaders, medical students, and community volunteers. Various screening centres such as permanent centers (in health clinics, community centers, etc.) and temporary screening centers (in schools, clubs, houses of worship, and private homes) were used to screen the population. Each center used a group of five to seven people as community volunteers and consisted of a local leader (priest, administrator, school teachers, and local political leaders), a laboratory technician, and nurse. Medical students (approximately 100 in number) and nursing students (around 25) assisted the community volunteers.

Prior to screening, the community volunteers went from door to door to record the number of family members residing permanently and to inform the members of the family, about the need of the project. All people of ≥20 years were invited to come to a predefined place in very close vicinity to their house. They were requested to avoid food for the previous 12 hours. Pregnant or menstruating women at the time of analysis, people with a fever or acute illness, and those who had recently engaged in heavy exercise were excluded.

The research team also collected general information on the participants' demographic data, diet, smoking, alcohol consumption, and physical activity. The data recorded included family and medical history for kidney disease, high blood pressure, diabetes, cardiovascular disease and any current medication or treatment.

2.3. Physiological Measurements. Blood pressure was measured by the auscultatory method with a random zero mercury sphygmomanometer and standard cuff (**12** × **34** cm). The blood pressure measurement was taken in the seated position, quietly in a chair with feet on the floor and an arm support at the heart level.

Hypertension was defined according to the guidelines of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure [13], that is, systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg and/or concomitant use of antihypertensive medications. Body weight and height were assessed with all subjects standing without shoes and heavy outer garments to the nearest 0.1 kg and 1 cm, respectively. Body mass index was estimated according to standard nomograms. Waist circumference was measured over light clothing at a level midway between the lower rib margin and the iliac crest in centimetres rounded up to nearest 0.5 cm. Abdominal obesity is defined as an abdominal circumference > 102 cm (40 in) in males and > 88 cm (35 in) in females for NCEP criteria and > 90 cm in males and >80 cm in females for IDF criteria for South Asians.

Plasma glucose concentration was determined by the glucose oxidase-peroxidase method (Vitalab Selectra-2, Merck, Germany). The diagnosis of diabetes was defined by either casual plasma glucose ≥ 200 $mg \cdot dL^{-1}$ associated with symptoms of diabetes and on fasting samples—plasma glucose ≥ 126 $mg \cdot dL^{-1}$. Individuals with self reported, prior physician-diagnosis of diabetes were classified as having previously diagnosed diabetes.

Serum lipids that include total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides (TG) were also measured (Vitalab Selectra-2, Merck, Germany).

2.4. Quality Control. The results from any person having a history of hypertension or found to have hypertension were verified by qualified doctors. All biochemical abnormalities were reconfirmed. The biochemical tests were completed in semiautomatic analysers (Microlab 300, Vital Scientific, The Netherelands). The tests were undertaken in the same machine using standard biochemical reagents. Regular internal quality controls were undertaken and routinely crosschecked with other laboratories.

2.5. Data Handling. Data were stored in a central electronic database using "Epidata" software. Epidata refers to a group of applications used in combination for creating documented data structures and analysis of quantitative data. In this study, Epidata was used for simple and programmed data entry and data documentation.

2.6. Data Analysis. Data were extracted from "Epidata" and imported to SPSS 18.0 software. The data were recoded as necessary, and frequencies were analysed. The IDF and NCEP ATP III's criteria for metabolic syndrome were used to calculate and compare the frequency of metabolic syndrome. The NCEP criterion was used to find the correlations with other findings. The relationships between the prevalence of cardiovascular risk factors, demographic details, lifestyle, and physiological test results were analysed using the Spearman correlation test. Further, the differences in the categorical variables were examined using chi-squared test. Odds Ratios (ORs) and their 95% confidence interval were calculated using binary logistic regression (for gender and age) and multinomial logistic regression (for life style factors).

3. Results

In total, 14,425 people, aged 20–100 (mean age 41.4 ± 15.1), were included in the study. Among them, 99.9% were South Asians who were living in Nepal.

The participants' demographic and lifestyle details are listed in Table 1. The participants were a mixture of various levels of education. The percentage of education level is illustrated in accordance to the number of years in education (1–5 years—primary, 6–10 years—secondary, >10 years—higher secondary level). The participants were divided into four categories according to their work: labourer/farm, office, house, and none/unknown. The age was divided into four categories. Participants' physical activities were defined according to the time spent every day on physical activity as >60 min, 30–60 min, <30 min/day, and none. This information was recorded verbally.

3.1. Obesity, Diabetes, and Hypertension. Abdominal obesity was observed in 11.5% (n = 1607/14002) of the participants as per NCEP criteria (mean waist circumference: male—107.38 ± 6.19 cm, female—94.84 ± 5.84 cm) and in 34.7% (n = 5006/14418) of the participants as per IDF criteria. According to the revised BMI, 10.6% (n = 1534/14423) were underweight (BMI < 18.5), 28.2% (n = 4065/14423) were overweight (BMI = 22–24.9), and 32.5% (n = 4689/14423) were obese (BMI > 25) [14].

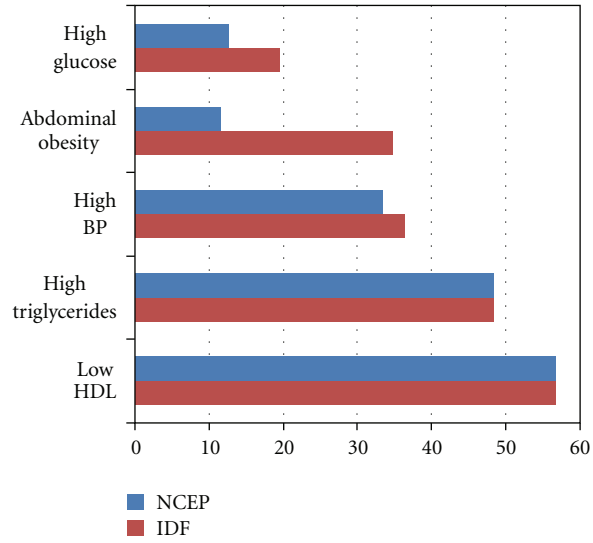


Figure 1: Percentage of traits of metabolic syndrome in the total participants.

Diabetic prevalence was 6.3% (889/14008) of which 4.8% (n = 673/14008) were under treatment. A figure of 12.3% (n = 1718/14009) had a family history of diabetes. Hypertension was observed in 33.9% (n = 4894/14422) of the participants (mean systolic 138.72 ± 18.03 mm Hg and mean diastolic 93.09 ± 8.45 mm Hg). Only 12.9% (1812/14009) were previously diagnosed, and 8.5% were receiving treatment for hypertension. A history of coronary artery disease was present in 1.6% (n = 218/14007), and 1% (n = 142) were under treatment for ischemic heart disease or stroke.

Table 2 shows the goodness of fit for the prevalence of obesity, hypertension, and diabetes. The comparison was against the latest available prevalence data [15–17]. Prevalence of hypertension showed no difference from these data, and obesity showed only a small difference. Diabetes showed a large statistically significant difference from the previous available data.

The percentages of the participants who had abnormal lipid profile that includes total serum cholesterol, serum LDL cholesterol, serum HDL cholesterol, serum triglycerides are listed in Table 3.

3.2. Prevalence of Metabolic Syndrome. There were 2191 sets of data eligible to meet the criteria for metabolic syndrome. MS was observed in 22.5% (n = 494/2191) of the participants according to the IDF criteria and 20.7% (454/2191) according to the NCEP criteria. The percentages of individual MS risk factors among the total participants and the participants with MS are illustrated in Figures 1 and 2. Generally, among the total participants and the specific participants with MS, the presence of abnormal lipids was higher than the other factors defining MS. However,

Table 1: Demographic and lifestyle details of the participants.

Demographic detail	% in total participants
Age (n = 14425)	20–40 years—53.6% (n = 7729) 41–60 years—33.8% (n = 4880) 61–80 years—11.9% (n = 1716) 80–100 years—0.7% (n = 100)
Gender (n = 14009)	Male—38% (n = 5327) Female—62% (n = 8682)
Level of education (n = 14009)	Higher secondary—33.1% (n = 4635) Secondary—22% (n = 3079) Primary—14.9% (n = 2092) None—30% (n = 4197)
Work category (n = 13982)	Labour—12.9% (n = 1797) House—57.1% (n = 7977) Office—14.9% (n = 2090) None—15.1% (n = 2118)
Physical activity (n = 14001)	>60 min/day—37.1% (n = 5190) 30–60 min/day—25.3% (n = 3543) <30 min/day or None—37.6% (n = 5628)
Fruits and vegetables in diet (n = 14009)	Everyday—31.4% (n = 4403) 1–5 days—56% (n = 7842) Once/week or None—12.6% (n = 1764)
Smoking (n = 14004)	
Current—11.9% (n = 1673)	>10 years—8.5% 1–10 years—32.3% <1 year—59.2%
Previous—8.8% (n = 1232)	
Alcohol consumption (n = 13998)	
Total—24.8%	Every day—6% (n = 838) Once/week—9.5% (n = 1189) Once/month—9.3% (n = 1306)

Table 2: Chi-squared "goodness of fit" for the prevalence of cardiac risk factors in participants.

Category		Observed n	Expected n	Chi-squared significance (P)
Obesity (n = 14423)	No	9734	9605.7	.024*
	Yes	4689	4817.3	
Hypertension (n = 14422)	No	9528	9547.4	.733
	Yes	4894	4874.6	
Diabetes (n = 14008)	No	13119	13461.7	.001**
	Yes	889	546.3	

** Significant at the .01 level (2 tailed).
* Significant at the .05 level (2 tailed).

Table 3: Percentage of participants' abnormal lipid profile.

	Percentage among participants	Mean (mg·dL^{-1})	Reference Value (mg·dL^{-1}) [18]
High cholesterol	17.2% (n = 1663/9696)	227.9 ± 34.06	>200
High LDL	36.2% (n = 791/2188)	129.91 ± 27.09	>100
Low HDL	56.7% (n = 1242/2192)	Male—33.63 ± 3.83 Female—39.08 ± 5.71	Male <40 Female <50
High triglycerides	48.3% (n = 4681/9689)	231.52 ± 101.91	>150

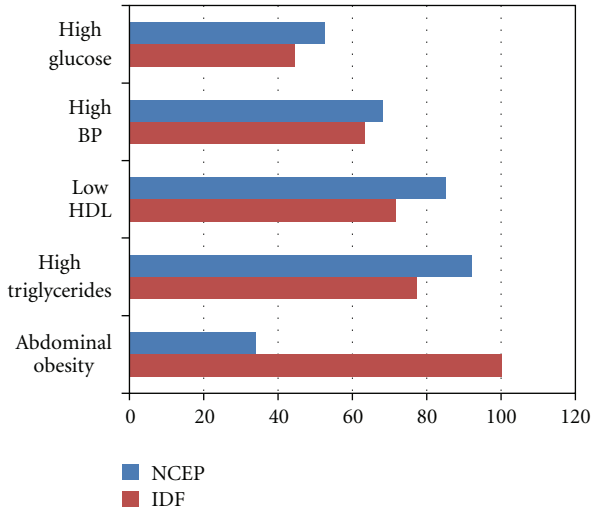


Figure 2: Percentage of individual risk factor among participants with MS.

the presence of abdominal obesity was higher among MS participants using IDF criteria (Figure 2).

Table 4 provides the MS prevalence in relation to demographic and lifestyle factors. The females had a higher prevalence of MS than males. According to the NCEP criteria, the age groups 41–60 and 61–80 had a higher prevalence of MS than the lower age group. According to IDF criteria, the age groups 41–60 and 20–40 had a higher prevalence of MS. The prevalence of MS was higher in participants with less education. The participants who worked at home had a high incidence of MS according to both the criteria used. The sedentary group had a higher incidence of MS than the participants who were physically active.

The univariate correlations between cardiac risk factors are shown in Table 5, and the chi-squared independence of them in the metabolic syndrome prevalence is listed in Table 6.

The prevalence of MS (NCEP scores) had a significant positive relationship with education levels and physical activity. There were significant positive correlations between physical activity and the three individual MS components: high glucose ($r = 0.03$, $P < .01$), high BP ($r = 0.04$, $P < .01$), and low HDL ($r = 0.23$, $P < .01$). There was no correlation between physical activity and the other two MS components: high triglyceride ($r = 0.003$, $P > .05$) and abdominal obesity ($r = -0.003$, $P > .05$). There was no relationship with diet and work. The NCEP scores had a positive correlation between the family history of diabetes ($r = 0.83$, $P < .01$) and hypertension ($r = 0.115$, $P < .01$). Although a number of these correlations show high levels of significance, the common variance is extremely low, suggesting that the sample size is having a major impact on the significance. As a result of this, we do not propose to develop this outcome in any great detail.

Table 7 lists the chi-squared independence, odds ratios, and confidence intervals in the association between age, gender, and specific lifestyle factors in metabolic syndrome prevalence. Gender, age, education level, and physical activity show a positive association with the prevalence of metabolic syndrome.

4. Discussion

It is important to observe the prevalence of diabetes, hypertension, and obesity individually and also the combination of risk factors as metabolic syndrome to predict the risk of cardiovascular disease. Any association between lifestyle factors and these risk factors would provide the opportunity to encourage a change in lifestyle to promote lower levels of subsequent CVD.

4.1. Education, Work, and Physical Activity. The large number of poorly educated people and the large number of school dropouts could be linked to the disease prevalence. The prevalence of hypertension and metabolic syndrome in poorly educated people was large when compared with the educated participants. Though the results are not generalized, the relationship between education levels and the prevalence of hypertension agrees with earlier studies [19, 20]. These found that education levels significantly influence the knowledge of hypertension and the awareness of cardiovascular risk. This suggests that there is a need to improve the awareness of health and use education to prevent or reduce the risk of MS and cardiovascular risks in these groups. The office workers had a lower prevalence of MS (NCEP scores) than the other groups. A considerable number of office workers (64%) undertook regular physical activity of more than 30 min/day. This may be due to health awareness gained from higher education. Most of the poorly educated or less educated people were labourers or home workers. The labourers had a lower MS prevalence than the home workers. The home workers education levels and physical activities were comparatively lower than the other work groups. These findings clearly show that education and physical activity have an influence on the prevalence of MS. Most of the females were home workers (75.5%), and their education was comparatively lower than the males. This may be the reason for the higher prevalence of MS in females. The amount of physical activity involved in home workers is unknown, but the results suggest it is less than that undertaken by other workers.

Asian populations continue to modernize, and levels of physical activity are declining as (i) home and work place jobs become more automated and sedentary and (ii) transportation is more readily available [7]. The prevalence of MS among the participants who had no physical activity was surprisingly no different than others. This may be due to a higher than average number of missing values in these data (2191/14425 complete data to meet the criteria for MS) or to other unknown socioeconomic factors.

4.2. Diet and Age. Controversially, there was a high prevalence of MS among people who regularly ate fruit and vegetables. Lee et al. [21] found that a higher intake of

Table 4: Demographic details and prevalence of metabolic syndrome and other risks.

		Disease prevalence in participant category				
		Obesity/overweight	Diabetes	Hypertension	MS—NCEP criteria	MS—IDF criteria
Gender	Male	59.1% $n = 3146/5327$	8.1% $n = 429/5326$	40.7% $n = 2164/5327$	18.6% $n = 150/805$	17.1% $n = 138/805$
	Female	61.8% $n = 5360/8680$	5.3% $n = 460/8682$	30.0% $n = 2603/8679$	21.9% $n = 304/1386$	25.7% $n = 356/1386$
Age group	20–40 Years	55.5% $n = 4293/7727$	1.9% $n = 140/7519$	19.6% $n = 1514/726$	9.8% $n = 110/1124$	13.1% $n = 147/1124$
	41–60 Years	70.5% $n = 3440/4880$	10.2% $n = 480/4727$	46.1% $n = 2252/4880$	31.4% $n = 256/815$	34.7% $n = 283/815$
	61–80 Years	56.7% $n = 973/1716$	15.4% $n = 257/1664$	62% $n = 1064/1726$	34.8% $n = 86/247$	25.1% $n = 62/247$
	80–100 Years	48% $n = 48/100$	12.2% $n = 12/98$	64% $n = 64/100$	40% $n = 2/5$	40% $n = 2/5$
Level of education	Higher Secondary	59.9% $n = 2775/4634$	5.1% 238/4634	27.2% $n = 1262/4633$	13.3% $n = 117/880$	15.8% 139/880
	Secondary	64.1% $n = 1972/3098$	5.3% $n = 163/3079$	27.8% $n = 857/3078$	19.2% $n = 69/360$	22.2% 80/360
	Primary	63.9% $n = 1337/2092$	8.3% $n = 174/2092$	38.3% $n = 802/2092$	22.7% 90/396	25.5% 101/396
	None	57.6% $n = 2419/4197$	7.5% $n = 314/4197$	44.0% $n = 1847/4197$	32.1% $n = 178/555$	31.4% 174/555
Work category	Labour	56.5% $n = 1015/1797$	5.3% $n = 96/1997$	35.4% $n = 636/1797$	17.9% $n = 40/224$	17% $n = 38/224$
	Office	69.3% $n = 1448/2089$	7.8% $n = 162/2090$	34.7% $n = 724/2089$	16% $n = 58/362$	21.5% $n = 78/362$
	House	69.3% $n = 1448/2089$	6.3% $n = 506/7976$	34% $n = 2712/7975$	23.9% $n = 303/1269$	25.1% $n = 318/1269$
	None	50.2% $n = 1064/2118$	5.8% $n = 122/2118$	32.6% $n = 690/2118$	15.8% $n = 53/336$	17.5% $n = 60/336$
Physical activity	>60 min/day	62% $n = 3215/5188$	5.2% $n = 270/5190$	29.6% $n = 1535/5187$	22.3% $n = 79/355$	24.2% $n = 86/355$
	30–60 min/day	62.8% $n = 2226/3543$	8.2% $n = 291/3542$	37.6% $n = 1333/3543$	23.6% $n = 154/653$	25.0% $n = 163/653$
	<30 min/day	59.1% $n = 1805/3053$	6.9% $n = 212/3053$	36.9% $n = 1128/3053$	25.4% $n = 171/674$	26.3% $n = 177/674$
	None	56.7% $n = 1805/3053$	5.1% $n = 114/2215$	34.8% $n = 770/2215$	9.8% $n = 50/509$	13.4% $n = 68/509$
Fruits and vegetable in diet	Every day	61.0% $n = 2686/4401$	7.4% $n = 325/4403$	32.2% $n = 1416/4400$	23.2% $n = 68/293$	23.5% $n = 69/293$
	3–5 days/week	61.3% $n = 4804/7842$	5.8% $n = 451/7841$	34.0% $n = 2664/7842$	20.3% $n = 326/1604$	23.6% $n = 378/1604$
	Once/week	58.1% $n = 947/1630$	6.0% $n = 97/1630$	38.3% $n = 637/1630$	21.0% $n = 57/272$	16.9% $n = 46/272$
	None	51.5% $n = 69/134$	11.9% $n = 16/134$	41.0% $n = 55/134$	13.6% $n = 3/22$	4.5% $n = 1/22$

macronutrients such as fruits and vegetables is associated with general obesity. However, it is not clear how the vegetables and fruits were eaten, for example, overcooked, processed, and so forth. The exact quantity of the dietary intake was not recorded as it was not the primary area of focus of the study. In these populations, several dietary imbalances have been reported in previous studies. These tend to report a low intake of mono-unsaturated fats

Table 5: Relationship between the prevalence of MS and other cardiovascular risks.

		Hypertension	Diabetes	Metabolic syndrome
Obesity	Spearman's correlation coefficient	.150**	.070**	.153**
Hypertension			.101**	.234**
Diabetes				.384**

** Correlation is significant at the .01 level (2 tailed).

Table 6: Chi-squared independence of cardiac risk factors in the prevalence metabolic syndrome ($n = 2191$).

	Hypertension	Obesity	Diabetes
Metabolic syndrome	31.9% $n = 292/914$	34.8% $n = 241/693$	58.6% $n = 78/133$
Significance (P)	.001**	.001**	.001**

** Correlation is significant at the .01 level (2 tailed).

(MUFAs), n-3 polyunsaturated fats (PUFA), and transfatty acids (mostly related to widespread use of vanaspati, a hydrogenated oil) [9]. The healthy traditional plant-based diets are being replaced by cheaper calorie dense high-fat foods. These changes are resulting in a rapid increase in the prevalence of obesity throughout Asia and the subsequent development of MS [8]. Ness and Powles also found in their review [22] that many studies were reporting the null or negative effects of fruit and vegetable intake on the prevalence of cardiovascular diseases. However, the correlations found in those studies were generally low, as seen in our study. Further, they suggest that a food-based analysis would complement the nutrient-based analysis to clarify these issues [22]. In Nepal, the regular diet in addition to fruits and vegetables, that is, such as rice, which is high in carbohydrates, and the methods of cooking may be dietary causes of metabolic syndrome.

The age groups 40–60 had a large prevalence of MS in this study. Also, it is important to note that this middle-aged group had a high incidence of overweight or general obesity and abdominal obesity. The other age groups had a lower prevalence of MS than the 40–60 years old, yet it was still relatively high. This included the younger population (20–40 yrs) at nearly 10%. Inadequate maternal nutrition in pregnancy, low birth weight, and childhood obesity may be important factors for the development of metabolic syndrome and diabetes [9]. Specifically in children and young individuals, a high intake of n-6 PUFA is correlated with hyperinsulinaemia. In adults, high carbohydrate meal consumption is related to hyperinsulinaemia, postprandial hyperglycaemia, and hypertriacylglycerolaemia [9].

4.3. Obesity and Lipids. Unger described metabolic syndrome as "a failure of the system of intracellular lipid homeostasis which prevents lipotoxicity in organs of overnourished individuals" [23]. In this study, a large number of participants had increased triglycerides levels and low HDL levels. In addition to low levels of HDL, the HDL particles are small, dense, and dysfunctional in South Asians [24]. These are strong predictors of cardiovascular disease. Hypertriglyceridaemia is a direct reflection of an insulin resistance condition, and it is interrelated to the low HDL concentrations in developing endothelial dysfunction [25].

In Nepal, a high number of the participants had abdominal obesity and were overweight/obese, according to their BMI. The BMI is a simple useful measure for overall abnormal weight, yet not a standard measure for obesity. BMI cannot differentiate between whether the condition was due to unusual muscular development or the accumulation or distribution of fat in the body [26, 27]. Despite the low prevalence of general body obesity compared to western countries, metabolic syndrome is growing into a significant public health problem in Asia [28]. This may be mainly due to the large number of people with central obesity, a feature which was also observed in this study. The higher prevalence of MS in females is also more likely to be due to a higher incidence of abdominal obesity. Abdominal obesity is an important factor because metabolic syndrome and increased abdominal fat are related to a reduction of adiponectin, an adopicyte-derived hormone with antiatherogenic and anti-inflammatory properties [29]. The abdominal adipose tissue results in release of free fatty acids directly in the portal veins and altered lipid levels in the blood [30]. Further abdominal adiposity increases insulin secretion, and it would be exaggerated by decreased hepatic clearance leading to hyperinsulinemia [31]. The free fatty acid release also results in endothelial dysfunction that develops hypertension. Thus abdominal obesity is an important indicator of cardiovascular disease due to its link to dyslipidemia, hyperinsulinemia, hypertension, and impaired fibrinolytic capacity [32].

4.4. IDF versus NCEP Definitions. Tan et al. [33] state that if the NCEP's criteria were applied to the Asian population, it might underestimate the prevalence of metabolic syndrome and the risk of cardiovascular disease. So a reduced cut-off point for abdominal obesity for Asians was suggested. IDF's specific reference values for abdominal obesity make a substantial difference to the prevalence of MS between the two criteria. The IDF's cut-off points for South Asians' waist circumference are lower than the NCEP's general cut-off points ($\geq$90 cm versus $\geq$102 cm in men and $\geq$80 cm versus $\geq$88 cm in women). Another study on Chinese population also found a large increase in the prevalence of metabolic syndrome using IDF criteria compared with NCEP criteria [34]. However, in our study both definitions demonstrated a higher prevalence of metabolic syndrome (20.7–22.5%)

Table 7: Chi-squared significance for the independence, odds ratios and 95% confidence interval of age, gender and life style factors in the prevalence of metabolic syndrome.

	Chi-squared independence Sig (*P*)	Odds ratio (ORs)	95% confidence interval	ORs Sig (*P*)
Gender	.066	1.403	1.115–1.766	.004*
Age	.001**	1.052	1.044–1.060	.001**
Education level				
Higher secondary	.001**	1.348	0.951–1.910	.093
Secondary		0.990	0.691–1.419	.957
Primary		1.368	1.002–1.867	.049*
None		#	#	#
Work				
Labour	.001**	1.101	0.676–1.796	.699
Office		0.945	0.594–1.503	.810
House		0.739	0.517–1.057	.098
None		#	#	#
Fruit/Veg in diet				
Everyday	.585	0.725	0.199–2.638	.625
3–5 days/week		0.843	0.238–2.993	.792
Once a week		0.960	0.262–3.520	.951
None		#	#	#
Smoking				
Current	.005**	0.968	0.651–1.439	.871
Former		0.870	0.584–1.295	.493
Never		#	#	#
Physical activity				
>60 min/day	.001**	0.369	0.246–0.553	.001*
30–60 min/day		0.351	0.245–0.502	.001*
<30 min/day		0.337	0.236–0.479	.001*
None		#	#	#

** Correlation is significant at the .01 level (2 tailed).
* Correlation is significant at the .05 level (2 tailed).
# The parameter is set to 0 because it is redundant.

in Nepal when compared with the studies done in other Southeast Asian countries such as Thailand (12–18% using NCEP definition) and India (18.3% using IDF definition) [35]. These findings suggest the need for specific attention to control the disease prevalence in Nepal.

4.5. Limitations. Our study has several limitations that should be considered. Although data were prospectively collected, they may not be generalizable outside of Eastern Nepal. The results did not show substantiate relationship between smoking histories, diet, family history of cardiovascular, and metabolic syndrome. Matched groups may be more appropriate to explore these relationships.

5. Conclusion

There was high prevalence of hypertension and obesity in Nepal. High triglycerides and low HDL levels substantially contribute the prevalence of MS in Nepal. Abdominal obesity, with the revised reference values, is an important risk due to its physiological relationship to the other MS risk factors. There was also a high level of blood glucose. The MS prevalence may be due to lack of awareness and unhealthy lifestyles, so health education and more preventive measures should decrease the prevalence of MS and cardiac risks in Nepal.

References

[1] World Health Organization, *Global Health Risks: Mortality and Burden of Disease Attributable to Selected Major Risk*, World Health Organization, Geneva, Switzerland, 2009.

[2] J. E. Shaw, R. A. Sicree, and P. Z. Zimmet, "Global estimates of the prevalence of diabetes for 2010 and 2030," *Diabetes Research and Clinical Practice*, vol. 87, no. 1, pp. 4–14, 2010.

[3] Third Report of the National Cholesterol Education Program (NCEP), "Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III) final report," *Circulation*, vol. 106, no. 25, pp. 3143–3421, 2002.

[4] S. M. Grundy, B. Hansen, S. C. Smith, J. I. Cleeman, and R. A. Kahn, "Clinical management of metabolic syndrome: report of the American Heart Association/National Heart, Lung, and Blood Institute/American Diabetes Association conference

on scientific issues related to management," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 24, no. 2, pp. e19–e24, 2004.

[5] P. Nestel, R. Lyu, P. L. Lip et al., "Metabolic syndrome: recent prevalence in East and Southeast Asian populations," *Asia Pacific Journal of Clinical Nutrition*, vol. 16, no. 2, pp. 362–367, 2007.

[6] L. E. Eberly, R. Prineas, J. D. Cohen et al., "Metabolic syndrome: risk factor distribution and 18-year mortality in the multiple risk factor intervention trial," *Diabetes Care*, vol. 29, no. 1, pp. 123–130, 2006.

[7] P. Poirier and J. P. Després, "Waist circumference, visceral obesity, and cardiovascular risk," *Journal of Cardiopulmonary Rehabilitation*, vol. 23, no. 3, pp. 161–169, 2003.

[8] B. M. Y. Cheung and G. N. Thomas, "The metabolic syndrome and vascular disease in Asia," *Cardiovascular and Hematological Disorders*, vol. 7, no. 2, pp. 79–85, 2007.

[9] A. Misra, L. Khurana, S. Isharwal, and S. Bhardwaj, "South Asian diets and insulin resistance," *British Journal of Nutrition*, vol. 101, no. 4, pp. 465–473, 2009.

[10] E. M. Scott, A. M. Carter, and P. J. Grant, "Diabetes and cardiovascular disease: related disorders created by disturbances in the endogenous clock," *Journal of the Indian Medical Association*, vol. 106, no. 11, pp. 736–740, 2008.

[11] A. Ringborg, C. Cropet, B. Jönsson, J. J. Gagliardino, A. Ramachandran, and P. Lindgren, "Resource use associated with type 2 diabetes in Asia, Latin America, the Middle East and Africa: results from the International Diabetes Management Practices Study (IDMPS)," *International Journal of Clinical Practice*, vol. 63, no. 7, pp. 997–1007, 2009.

[12] S. K. Sharma, H. Zou, A. Togtokh et al., "Burden of CKD, proteinuria, and cardiovascular risk among Chinese, Mongolian, and Nepalese participants in the international society of nephrology screening programs," *American Journal of Kidney Diseases*, vol. 56, no. 5, pp. 915–927, 2010.

[13] A. V. Chobanian, G. L. Bakris, H. R. Black et al., "Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure," *Hypertension*, vol. 42, no. 6, pp. 1206–1252, 2003.

[14] F. Razak, S. S. Anand, H. Shannon et al., "Defining obesity cut points in a multiethnic population," *Circulation*, vol. 115, no. 16, pp. 2111–2118, 2007.

[15] World Hypertension League News Letter, *The Nepal Hypertension Society*, vol. 119, pp.1–3, 2008.

[16] A. Vaidya, S. Shakya, and A. Krettek, "Obesity prevalence in nepal: public health challenges in a low-income nation during an alarming worldwide trend," *International Journal of Environmental Research and Public Health*, vol. 7, no. 6, pp. 2726–2744, 2010.

[17] *IDF Diabetes Atlas*, International Diabetic Federation, 4th edition, 2009, http://www.diabetesatlas.org/.

[18] "American Heart Association recommendations for normal cholesterol levels," http://www.heart.org/HEARTORG/Conditions/What-Your-Cholesterol-Levels-Mean_UCM_305562_Article.jsp.

[19] R. De Gaudemaris, T. Lang, G. Chatellier et al., "Socioeconomic inequalities in hypertension prevalence and care: the IHPAF study," *Hypertension*, vol. 39, no. 6, pp. 1119–1125, 2002.

[20] D. Samal, S. Greisenegger, E. Auff, W. Lang, and W. Lalouschek, "The relation between knowledge about hypertension and education in hospitalized patients with stroke in Vienna," *Stroke*, vol. 38, no. 4, pp. 1304–1308, 2007.

[21] S. A. Lee, W. Wen, W. H. Xu et al., "Prevalence of obesity and correlations with lifestyle and dietary factors in Chinese men," *Obesity*, vol. 16, no. 6, pp. 1440–1447, 2008.

[22] A. R. Ness and J. W. Powles, "Fruit and vegetables, and cardiovascular disease: a review," *International Journal of Epidemiology*, vol. 26, no. 1, pp. 1–13, 1997.

[23] R. H. Unger, "Lipid overload and overflow: metabolic trauma and the metabolic syndrome," *Trends in Endocrinology and Metabolism*, vol. 14, no. 9, pp. 398–403, 2003.

[24] E. A. Enas, V. Mohan, M. Deepa, S. Farooq, S. Pazhoor, and H. Chennikkara, "The metabolic syndrome and dyslipidemia among Asian Indians: a population with high rates of diabetes and premature coronary artery disease," *Journal of the Cardiometabolic Syndrome*, vol. 2, no. 4, pp. 267–275, 2007.

[25] R. H. Eckel, S. M. Grundy, and P. Z. Zimmet, "The metabolic syndrome," *The Lancet*, vol. 365, no. 9468, pp. 1415–1428, 2005.

[26] V. Marks, "The metabolic syndrome," *Nursing Standard*, vol. 17, no. 49, pp. 37–44, 2003.

[27] H. M. Lakka, T. A. Lakka, J. Tuomilehto, and J. T. Salonen, "Abdominal obesity is associated with increased risk of acute coronary events in men," *European Heart Journal*, vol. 23, no. 9, pp. 706–713, 2002.

[28] W. H. Pan, W. T. Yeh, and L. C. Weng, "Epidemiology of metabolic syndrome in Asia," *Asia Pacific Journal of Clinical Nutrition*, vol. 17, no. 1, supplement, pp. 37–42, 2008.

[29] U. Salmenniemi, E. Ruotsalainen, J. Pihlajamäki et al., "Multiple abnormalities in glucose and energy metabolism and coordinated changes in levels of adiponectin, cytokines, and adhesion molecules in subjects with metabolic syndrome," *Circulation*, vol. 110, no. 25, pp. 3842–3848, 2004.

[30] B. Larsson, K. Svardsudd, L. Welin et al., "Abdominal adipose tissue distribution, obesity, and risk of cardiovascular disease and death: 13 year follow up of participants in the study of men born in 1913," *British Medical Journal*, vol. 288, no. 6428, pp. 1401–1404, 1984.

[31] P. Bjorntorp, "" Portal" adipose tissue as a generator of risk factors for cardiovascular disease and diabetes," *Arteriosclerosis*, vol. 10, no. 4, pp. 493–496, 1990.

[32] A. R. Folsom, L. H. Kushi, K. E. Anderson et al., "Associations of general and abdominal obesity with multiple health outcomes in older women: The Iowa Women's Health Study," *Archives of Internal Medicine*, vol. 160, no. 14, pp. 2117–2128, 2000.

[33] C. E. Tan, S. Ma, D. Wai, S. K. Chew, and E. S. Tai, "Can we apply the National Cholesterol Education Program Adult Treatment Panel definition of the metabolic syndrome to Asians?" *Diabetes Care*, vol. 27, no. 5, pp. 1182–1186, 2004.

[34] Y. He, B. Jiang, J. Wang et al., "Prevalence of the metabolic syndrome and its relation to cardiovascular disease in an elderly Chinese population," *Journal of the American College of Cardiology*, vol. 47, no. 8, pp. 1588–1594, 2006.

[35] S. M. Grundy, "Metabolic syndrome pandemic," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 28, no. 4, pp. 629–636, 2008.

SAGE-Hindawi Access to Research
International Journal of Hypertension
Volume 2011, Article ID 952537, 8 pages
doi:10.4061/2011/952537

Research Article

Prevalence of Elevated Blood Pressure and Association with Obesity in Egyptian School Adolescents

Mostafa A. Abolfotouh,[1] Sunny A. Sallam,[2] Mohammed S. Mohammed,[2] Amany A. Loutfy,[2] and Ali A. Hasab[2]

[1] *King Abdullah International Medical Research Center (KAIMRC), King Saud bin Abdulaziz University for Health Sciences (KSAU-HS), P.O. Box 22490, Riyadh 11426, Saudi Arabia*
[2] *Department of Epidemiology, High Institute of Public Health, Alexandria University, Alexandria 21526, Egypt*

Correspondence should be addressed to Mostafa A. Abolfotouh, mabolfotouh@gmail.com

Received 19 December 2010; Accepted 17 January 2011

Academic Editor: Kazuko Masuo

Aim. To investigate the relationship between high blood pressure (HBP) and obesity in Egyptian adolescents. *Methods*. A cross-sectional study of 1500 adolescents (11–19 years) in Alexandria, Egypt, was conducted. Resting BP was measured and measurements were categorized using the 2004 fourth report on blood pressure screening recommendations. Additional measures included height, weight, and waist and hip circumferences. Obesity was determined based on BMI, waist circumference (WC) and waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR) indicators. Crude and adjusted odds ratios were used as measures of association between BP and obesity. *Results*. Prevalence rates of prehypertension and hypertension were 5.7% and 4.0%, respectively. Obesity was seen in 34.6%, 16.1%, 4.5%, and 16.7% according to BMI, WHR, WC, and WHtR, respectively. Adjusting for confounders, HBP was significantly associated with overall obesity based on BMI (OR = 2.18, 95%, CI = 1.38–3.44) and central obesity based on WC (OR = 3.14, 95%, CI = 1.67–5.94). *Conclusion*. Both overall obesity and central obesity were significant predictors of HBP in Egyptian adolescents.

1. Introduction

The importance of hypertension in the pediatric population has not been as well appreciated as in adults. Children with elevated blood pressure (BP) can develop target organ damage [1], and they are also at increased risk of cardiovascular disease in adulthood [2]. Consequently, detection and management of elevated BP at an early age may be an important means for limiting the disease burden due to hypertension [3].

The prevalence of HBP among children in several recently conducted studies in Western countries ranged from 7 to 19% [4–6]. However, few studies have been conducted in children in developing countries. A study of blood pressure levels among primary school students in Kuwait found that the overall prevalence of hypertension was 5.1% [7], 3.6% among school children in Jordan [8], and 4.30% among preparatory school children in Alexandria [9].

The prevalence of childhood obesity has increased markedly over the last 2 decades [10–14]. This increase is associated with an increase in hypertension rates which could lead to atherosclerotic disease in adulthood [15, 16]. Primary hypertension in children has become increasingly common in association with other cardiovascular risk factors that include being overweight, insulin resistance, and dyslipidemia [16].

Many studies have shown that blood pressure is associated with being overweight in children and adolescents of Western countries [4–6, 17]. However, few data are available in non-Western countries and in non-Caucasian populations [18–20]. Previous studies [21–23] reported ethnic variation in the relationship of overweight/obesity and change in blood pressure, and this ethnic variations could be either genetic or environmental or both. Thus, the aims of the present study were (i) to estimate the prevalence of HBP, and (ii) to investigate the relationship between BP and different body

composition measures in Egyptian school adolescents in Alexandria city, Egypt. To our knowledge this study is the first to investigate this relationship in Egyptian adolescents.

2. Materials and Methods

2.1. Study Design. A cross-sectional study was conducted with a total of 1500 school adolescents from different preparatory and secondary schools in Alexandria city, Egypt.

2.2. Study Population and Sampling Technique. The minimum required sample was calculated by using Epi-Info software program, on assumption that the prevalence of hypertension among school children is 4.30% [9]. The calculated sample at 95% confidence level was found to be 1475 students. Thus, a total sample of 1500 school adolescents enrolled in preparatory and secondary schools was considered, to compensate for drop out.

Three educational zones were selected randomly of the seven zones in Alexandria. Of each zone, four governmental schools were allocated randomly to represent preparatory and secondary education for both sexes. Thus, a total number of 12 schools were chosen. Of each selected school, 3 classrooms were selected at random to represent the 3 educational grades.

2.3. Techniques

2.3.1. Assessment of Body Composition. Anthropometric measures were taken in school clinics by a trained team. All measurements were performed twice. Height was measured without shoes to the nearest 0.1 cm using a portable stadiometer. Weight was measured in light clothing to the nearest 0.1 kg using a digital Heine portable scale. WC was measured at the narrowest area above the umbilicus or mid way between the coastal margin and the iliac crest, in a horizontal plane at the end of normal expiration, with the tape measure snugly fitted [24, 25]. Hip circumference was measured at the maximal gluteal protrusion or at the most prominent area of the buttocks at the level of symphysis pubis in a horizontal plane. The tape measure was held snugly against the body but without compression [24, 25].

BMI was calculated as the ratio of weight (kg) to height (m) squared (kg/m^2). The 5th, 85th, and 95th percentiles were calculated according to the international statistics standards [26]. Adolescents were classified based on these percentiles as follows: <5th underweight, 5th–85th normal weight, 85th–95th overweight, and 95th + considered obese [27].

The 90th percentile values for *WC* for gender and age generated in the National Health and Nutrition Examination Survey (NHANES III) were used as cut-off values to identify adolescents with abdominal obesity [24, 28].

WHR was calculated by dividing waist by hip circumference, and abdominal obesity was diagnosed when the WHR was >0.80 in girls and 0.95 in boys [29]. *WHtR* was calculated as the ratio of waist (cm) and height (cm). A *WHtR* cut-off of 0.5 is used to define abdominal obesity for both 6–19-year-old boys and girls [24].

2.3.2. Blood Pressure Measurement. BP was measured using the standardized mercury sphygmomanometer with manually inflated cuff of suitable size and a stethoscope. It was measured on the right arm after the child was sitting quietly for 5 minutes to relieve anxiety, and seated with his or her back supported, feet on the floor, right arm supported, and cubital fossa at heart level left arm. Two readings were obtained at a 1-min. interval, and the average was recorded. The blood pressure was measured two times with zero device. SBP was determined by the onset of the "tapping" korotkoff sounds (K1) and the fifth korotkoff sound (K5), or the disappearance of korotkoff sounds, as the definition of DBP.

The mean values of blood pressure were measured and corrected for age and sex in the form of centile bands and compared with US National Childhood Blood Pressure standards [30]. The blood pressure percentiles were determined accordingly.

When the BP was greater than the 90th percentile for age, gender, and height, measuring BP was repeated twice at the same visit, and average SBP and DBP were used. If BP was greater than the 95th percentile, BP was staged to stage I (95th percentile to the 99th percentile plus 5 mmHg) and stage 2 (>99th percentile plus 5 mmHg) [30]. Adolescents aged 18 and 19 years in the study were considered as adults and were classified as follows: hypertension is defined as average SBP > 120 and DBP > 80 mmHg. Prehypertension is defined as average SBP 120–139 or DBP 80–89 mmHg. Stage I hypertension is defined as average SBP 140–159 or DBP 90–99 mmHg. Stage II hypertension is defined as average SBP greater than or equal 160 or DBP greater than or equal 100 mmHg [31].

2.3.3. Interview Questionnaire. In order to adjust for the many of the possible confounders for the association between obesity and high blood pressure among adolescents, all students of the study sample were subjected to a self-administered questionnaire. The designed questionnaire was composed of the following.

(1) Personal history of chronic diseases, such as, hypertension, diabetes mellitus, renal diseases, and endocrine diseases, and taking antihypertensive drugs, corticosteroid, insulin, or penicillin.

(2) Family history of chronic disease, such as hypertension, obesity, and diabetes mellitus. The degree of relative divided to near and far. The near relative was considered father, mother, brother, and sister. The far relative was considered as others such as aunt, uncle, grandfather, and grandmother.

(3) Lifestyle: this includes the following: (a) Dietary habits: intake of salty and fatty diet (very high, high, moderate, and little consumption). (b) Physical activity: physically active or nonactive. (c) Smoking: regular smoker/nonsmoker. Only daily and weekly smokers were considered as regular smokers. Daily

smokers were those who, at the time of the survey, smoked cigarettes every day. Weekly smokers were those who smoked less than once a day but at least once a week. Physically active adolescents were those who reported practicing exercise more than one hour at least 3 times per week [32].

A pilot study was carried out on 25 students in 2 schools (one preparatory and the other secondary) in Alexandria at the middle districts.

The pilot study aimed to test the validity and clarity of the structured questionnaire for the intended school adolescents, pretest the study tools in order to reveal any modifications needed, estimate the average time needed to obtain the required information, identify any possible potential difficulties in data collection, and examine the overall survey technique to be used.

2.4. Data Analysis. Statistical analysis was done with aid of the computer program SPSS (statistical package for the social sciences). Descriptive measures as arithmetic mean and standard deviation were used to describe quantitative data. Student's t-test was used to compare between sample means for quantitative data. Person's chi-square "χ^2", Mantel- Haenszel chi-square, and chi-square for linear trend were applied to gauge the difference between categorical data. Logistic regression was used to assess the relationship between the different body composition measures and elevated BP, adjusting for age, sex, smoking behaviour, food and salt consumption, history of chronic disease, family history of hypertension, diabetes mellitus, and obesity. Statistical significance was set at $P < .05$.

2.5. Ethical Consideration. All measurements were done in private rooms in the school clinics. All collected data by the self-reported questionnaires were kept confidential. All participants had the right not to participate in the study or to withdraw from the measurements prior to its completion. The study protocol received ethical approval from the Research Committee of the High Institute of Public Health, Alexandria university, Egypt.

3. Results and Discussion

Table 1 shows the distribution of study sample according to the levels of blood pressure and body composition measures. The prevalence rates of prehypertension and hypertension were 5.7% and 4.0%, respectively, with no sex difference ($\chi^2 = 5.86$, df = 4, $P = .12$). Overall obesity prevalence—based on BMI measure—was 10.3%. Overall obesity was significantly more prevalent in male than in female adolescents (11.8% versus 8.7%, $P = .002$). Central obesity was prevalent in 16.1%, 4.5%, and 16.7% based on WHR, WC, and WHtR measures, respectively. Males showed significantly higher prevalence of central obesity based on WC (5.9% versus 3.2%, $\chi^2 = 6.16$, df = 1, $P = .013$) while female adolescents showed significantly higher prevalence of central obesity based on WHR (31.9% versus 0.3%, $\chi^2 = 277.7$, df = 1, $P < .001$).

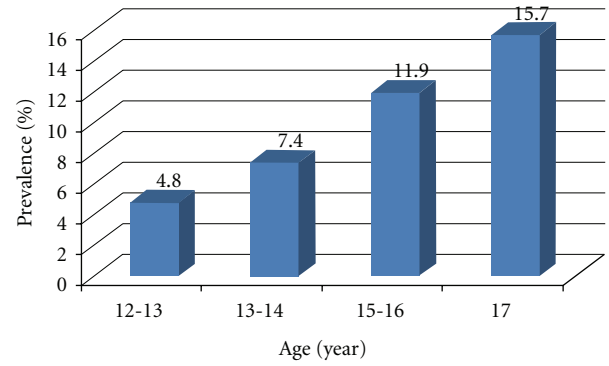


Figure 1: Prevalence of elevated blood pressure in Egyptian adolescents according to age.

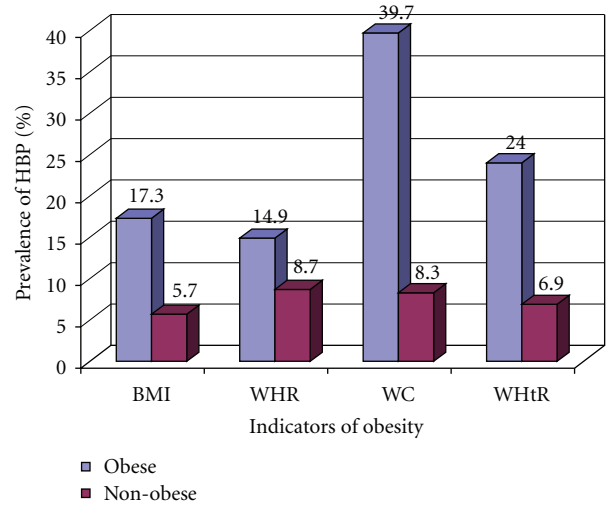


Figure 2: Prevalence of elevated blood pressure in Egyptian adolescents according to different obesity indicators.

Figure 1 shows that there was a significant gradual increase in the prevalence of elevated blood pressure with the advancement of age of the adolescents. This prevalence increased from 4.8% in adolescents aged 13 to 14 years to 15.7% in adolescents 17 years of age. ($\chi^2_L = 18.603$, $P < .001$).

Table 2 and Figure 2 show the association between body composition measures and high blood pressure among school adolescents. Compared with those of normal weight, obese adolescents had significantly greater odds of having high blood, whether defined by BMI (OR = 3.47, 95% CI = 2.44–4.93), WC (OR = 4.27, 95% CI = 2.97–6.15), WHR (OR = 1.83, 95% CI = 1.22–2.75), or WHtR (OR = 7.27, 95% CI = 4.32–12.23). When all body composition measures were adjusted for all the potential confounders in a logistic analysis (age, history of chronic diseases, family history of hypertension, and family history of diabetes mellitus), both BMI and the WC measures were the only significant predictors of high blood pressure in school adolescents. Blood pressure was significantly high among adolescents

Table 1: Distribution of the study sample of school adolescents according to patterns of blood pressure and body composition by sex.

	Male ($n = 750$)		Female ($n = 750$)		Total (1500)	
	No.	%	No.	%	No.	%
BP						
Normal BP	667	89.0	687	91.6	1354	90.3
Prehypertension	49	6.5	36	4.8	85	5.7
Stage I HBP	21	2.8	22	2.9	43	2.8
Stage II HBP	13	1.7	5	0.7	18	1.2
Prevalence[@]	83	10.0	63	8.4	146	9.7
Sex difference		$\chi^2 = 5.86$, df = 4, $P = .12$				
BMI percentiles						
<5th underweight	312	41.6	291	38.8	603	40.2
5th–85th (normal weight)	349	46.5	394	52.5	743	49.5
85th–95th (overweight)	46	6.1	48	6.4	94	6.3
≥95th (obese)	43	5.7	17	2.3	60	4.0
Prevalence[#]	89	11.8	65	8.7	155	10.3
Sex difference		$\chi^2 = 14.77$, df = 3, $P = .002$				
WHR						
Nonobese	748	99.7	511	68.1	1259	83.9
Obese (Prev.)	2	0.3	239	31.9	241	16.1
		$\chi^2 = 277.7$, df = 1, $P = < .001$				
WC percentiles						
Non obese <90th	706	94.1	726	96.8	1432	95.5
Obese ≥90th (Prev.)	44	5.9	24	3.2	68	4.5
Sex difference		$\chi^2 = 6.16$, df = 1, $P = .013$				
WHtR						
<0.5	611	81.5	639	85.2	1250	83.3
≥0.5 (Prev.)	139	18.5	111	14.8	250	16.7
Sex difference		$\chi^2 = 3.76$, df = 1, $P = .052$				

[@] Prevalence of elevated BP includes prehypertensive adolescents.
[#] Prevalence of overweight and obesity.

who are obese by BMI (OR = 2.18, 95% CI = 1.38–3.44) and those who are obese by WC (OR = 3.14, 95% CI = 1.67–5.94).

Table 3 shows that high blood pressure was significantly more prevalent among school adolescents with positive history of chronic diseases (OR = 2.46, 95%CI = 1.46–4.15), those with positive family history of high blood pressure (OR = 1.61, 95%CI = 1.14–2.27), and those with positive family history of diabetes mellitus (OR = 1.53, 95%CI = 1.08–2.15). However, there was no significant association between high blood pressure and family history of obesity. With regard to the lifestyles and health-related behavior of adolescents, high blood pressure showed no significant association with any of these behaviours.

In the present study, prevalence rates of prehypertension and hypertension were 5.7% and 4.0%, respectively. These figures were lower than those among Iranian adolescent girls (13.9%, and 19.4%) [33], and figures among US adolescents (15.7%, and 3.2%) [34]. They were also similar to prevalences in urban South Africa [35]. There was a gradual and progressive significant increase in the prevalence of elevated blood pressure from 4.8% in young adolescents aged 13 to 14 years up to 15.7% in those aged 17 years. However, comparison of the prevalence of elevated BP with other studies is limited due to differences in the procedures used for BP measurement across studies.

Many studies have documented an association between BP and body weight. Few population-based data on the relation between BP and BMI are available in children and adolescents in developing countries [36]. In a school-based survey of a representative sample of youth aged 9, 13, and 16 years in Canada, body mass index was consistently associated with SBP and DBP in all age-gender groups [37]. The present study revealed that adolescents with high blood pressure were 3.5 times more likely to be overweight or obese as compared to adolescents with normal blood pressure. BMI was a significant predictor of high blood pressure among adolescents of the present study, even after adjustment for all potential predictors. This finding was in agreement with

Table 2: Prevalence of elevated blood pressure among study sample of school adolescents in relation to different types of obesity.

Indicators of obesity	Prevalence		χ^{2MH} (P)	cOR (95% CI)	aOR (95% CI)[#]
	No.	%			
BMI percentiles					
Overweight/obese (519, 34.6%)	90	17.3	50.93 (<.001)	3.47 (2.44–4.93)	2.18 (1.38–3.44)
Nonoverweight/nonobese (981, 65.4%)	56	5.7		1[@]	
WHR					
Obese (241, 16.1%)	36	14.9	8.12 (.004)	1.83 (1.22–2.75)	1.27 (0.82–1.96)
Non obese (1295, 83.9%)	110	8.7		1[@]	
WC percentiles					
Obese (68, 4.5%)	27	39.7	67.52 (<.001)	4.27 (2.97–6.15)	3.14 (1.67–5.94)
Non obese (1432, 95.5%)	119	8.3		1[@]	
WHtR					
Obese (250, 16.7%)	60	24.0	69.23 (<.001)	7.27 (4.32–12.23)	1.61 (0.94–2.74)
Non obese (1250, 83.3%)	86	6.9		1[@]	

[@] Reference category.
[#]Adjustment was made for age, sex, smoking behaviour, food and salt consumption, history of chronic disease, family history of hypertension, diabetes mellitus, and obesity.

Table 3: Prevalence of elevated blood pressure among study sample of school adolescents in relation to medical and family history of chronic diseases/conditions and health behaviours.

	Prevalence		χ^{2MH} (P)	OR (95% CI)
	No.	%		
(a) Medical and family history				
History of chronic disease				
Positive (102, 6.8%)	20	19.6	10.96 (<.001)	2.46 (1.46–4.15)
Negative (1398, 93.2%)	126	9.0		1[@]
FH hypertension				
Positive (641, 42.7%)	78	12.2	7.07 (.008)	1.61 (1.14–2.27)
Negative (859, 57.3%)	68	7.9		1[@]
FH diabetes mellitus				
Positive (721, 48.1%)	84	11.7	5.39 (.02)	1.53 (1.08–2.15)
Negative (779, 51.9%)	62	8.4		1[@]
FH obesity				
Positive (571, 38.1%)	63	11.0	1.54 (.21)	1.26 (0.89–1.79)
Negative (929, 61.9%)	83	8.9		1[@]
(b) Health behaviors				
Sport participation				
Never (415, 27.7%)	35	8.4	0.91 (.34)	0.81 (0.54–1.21)
Yes (1085, 72.3%)	111	10.2		1[@]
Smoking behavior				
Smoker (57, 3.8%)	9	15.8	1.81 (.12)	1.79 (0.86–3.72)
Nonsmoker (443, 96.2%)	137	9.5		1[@]
Salt consumption				
Very high/high (268, 17.9%)	28	10.4	0.10 (.75)	1.10 (0.71–1.70)
Moderate + little (1232, 82.1%)	118	9.6		1[@]
Fat consumption				
Very high + high (149, 9.9%)	11	7.4	0.76 (.38)	0.72 (0.38–1.36)
Moderate + little (1351, 90.1%)	135	10.0		1[@]

a previous followup study of adolescents for 31.5 years, where a BMI above the 95th percentile in adolescence predicted adult mortality rates, and a 10-kg higher body weight was associated with a 3.0-mmHg higher systolic and a 2.3-mmHg higher diastolic blood pressure. These increases translate into an estimated 12% increased risk for CHD and 24% increased risk for stroke [38].

WC was more powerful than BMI for predicting the incidence of hypertension in a previous study [39]. In obese adolescents, the accumulation of excess fat is known to occur predominantly in the upper body rather than in the peripheral region [40]. The increased waist circumference is unlikely to be due to visceral adipose tissue alone; it probably reflects both visceral and subcutaneous fat, and, hence, total fatness. In contrast, the body mass index measures the sum of fat mass and fat-free mass, and it is impossible to know the relative contributions of each. The present study showed that adolescents with high blood pressure were more than 7 times more likely to be obese with central obesity (WC percentiles >90th for gender and age) as compared to those with normal blood pressure. In a study of British youth aged 11–16 years, waist circumference, representing central fatness, has increased much faster than body mass index over 10–20 years [40].

It has been reported in a previous study that combination of BMI and WC is more strongly related to CVD risk factors than BMI or WC alone [41]. In the present study, after adjustment for all other body composition measures, both WC and BMI were the only significant predictors of high blood pressure in adolescents. Few studies have shown that waist circumference may be a better predictor of cardiovascular disease than BMI [42, 43] and waist-to-hip ratio [43].

Adjustments of WC by stature (WHtR) or hip circumference (WHR) were found to improve its association with the incidence of hypertension [39]. WHtR was recommended, being more highly correlated with visceral fat mass and clustering of cardiovascular risk factors in children and adults [24]. It may be a more accurate tracking indicator of fat distribution and accumulation by age, because it accounts for the growth in both WC and height over age, particularly in children and adolescents [24]. In the present study, adolescents with high blood pressure were 2 times and 7 times to be obese according to the WHR and WHtR, respectively. However, after adjustment with all other body composition measures, this association was not significant. This finding is in accordance with what was reported in a previous study that the use of ratios such as WHR to assess obesity in children and adolescents may not be appropriate because they are highly age dependent and may obscure stronger relations that may be present with separate circumference measurements. Furthermore, differences in skeletal structure may confound the results [44].

This study has some limitations which should be considered when interpreting these findings. First, BP was measured on one single visit whereas hypertension should be based on readings taken on several visits [45]. However, most other epidemiological studies of BP in children also relied on single-visit readings [46–49]. Second, we relied upon the US reference BP values. However, these US reference data have the advantage of being adjusted for sex, age, and height, which are the main known physiological determinants of BP in children [45]. This might affect the estimates of elevated BP, yet it is unlikely to have biased our findings on the relationship between BP and body composition measures. Third, the study relied upon a written questionnaire for information on lifestyles and health behaviours, such as exercising, food and salt consumption, and smoking behaviour. If the accuracy of self-reported lifestyles differed by obesity, then our effect estimate might have been biased. Fourth, we cannot be certain of the causal direction of the associations observed between obesity and high blood pressure, due to the study's cross-sectional design. A longitudinal study with repeated measures of body composition and blood pressure would be desirable in the future.

In conclusion, this study provides important evidence of the association between both overall obesity, based on BMI percentiles and central obesity, based on WC percentiles and high blood pressure among Egyptian adolescents.

From this work, the following recommendations could be suggested.

(1) Hypertension screening should be included in a school health program. Followup and regular blood pressure measurement should be an important step in school health programs. Waist circumference should be measured in the school clinic. It could be used in a health promotion program to identify individuals who should seek, and be offered, weight management and those at risk of developing hypertension.

(2) Prevention of cardiovascular risk factors as early as childhood may be an important strategy to prevent noncommunicable diseases in a life course perspective, particularly in settings with scarce resources and limited health care capacity. Programs and policies to limit sedentary behaviours and promote physical activity and healthy nutrition among children are recommended.

References

[1] M. B. Lande, N. L. Carson, J. Roy, and C. C. Meagher, "Effects of childhood primary hypertension on carotid intima media thickness: a matched controlled study," *Hypertension*, vol. 48, no. 1, pp. 40–44, 2006.

[2] A. Must, P. F. Jacques, G. E. Dallal, C. J. Bajema, and W. H. Dietz, "Long-term morbidity and mortality of overweight adolescents—a follow-up of the Harvard Growth Study of 1922 to 1935," *The New England Journal of Medicine*, vol. 327, no. 19, pp. 1350–1355, 1992.

[3] D. R. Labarthe, "Prevention of cardiovascular risk factors in the first place," *Preventive Medicine*, vol. 29, no. 6, pp. S72–S78, 1999.

[4] J. M. Sorof, D. Lai, J. Turner, T. Poffenbarger, and R. J. Portman, "Overweight, ethnicity, and the prevalence of hypertension in school-aged children," *Pediatrics*, vol. 113, no. 3, pp. 475–482, 2004.

[5] G. Paradis, M. Lambert, J. O'Loughlin et al., "Blood pressure and adiposity in children and adolescents," *Circulation*, vol. 110, no. 13, pp. 1832–1838, 2004.

[6] S. Genovesi, M. Giussani, F. Pieruzzi et al., "Results of blood pressure screening in a population of school-aged children in the province of Milan: role of overweight," *Journal of Hypertension*, vol. 23, no. 3, pp. 493–497, 2005.

[7] E. A. Saleh, A. A. Mahfouz, K. Y. Tayel, M. K. Naguib, and N. M. Bin-AL-Shaikh, "Study of blood pressure levels among Kuwaiti primary school children," *Eastern Mediterranean Health Journal*, vol. 6, pp. 333–337, 2000.

[8] H. Y. Jaddou, A. M. Bateiha, A. M. Khawaldeh, Y. M. Goussous, and K. M. Ajlouni, "Blood pressure profile in schoolchildren and adolescents in Jordan," *Annals of Saudi Medicine*, vol. 21, no. 1-2, pp. 123–126, 2001.

[9] O. Darwish, A. El Ghamry, M. Hussein, and S. Omara, "Prevalence and some etiological factors of hypertension in school children," *Bulletin High Institute of Public Health*, vol. 15, no. 3, pp. 97–110, 1985.

[10] P. Bundred, D. Kitchiner, and I. Buchan, "Prevalence of overweight and obese children between 1989 and 1998: population based series of cross sectional studies," *The British Medical Journal*, vol. 322, no. 7282, pp. 326–328, 2001.

[11] J. O'loughlin, G. Paradis, G. Meshefedjian, and K. Gray-Donald, "A five-year trend of increasing obesity among elementary schoolchildren in multiethnic, low-income, inner-city neighborhoods in Montreal, Canada," *International Journal of Obesity*, vol. 24, no. 9, pp. 1176–1182, 2000.

[12] Q. He, Z. Y. Ding, D. Y. T. Fong, and J. Karlberg, "Blood pressure is associated with body mass index in both normal and obese children," *Hypertension*, vol. 36, no. 2, pp. 165–170, 2000.

[13] F. Z. Tan, H. M. Dong, G. H. Feng et al., "Study on the relations between overweight, obesity, blood pressures, serum lipids and glucose in schoolchildren of Shijiazhunag," *Zhonghua Liu Xing Bing Xue Za Zhi*, vol. 26, no. 8, pp. 592–595, 2005.

[14] P. Muntner, J. He, J. A. Cutler, R. P. Wildman, and P. K. Whelton, "Trends in Blood Pressure among Children and Adolescents," *Journal of the American Medical Association*, vol. 291, no. 17, pp. 2107–2113, 2004.

[15] J. Ribeiro, S. Guerra, A. Pinto, J. Oliveira, J. Duarte, and J. Mota, "Overweight and obesity in children and adolescents: relationship with blood pressure, and physical activity," *Annals of Human Biology*, vol. 30, no. 2, pp. 203–213, 2003.

[16] J. M. Sorof, D. Lai, J. Turner, T. Poffenbarger, and R. J. Portman, "Overweight, ethnicity, and the prevalence of hypertension in school-aged children," *Pediatrics*, vol. 113, no. 3, pp. 475–482, 2004.

[17] C. B. Ebbeling, D. B. Pawlak, and D. S. Ludwig, "Childhood obesity: public-health crisis, common sense cure," *The Lancet*, vol. 360, no. 9331, pp. 473–482, 2002.

[18] T. H. Jafar, M. Islam, N. Poulter et al., "Children in South Asia have higher body mass-adjusted blood pressure levels than white children in the United States: a comparative study," *Circulation*, vol. 111, no. 10, pp. 1291–1297, 2005.

[19] C. Agyemang, W. K. Redekop, E. Owusu-Dabo, and M. A. Bruijnzeels, "Blood pressure patterns in rural, semi-urban and urban children in the Ashanti region of Ghana, West Africa," *BMC Public Health*, vol. 5, article 114, 2005.

[20] K. D. Monyeki, H. C. G. Kemper, and P. J. Makgae, "The association of fat patterning with blood pressure in rural South African children: the Ellisras Longitudinal Growth and Health Study," *International Journal of Epidemiology*, vol. 35, no. 1, pp. 114–120, 2006.

[21] L. Ke, K. E. Brock, R. V. Cant, Y. Li, and S. L. Morrell, "The relationship between obesity and blood pressure differs by ethnicity in Sydney school children," *American Journal of Hypertension*, vol. 22, no. 1, pp. 52–58, 2009.

[22] Q. He, Z. Y. Ding, D. Y. T. Fong, and J. Karlberg, "Blood pressure is associated with body mass index in both normal and obese children," *Hypertension*, vol. 36, no. 2, pp. 165–170, 2000.

[23] R. Y. T. Sung, C. C. W. Yu, K. C. Choi et al., "Waist circumference and body mass index in Chinese children: cutoff values for predicting cardiovascular risk factors," *International Journal of Obesity*, vol. 31, no. 3, pp. 550–558, 2007.

[24] C. Li, E. S. Ford, A. H. Mokdad, and S. Cook, "Recent trends in waist circumference and waist-height ratio among US children and adolescents," *Pediatrics*, vol. 118, no. 5, pp. e1390–e1398, 2006.

[25] M. E. Lean, T. S. Han, and C. E. Morrison, "Waist circumference as a measure for indicating need for weight management," *The British Medical Journal*, vol. 311, no. 6998, pp. 158–161, 1995.

[26] Centers for Disease Control and Prevention. Growth charts. Available at: http://www.cdc.gov/growthcharts/, November, 2010.

[27] M. I. Goran, G. D. C. Ball, and M. L. Cruz, "Cardiovascular endocrinology 2: obesity and risk of type 2 diabetes and cardiovascular disease in children and adolescents," *Journal of Clinical Endocrinology and Metabolism*, vol. 88, no. 4, pp. 1417–1427, 2003.

[28] Centers for Disease Control and Prevention, *The Third National Health and Nutrition Examination Survey (NHANES III 1988–1994) Reference Manuals and Reports [CD-ROM]*, National Center for Health Statistics, Bethesda, Md, USA, 2005.

[29] WHO, *Measuring Obesity: Classification and Description of Anthropometric Data*, WHO, Copenhagen, Germany, 1989.

[30] B. Falkner and S. R. Daniels, "Summary of the fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents," *Hypertension*, vol. 44, no. 4, pp. 387–388, 2004.

[31] A. V. Chobanian, G. L. Bakris, H. R. Black et al., "The Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 Report," *Journal of the American Medical Association*, vol. 289, no. 19, pp. 2560–2572, 2003.

[32] M. A. Abolfotouh, F. A. Bassiouni, G. M. Mounir, and R. C. Fayyad, "Health-related lifestyles and risk behaviours among students living in Alexandria University hostels," *Eastern Mediterranean Health Journal*, vol. 13, no. 2, pp. 376–391, 2007.

[33] M. Rafraf, B. P. Gargari, and A. Safaiyan, "Prevalence of prehypertension and hypertension among adolescent high school girls in Tabriz, Iran," *Food and Nutrition Bulletin*, vol. 31, no. 3, pp. 461–465, 2010.

[34] K. L. McNiece, T. S. Poffenbarger, J. L. Turner, K. D. Franco, J. M. Sorof, and R. J. Portman, "Prevalence of hypertension and pre-hypertension among adolescents," *Journal of Pediatrics*, vol. 150, no. 6, pp. 640–644, 2007.

[35] K. D. Monyeki, H. C. G. Kemper, and P. J. Makgae, "The association of fat patterning with blood pressure in rural South African children: the Ellisras Longitudinal Growth and Health Study," *International Journal of Epidemiology*, vol. 35, no. 1, pp. 114–120, 2006.

[36] A. Chiolero, G. Madeleine, A. Gabriel, M. Burnier, F. Paccaud, and P. Bovet, "Prevalence of elevated blood pressure and

association with overweight in children of a rapidly developing country," *Journal of Human Hypertension*, vol. 21, no. 2, pp. 120–127, 2007.

[37] G. Paradis, M. Lambert, J. O'Loughlin et al., "Blood pressure and adiposity in children and adolescents," *Circulation*, vol. 110, no. 13, pp. 1832–1838, 2004.

[38] P. Poirier, T. D. Giles, G. A. Bray et al., "Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss," *Circulation*, vol. 113, no. 6, pp. 898–918, 2006.

[39] F. D. Fuchs, M. Gus, L. B. Moreira et al., "Anthropometrie indices and the incidence of hypertension: a comparative analysis," *Obesity Research*, vol. 13, no. 9, pp. 1515–1517, 2005.

[40] H. D. McCarthy, S. M. Ellis, and T. J. Cole, "Central overweight and obesity in British youth aged 11–16 years: cross sectional surveys of waist circumference," *The British Medical Journal*, vol. 326, no. 7390, pp. 624–626, 2003.

[41] S. Zhu, S. Heshka, Z. Wang et al., "Combination of BMI and waist circumference for identifying cardiovascular risk factors in whites," *Obesity Research*, vol. 12, no. 4, pp. 633–645, 2004.

[42] I. Janssen, P. T. Katzmarzyk, and R. Ross, "Waist circumference and not body mass index explains obesity-related health risk," *American Journal of Clinical Nutrition*, vol. 79, no. 3, pp. 379–384, 2004.

[43] C. Maffeis, A. Pietrobelli, A. Grezzani, S. Provera, and L. Tatò, "Waist circumference and cardiovascular risk factors in prepubertal children," *Obesity Research*, vol. 9, no. 3, pp. 179–187, 2001.

[44] R. W. Taylor, I. E. Jones, S. M. Williams, and A. Goulding, "Evaluation of waist circumference, waist-to-hip ratio, and the conicity index as screening tools for high trunk fat mass, as measured by dual-energy X-ray absorptiometry, in children aged 3-19 y," *American Journal of Clinical Nutrition*, vol. 72, no. 2, pp. 490–495, 2000.

[45] B. Falkner, S. R. Daniels, J. T. Flynn et al., "The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents," *Pediatrics*, vol. 114, no. 2, supplement, pp. 555–576, 2004.

[46] G. Paradis, M. Lambert, J. O'Loughlin et al., "Blood pressure and adiposity in children and adolescents," *Circulation*, vol. 110, no. 13, pp. 1832–1838, 2004.

[47] T. H. Jafar, M. Islam, N. Poulter et al., "Children in South Asia have higher body mass-adjusted blood pressure levels than white children in the United States: a comparative study," *Circulation*, vol. 111, no. 10, pp. 1291–1297, 2005.

[48] S. Greenland and K. Drescher, "Maximum likelihood estimation of the attributable fraction from logistic models," *Biometrics*, vol. 49, no. 3, pp. 865–872, 1993.

[49] B. Falkner, S. S. Gidding, G. Ramirez-Garnica, S. A. Wiltrout, D. West, and E. B. Rappaport, "The relationship of body mass index and blood pressure in primary care pediatric patients," *Journal of Pediatrics*, vol. 148, no. 2, pp. 195–200, 2006.

SAGE-Hindawi Access to Research
International Journal of Hypertension
Volume 2011, Article ID 257168, 6 pages
doi:10.4061/2011/257168

Clinical Study

Metabolic Syndrome in Italian Obese Children and Adolescents: Stronger Association with Central Fat Depot than with Insulin Sensitivity and Birth Weight

Claudia Brufani,[1] Danilo Fintini,[2] Ugo Giordano,[2] Alberto Enrico Tozzi,[3] Fabrizio Barbetti,[4,5] and Marco Cappa[1]

[1] *Endocrinology and Diabetes Unit, University Department of Paediatric Medicine, Bambino Gesù Children's Hospital, IRCCS, Piazza S.Onofrio 4, 00165 Rome, Italy*
[2] *Cardiorespiratory and Sport Medicine Unit, Bambino Gesù Children's Hospital, IRCCS, Piazza S.Onofrio 4, 00165 Rome, Italy*
[3] *Epidemiology Unit, Bambino Gesù Children's Hospital, IRCCS, Piazza S.Onofrio 4, 00165 Rome, Italy*
[4] *Laboratory of Monogenic Diabetes, Bambino Gesù Children's Hospital, IRCCS, Piazza S.Onofrio 4, 00165 Rome, Italy*
[5] *Department of Internal Medicine, University of Rome, "TorVergata", Viale Oxford 81, 00127 Rome, Italy*

Correspondence should be addressed to Claudia Brufani, cbrufani@libero.it

Received 14 December 2010; Accepted 5 January 2011

Academic Editor: Kazuko Masuo

Aim. To evaluate whether body fat distribution, birth weight, and family history for diabetes (FHD) were associated with metabolic syndrome (MetS) in children and adolescents. *Methods*. A total of 439 Italian obese children and adolescents (5–18 years) were enrolled. Subjects were divided into 2 groups: prepubertal and pubertal. MetS was diagnosed according to the adapted National Cholesterol Education Program criteria. Birth weight percentile, central obesity index (measured by dual-energy X-ray absorptiometry), insulin sensitivity (ISI), and disposition index were evaluated. Multivariate logistic regression models were used to determine variables associated with MetS. *Results*. The prevalence of MetS was 17%, with higher percentage in adolescents than in children (21 versus 12%). In the overall population, central obesity index was a stronger predictor of MetS than insulin sensitivity and low birth weight. When the two groups were considered, central fat depot remained the strongest predictor of MetS, with ISI similarly influencing the probability of MetS in the two groups and birth weight being negatively associated to MetS only in pubertal individuals. Neither FHD nor degree of fatness was a significant predictor of MetS. *Conclusion*. Simple clinical parameters like increased abdominal adiposity and low birth weight could be useful tools to identify European obese adolescents at risk for metabolic complications.

1. Introduction

In Western countries, the prevalence of paediatric obesity and comorbidities, which cluster together in the metabolic syndrome (MetS) [1], is going to reach epidemic proportions. Data from the National Heart Lung and Blood Institute Lipid Research Clinics and the Princeton Prevalence Study (1973–1976) and Princeton Follow-up Study (2000–2004) show that MetS in 5- to 19-year olds represents a risk factor for cardiovascular disease in adulthood [2]. This finding highlights the importance of early recognition of MetS in obese children as a strategy for primary prevention of cardiovascular disease later in life.

Clinical studies have shown that low birth weight increases the risk of MetS in adulthood [3]. The association between birth weight and MetS in childhood is far to be clear, and results are controversial, with studies showing a strong [4–6] or a weak [7–9] association between low or high birth weight and MetS.

Moreover, several reports indicate that family history of diabetes and increased abdominal fat adiposity are strong risk factors for MetS since childhood [5, 10–13].

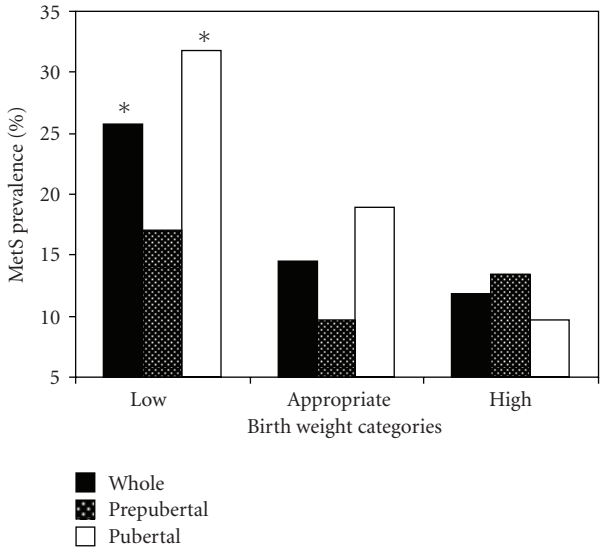


Figure 1: Prevalence of metabolic syndrome according to birth weight categories SGA, AGA, and LGA denoting small, appropriate, and large birth weight individuals, respectively. Symbols refer to comparison (Chi-square test) of prevalence of metabolic syndrome among birth weight categories, in the whole population, prepubertal subjects, and pubertal subjects. $^*P < .05$

Additionally, the marked decrease of insulin sensitivity associated with the onset of puberty in growing individuals [14, 15] may act as a further risk factor for the development of metabolic comorbidities, particularly in obese subjects. It is not clear if onset of puberty and its progression are characterized by different determinants of MetS in adolescents, compared to children.

The aim of the study was to evaluate whether family history of type 2 diabetes (FHD) in first-degree relatives, either low or high birth weight, and increased central body fat depot are independent risk factors for the development of MetS in Italian obese children and adolescents.

2. Methods

2.1. Study Population. The children who participated in the present cross-sectional investigation are a subsample of an ongoing longitudinal study exploring risk factors for the development of type 2 diabetes in young Italian subjects.

Obese children and adolescents, referred to the Endocrinology and Diabetes Unit of Bambino Gesù Children's Hospital for obesity from January 2003 to January 2010, were included in the present investigation if they met the following criteria: (1) being overweight or obese according to the International Obesity Task Force [16]; (2) absence of underlying diseases; (3) Italian origin (all four grandparents of Italian descent); (4) availability of data relative to gestation, birth, and FHD among first-degree relatives. Moreover, as we were interested in the role of fetal factor in the development of metabolic comorbidities [17], low and high birth weights (as defined below) were additional selection factors. Participants were not following a weight-reducing diet, taking any medication, or carrying a previous clinical diagnosis known to influence body composition, glucose metabolism, physical activity, or dietary intake.

Information on birth weight, FHD, and gestational diabetes was obtained. Birth weight was based on information recorded at the time of birth. The gestational age was determined by ultrasound in the first trimester, if available, and otherwise calculated from the date of the last menstruation. Weight at birth was converted into percentiles for gestational age and sex, according to the Italian birth weight curves [18]. Participants were defined on the basis of their birth weight percentile as small for gestational age (SGA) (birth weight $\leq$10th percentile), appropriate for gestational age (AGA) (birth weight >10th and <90th percentile), and large for gestational age (LGA) (birth weight $\geq$90th percentile). FHD was defined by the presence of type 2 diabetes in at least one parent. FHD, maternal gestational, and pre-existing diabetes were ascertained by a self-administered parents' questionnaire.

Written informed consent and assent were obtained from parents before any testing procedure. Approval of the protocol was obtained by the Local Scientific Committee. The study was conducted in accordance with The Declaration of Helsinki.

After a 12-hour overnight fast, at approximately 8:00 Am, all subjects were admitted in the clinic for one-day inpatient visit. Height was measured without shoes to the nearest 0.1 cm using a wall Stadiometer, and weight was measured in underwear to the nearest 0.1 kg using a medical balance beam scale. To compare body mass index (BMI) across different ages and between genders, values of BMI were expressed as standard deviation score (SDS) [16]. Blood pressure (BP) was measured using a standard mercury sphygmomanometer two times in the supine position, at the beginning and at the end of the visit, using the right arm after the subject had rested quietly for 5 minutes. On each occasion, three readings of blood pressure were obtained, and the average was recorded. Physical maturation was assessed on the basis of breast development in girls and genitalia development in boys according to Tanner [19]. Due to the well-known relationship between pubertal development and decrease in insulin sensitivity [14, 15], subjects were divided into two groups according to the pubertal stage: prepubertal (Tanner stage 1), pubertal (Tanner stage from 2 to 5).

2.2. Metabolic Evaluation. Fasting blood samples were taken via antecubital vein catheter for measurement of glucose, insulin, C peptide, high density lipoprotein (HDL), cholesterol, and triglycerides. Then subjects ingested 1.75 g of glucose solution per kilogram of body weight (to a maximum of 75 g). Plasma samples were drawn for determination of glucose, insulin, and C peptide concentration every 30 minutes, until 2 hours after glucose load.

Insulin sensitivity index (ISI) [20] was calculated from oral glucose tolerance test (OGTT). It has been demonstrated to strongly correlate with the euglycemic-hyperinsulinemic clamp in obese children and adolescents [21].

To asses beta cell function, we used the insulinogenic index, calculated as the ratio of the increment in the plasma C peptide level to that in the plasma glucose level during the first 30 minutes after the ingestion of glucose.

The disposition index (DI) [22] was defined as the product of ISI and insulinogenic index. It reflects the capacity of pancreatic islets to compensate for lower insulin sensitivity.

2.3. Body Composition Evaluation. At least 10 days after the first inpatient visit children were admitted again for body composition evaluation. Body composition was measured by dual-energy X-ray absorptiometry (DEXA) using Hologic QDR Delphi (Hologic Inc., Bedford, MA), as previously described [15]. Fat and lean mass were corrected for differences in height as follow fat mass/height^2 (fat BMI) and lean mass/height^2 (lean BMI), expressed as kg/m^2 [23]. Body fat distribution was evaluated by the central obesity index calculated as the ratio of the amount of fat tissue in the trunk region to the amount of fat tissue in the leg region [24].

2.4. Definition of Metabolic Syndrome. Identification of MetS among children was based on the adult criteria defined by the National Cholesterol Education Program [1]. In the adult definition, a minimum of three of five major criteria (obesity determined by waist circumference, hypertension, low HDL cholesterol levels, elevated triglycerides, and glucose intolerance) should be fulfilled. These criteria have been modified for children [6]. Overweight and obesity were defined according to the Obesity Task Force [16]: hypertriglyceridaemia as triglycerides >95th percentile for age and sex [25]; low HDL cholesterol as concentrations <5th percentile for age and sex [25]; elevated BP as systolic or diastolic BP >95th for age and sex [26]; glucose intolerance as fasting glucose ≥100 mg/dL and/or 2-hour post-OGTT glucose ≥140 [27]. Therefore, we defined MetS as the presence of at least 2 other findings out of overweight/obesity.

2.5. Assays. Serum insulin and C peptide were measured by chemiluminescence on ADVIA Centaur analyzer (Kyowa, Medex Co., Tokyo, Japan); both assays are two-site sandwich immunoassays using direct chemiluminescent technology [intra- and interassay coefficient of variation (CV) 3.3–4.6 and 2.6–5.9%; 3.7–4.1 and 1.0–3.3%, resp.].

Quantitative determination of blood glucose, HDL cholesterol, and triglycerides was measured by enzymatic method on Roche automated clinical chemistry analyser (Roche/Hitachi 904 analyzer, Roche Diagnostics, Mannheim, Germany).

Intra- and interassay, CV for glucose, HDL cholesterol, and triglycerides were 0.9 and 1.8%; 0.6–0.95 and 1.2-1.3%; 1.5% and 1.8%, respectively.

2.6. Statistical Analysis. Numerical values are reported as mean ± standard deviation and categorical variables as proportions. The Kolmogorov-Smirnov goodness-of-fit test was used for determining whether sample data are likely to derive from a normal distributed population. Variables that diverged significantly from normal distribution were logarithmically transformed before analysis.

Between-group differences were examined using independent sample t-test and Chi-square test for numerical and categorical variables, respectively.

First, bivariate logistic regression was used to determine the associations between MetS and gender, age, FHD, diabetes during pregnancy, birth weight percentile, BMI SDS, fat and lean BMI, central obesity index, ISI, insulinogenic index, and DI. Then, variables significantly associated with MetS were inserted into multivariate logistic regression analyses, with MetS as dependent variable. We performed the multivariate logistic regression analysis in successive steps. In the first step, variables influencing MetS were evaluated in the overall population. In the second step, the population was stratified according to the pubertal development.

Significance level for all tests was set at $P < .05$. SPSS software version 13.0 (SPSS Inc., Chicago, IL) was used for all analyses.

3. Results

Study participants included 439 obese subjects (213 boys, 226 girls), aging 5.2–17.9 years (mean age 11.3 ± 2.6) with a mean BMI SDS of 2.2 ± 0.3. Twohundred and one subjects were prepubertal and 238 were pubertal.

MetS was present in 17.1% of individuals with higher prevalence in pubertal than prepubertal subjects (21.4 versus 11.9%, $P = .008$).

Clinical and metabolic characteristics of subjects with and without MetS, divided according to pubertal development, are reported in Table 1.

Girls and boys were equally distributed among individuals with and without MetS in both groups. Surprisingly, rates of FHD were similar between subjects with and without MetS. As expected ISI and central obesity index were significantly different, with subjects with MetS being more insulin resistant (prepubertal: 3.0 ± 1.9 versus 4.1 ± 2.3, $P = .010$; pubertal: 2.5 ± 1.9 versus 3.6 ± 2.5, $P < .0001$) and having more central fat depot (prepubertal: 1.32 ± 0.20 versus 1.19 ± 0.39, $P = .017$; pubertal: 1.30 ± 0.29 versus 1.19 ± 0.24, $P = .024$) compared to individuals without MetS. Mean birth weight percentile and DI were lower in individuals with MetS compared to individuals without MetS, but differences were statistically significant only in the pubertal group (birth weight percentile prepubertal: 38.2 ± 34.0 versus 47.0 ± 32.2, $P = .117$; pubertal 33.5 ± 30.7 versus 45.0 ± 31.8, $P = .011$; DI prepubertal: 0.36 ± 0.22 versus 0.46 ± 0.38, $P = .204$; pubertal: 0.33 ± 0.31 versus 0.41 ± 0.28, $P = .012$).

3.1. Role of Birth Weight. To further analyze the relation between birth weight and MetS, we evaluated the prevalence of MetS into the three birth weight categories. Because low and high birth weights were selection factors, we had 22.3% of SGA ($n = 98$), 62.2% of AGA ($n = 273$), and 15.5% of LGA ($n = 68$).

Table 1: Clinical and metabolic characteristics of obese children and adolescents.

	Prepubertal (n.201)			Pubertal (n.238)		
	MetS	No MetS	*P*	MetS	No MetS	*P*
Number	24	177		51	187	
Male/female	10/14	92/85	.343	23/28	88/99	.804
Age (years)	9.4 ± 1.1	9.3 ± 1.7	.763	13.2 ± 1.9	13.1 ± 2.0	.835
Family history of diabetes (%)	15.0	20.5	.397	7.7	13.3	.399
Birth weight (kg)	3.1 ± 0.7	3.3 ± 0.7	.362	3.2 ± 0.6	3.3 ± 0.6	.098
Birth weight (percentile)	38.2 ± 34.0	47.0 ± 32.2	.117	33.5 ± 30.7	45.0 ± 31.8	.011
BMI (kg/m^2)	28.5 ± 3.9	27.8 ± 3.6	.379	32.7 ± 5.9	31.4 ± 4.9	.115
BMI SDS	2.3 ± 0.3	2.3 ± 0.3	.845	2.3 ± 0.3	2.2 ± 0.3	.077
Fat BMI (kg/m^2)	11.7 ± 2.7	11.4 ± 2.3	.531	12.2 ± 3.5	12.3 ± 3.1	.717
Lean BMI (kg/m^2)	15.7 ± 1.5	15.2 ± 1.5	.182	18.2 ± 2.7	17.6 ± 2.4	.613
Central obesity index	1.32 ± 0.20	1.19 ± 0.39	.017	1.30 ± 0.29	1.19 ± 0.24	.024
HDL cholesterol (mg/dL)	35.7 ± 6.5	49.3 ± 9.6	<.0001	37.0 ± 6.8	46.0 ± 8.9	<.0001
Triglycerides (mg/dL)	141.1 ± 45.6	78.3 ± 38.6	<.0001	177.5 ± 93.0	82.3 ± 40.3	<.0001
PAs (mmHg)	107.1 ± 12.0	106.9 ± 9.6	.961	124.2 ± 14.3	114.9 ± 12.8	<.0001
PAd (mmHg)	67.9 ± 8.4	66.9 ± 9.7	.916	72.1 ± 12.1	69.3 ± 10.0	.139
Fasting glucose (mg/dL)	83.3 ± 9.4	80.1 ± 6.3	.046	83.4 ± 11.8	81.4 ± 7.6	.192
2-hour glucose (mg/dL)	113.2 ± 32.1	108.2 ± 16.2	.671	125.7 ± 23.3	110.5 ± 20.4	<.0001
ISI	3.0 ± 1.9	4.1 ± 2.3	.010	2.5 ± 1.9	3.6 ± 2.5	<.0001
Insulinogenic index$_{(C\ peptide\ 30-0)}$	0.13 ± 0.06	0.11 ± 0.07	.094	0.27 ± 0.98	0.13 ± 0.14	.199
DI$_{(C\ peptide\ 30-0)}$	0.36 ± 0.22	0.46 ± 0.38	.204	0.33 ± 0.31	0.41 ± 0.28	.012

MetS, BMI, PAs, PAd, ISI, and DI denote metabolic syndrome, body mass index, systolic blood pressure, diastolic blood pressure, insulin sensitivity index, and disposition index, respectively.

Table 2: Variables significantly associated to metabolic syndrome.

Dependent variable: MetS		
Independent variables[a]	Beta[b] ± SE	*P*
Entire population		
Log central obesity index	2.815 ± 0.947	.003
Log ISI	−1.257 ± 0.306	<.001
Log birth weight	−0.411 ± 0.128	.001
Prepubertal group		
Log central obesity index	4.804 ± 1.587	.002
Log ISI	−1.1290.564	.045
Pubertal group		
Log central obesity index	2.491 ± 1.170	.033
Log ISI	−1.013 ± 0.371	.006
Log birth weight	−0.3850.167	.021

[a]All values are log-transformed to approximate normal distribution.
[b]Generalized equation estimation method regression coefficient.
MetS and ISI denote metabolic syndrome and insulin sensitivity index, respectively.

Prevalence of subjects with MetS was significantly higher in the SGA category (25.7%), with LGA having the lowest (11.8%) and AGA the intermediate (14.5%) prevalence (P = .015). This trend was maintained in the pubertal group (P = .027) but not in the prepubertal one (P = .423) (Figure 1).

As gestational diabetes is associated with large size at birth and is known to strongly influence the risk of developing MetS in the offspring [6, 28], we evaluated the prevalence of MetS in the different birth weight categories after excluding offspring of diabetic mothers. Diabetes during pregnancy (either gestational diabetes or pre-existing type 1 or 2 diabetes) was present in 28 cases (6.3%). Most cases of offspring of diabetic mothers were in the LGA group (18 out of 28). Prevalence of MetS in the different birth weight categories, after excluding offspring of mother with diabetes during pregnancy, did not change substantially (in the whole population 26.1, 13.7, and 10.9% in SGA, AGA, and LGA, resp., P = .007).

3.2. Logistic Regression Analysis. Bivariate logistic regression analysis revealed age, lean BMI, insulinogenic index, and central obesity index to be positively associated with MetS (P = .033, .004, .027, and .001, resp.) and birth weight, ISI, and DI to be negatively associated with MetS (P = .003, < .001, and = .002, resp.). Gender, FHD, diabetes during pregnancy, and degree of obesity expressed either as BMI SDS or fat BMI did not influence the dependent variable.

In the entire population, the multivariate logistic regression analysis revealed central obesity index to be positively and independently associated with MetS and ISI and birth weight to be negatively associated with MetS, with central obesity index being the strongest predictor of MetS (Table 2).

When the prepubertal and pubertal subjects were analysed separately, central obesity index remained the most powerful variable influencing MetS in both groups, with ISI similarly influencing MetS in the two populations and birth

weight being negatively associated to MetS only in pubertal individuals (Table 2).

4. Discussion

In the present study of Italian growing obese individuals, our findings revealed that increased central fat depot is the strongest determinant of MetS, no matter if subjects were children or adolescents, with central obesity index being more predictive of MetS than insulin sensitivity. Moreover, low birth weight appeared to be a less powerful risk factor for MetS with significant association only in pubertal individuals. Surprisingly, FHD, age, insulinogenic index, DI, and degree of obesity, expressed either as BMI SDS or total fat amount, were not significant determinants of MetS in this cohort of obese subjects.

The central role of abdominal adiposity and particularly of visceral adiposity in the development of MetS has been widely demonstrated in adulthood [29, 30]. Similar findings have been described in children, where waist circumference and increased visceral fat depot have been confirmed to be strong and independent predictors of metabolic alterations [12, 13]. In the present study, by directly measuring with the DEXA technique the total fat amount and the body fat distribution, we showed that in, obese Italian growing subjects, the preponderance of fat in the abdomen is the real determinant of MetS, rather than the total body fat amount. As a matter of fact, neither BMI SDS nor fat BMI appeared to be risk factors for MetS. Similar findings were reported by an Italian study, where waist-to-height ratio was the only clinical parameter directly related to MetS, with the same predictive power of insulin resistance [31].

In our study, SGA individuals showed a significant higher incidence of MetS, with subjects born LGA apparently protected from the development of MetS. However, small size at birth was not an important predictor of MetS as was central obesity index. The present data of increased metabolic risk in subjects born SGA confirm a large body of the literature in adulthood and also in childhood [3]. Moreover, our findings on apparently protective role of large size at birth are in contrast with other studies conducted in different ethnic groups, like Pima Indians [28] and Mexican children [5], that have showed an increased risk for metabolic alterations in children born LGA.

We have previously showed that obese children and adolescents born SGA manifest reduced insulin secretion in the context of increased insulin resistance milieu and more evident central repartition of fat than AGA and LGA, with LGA presenting the highest insulinogenic index, despite comparable degree of insulin resistance [17]. Similar to our findings, a study conducted in French obese children has showed a favourable metabolic profile in children born LGA, with obese children and adolescents born with high birth weight displaying approximately 60% higher insulin sensitivity and lower central fat distribution compared with those born eutrophic [9]. One could hypothesize that the role of large size at birth is different in the different ethnic groups, with European obese children being protected from metabolic complications if born LGA.

As the Pima Indian study has showed that the increased risk of metabolic alterations among Pima with high birth weight was largely explained by maternal diabetes during pregnancy [28], we evaluated the role of diabetes during pregnancy in our sample of obese children and adolescents. We found no association with diabetes during pregnancy, probably because cases of either gestational diabetes or pre-existing type 1 or 2 diabetes were only 28 and we had no statistical power to show any relation with MetS.

Surprisingly, FHD was not associated with MetS. Different findings have been reported by other authors, who described FHD to be a risk factor for MetS [5] and hyperinsulinemia [6] in children and adolescents. One explanation for this discrepancy could be due to the fact that type 2 diabetes in adults is age dependent. Additionally, we did not measure directly blood glucose in the parents. It is likely that in our study some currently healthy parents have silent diabetes or will develop diabetes in the future. This could be a potential source of bias in the classification of positive FHD. The specific role of FHD in the development of MetS could not be determined with certainty, and follow-up studies are needed to confirm our results.

Although our study has strengths, including the use of imaging technique to evaluate body fat portioning and a large representative sample of exclusively Italian obese children and adolescents, we acknowledge some limitations. First, we did not distinguish visceral from subcutaneous abdominal fat; secondly, we did not study insulin sensitivity with the gold standard hyperinsulinaemic euglycemic clamp technique for its complexity in pediatric patients; thirdly, because this was a cross-sectional analysis, causation could not be inferred.

In conclusion, simple clinical parameters like increased abdominal adiposity, eventually estimated by waist circumference and low birth weight, could be useful tools to identify obese growing European individuals at risk for metabolic complications.

As not all obese adults display the clustering of metabolic and cardiovascular risk factors, with some of them being metabolically healthy but obese individuals [32], one could speculate that obese adolescents born LGA, with predominantly peripheral fat portioning, could be healthy obese adolescents, having a favourable metabolic profile.

Prospective studies with serial measurements of cardiovascular risk factors are needed to confirm our findings.

Conflict of Interests

There is no conflict of interests that could be perceived as prejudicing the impartiality of the research reported. This research did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

References

[1] J. I. Cleeman, "Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III)," *Journal of the*

American Medical Association, vol. 285, no. 19, pp. 2486–2497, 2001.

[2] J. A. Morrison, L. A. Friedman, P. Wang, and C. J. Glueck, "Metabolic syndrome in childhood predicts adult metabolic syndrome and type 2 diabetes mellitus 25 to 30 years later," *Journal of Pediatrics*, vol. 152, no. 2, pp. 201–206, 2008.

[3] P. Saenger, P. Czernichow, I. Hughes, and E. O. Reiter, "Small for gestational age: short stature and beyond," *Endocrine Reviews*, vol. 28, no. 2, pp. 219–251, 2007.

[4] A. Bavdekar, C. S. Yajnik, C. H. D. Fall et al., "Insulin resistance syndrome in 8-year-old Indian children: small at birth, big at 8 years, or both?" *Diabetes*, vol. 48, no. 12, pp. 2422–2429, 1999.

[5] F. Guerrero-Romero, C. Aradillas-Garcia, L. E. Simental-Mendia, E. Monreal-Escalante, E. de la Cruz Mendoza, and M. Rodriguez-Moran, "Birth weight, family history of diabetes, and metabolic syndrome in children and adolescents," *Journal of Pediatrics*, vol. 156, no. 5, pp. 719–723, 2010.

[6] C. M. Boney, A. Verma, R. Tucker, and B. R. Vohr, "Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus," *Pediatrics*, vol. 115, no. 3, pp. e290–e296, 2005.

[7] V. Hirschler, J. Bugna, M. Roque, T. Gilligan, and C. Gonzalez, "Does low birth weight predict obesity/overweight and metabolic syndrome in elementary school children?" *Archives of Medical Research*, vol. 39, no. 8, pp. 796–802, 2008.

[8] T. Dwyer, L. Blizzard, A. Venn, J. M. Stankovich, A. L. Ponsonby, and R. Morleya, "Syndrome X in 8-y-old Australian children: stronger associations with current body fatness than with infant size or growth," *International Journal of Obesity*, vol. 26, no. 10, pp. 1301–1309, 2002.

[9] N. Bouhours-Nouet, S. Dufresne, F. B. de Casson et al., "High birth weight and early postnatal weight gain protect obese children and adolescents from truncal adiposity and insulin resistance," *Diabetes Care*, vol. 31, no. 5, pp. 1031–1036, 2008.

[10] R. M. van Dam, J. M. A. Boer, E. J. M. Feskens, and J. C. Seidell, "Parental history off diabetes modifies the association between abdominal adiposity and hyperglycemia," *Diabetes Care*, vol. 24, no. 8, pp. 1454–1459, 2001.

[11] M. Rodriguez-Moran and F. Guerrero-Romero, "Hyperinsulinemia in healthy children and adolescents with a positive family history for type 2 diabetes," *Pediatrics*, vol. 118, no. 5, pp. e1516–e1522, 2006.

[12] D. S. Freedman, M. K. Serdula, S. R. Srinivasan, and G. S. Berenson, "Relation of circumferences and skinfold thicknesses to lipid and insulin concentrations in children and adolescents: the Bogalusa Heart Study," *American Journal of Clinical Nutrition*, vol. 69, no. 2, pp. 308–317, 1999.

[13] S. Lee, F. Bacha, and S. A. Arslanian, "Waist circumference, blood pressure, and lipid components of the metabolic syndrome," *Journal of Pediatrics*, vol. 149, no. 6, pp. 809–816, 2006.

[14] A. Moran, D. R. Jacobs Jr., J. Steinberger et al., "Insulin resistance during puberty: results from clamp studies in 357 children," *Diabetes*, vol. 48, no. 10, pp. 2039–2044, 1999.

[15] C. Brufani, A. Tozzi, D. Fintini et al., "Sexual dimorphism of body composition and insulin sensitivity across pubertal development in obese Caucasian subjects," *European Journal of Endocrinology*, vol. 160, no. 5, pp. 769–775, 2009.

[16] T. J. Cole, M. C. Bellizzi, K. M. Flegal, and W. H. Dietz, "Establishing a standard definition for child overweight and obesity worldwide: international survey," *British Medical Journal*, vol. 320, no. 7244, pp. 1240–1243, 2000.

[17] C. Brufani, A. Grossi, D. Fintini et al., "Obese children with low birth weight demonstrate impaired β-cell function during oral glucose tolerance test," *Journal of Clinical Endocrinology and Metabolism*, vol. 94, no. 11, pp. 4448–4452, 2009.

[18] L. Gagliardi, F. Macagno, D. Pedrotti et al., "Standard antropometrici neonatali prodotti dalla task-force della società Italiana di neonatologia e basati su una popolazione Italiana nord-orientale," *Rivista Italiana di Pediatria*, vol. 25, no. 1, pp. 159–169, 1999.

[19] J. M. Tanner, "Growth and maturation during adolescence," *Nutrition Reviews*, vol. 39, no. 2, pp. 43–55, 1981.

[20] M. Matsuda and R. A. DeFronzo, "Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp," *Diabetes Care*, vol. 22, no. 9, pp. 1462–1470, 1999.

[21] C. W. Yeckel, R. Weiss, J. Dziura et al., "Validation of insulin sensitivity indices from oral glucose tolerance test parameters in obese children and adolescents," *Journal of Clinical Endocrinology and Metabolism*, vol. 89, no. 3, pp. 1096–1101, 2004.

[22] S. E. Kahn, R. L. Prigeon, D. K. McCulloch et al., "Quantification of the relationship between insulin sensitivity and β- cell function in human subjects: evidence for a hyperbolic function," *Diabetes*, vol. 42, no. 11, pp. 1663–1672, 1993.

[23] J. C. K. Wells and T. J. Cole, "Adjustment of fat-free mass and fat mass for height in children aged 8 y," *International Journal of Obesity*, vol. 26, no. 7, pp. 947–952, 2002.

[24] S. R. Daniels, J. A. Morrison, D. L. Sprecher, P. Khoury, and T. R. Kimball, "Association of body fat distribution and cardiovascular risk factors in children and adolescents," *Circulation*, vol. 99, no. 4, pp. 541–545, 1999.

[25] American Academy of Pediatrics, "National Cholesterol Education Program: report of the expert panel on blood cholesterol levels in children and adolescents," *Pediatrics*, vol. 89, pp. 525–584, 1992.

[26] "Report of the Second Task Force on Blood Pressure Control in Children—1987. Task Force on Blood Pressure Control in Children. National Heart, Lung, and Blood Institute, Bethesda, Maryland," *Pediatrics*, vol. 79, pp. 1–25, 1987.

[27] American Diabetes Association, "Standards of medical care in Diabetes—2010," *Diabetes Care*, vol. 33, pp. S11–S61, 2010.

[28] D. Dabelea, D. J. Pettitt, R. L. Hanson, G. Imperatore, P. H. Bennett, and W. C. Knowler, "Birth weight, type 2 diabetes, and insulin resistance in Pima Indian children and young adults," *Diabetes Care*, vol. 22, no. 6, pp. 944–950, 1999.

[29] A. H. Kissebah, "Central obesity: measurement and metabolic effects," *Diabetes Reviews*, vol. 5, no. 1, pp. 8–20, 1997.

[30] B. L. Wajchenberg, "Subcutaneous and visceral adipose tissue: their relation to the metabolic syndrome," *Endocrine Reviews*, vol. 21, no. 6, pp. 697–738, 2000.

[31] D. Viggiano, G. de Filippo, D. Rendina et al., "Screening of metabolic syndrome in obese children: a primary care concern," *Journal of Pediatric Gastroenterology and Nutrition*, vol. 49, no. 3, pp. 329–334, 2009.

[32] E. A. H. Sims, "Are there persons who are obese, but metabolically healthy?" *Metabolism*, vol. 50, no. 12, pp. 1499–1504, 2001.

SAGE-Hindawi Access to Research
International Journal of Hypertension
Volume 2011, Article ID 835805, 8 pages
doi:10.4061/2011/835805

Review Article

Addressing the Common Pathway Underlying Hypertension and Diabetes in People Who Are Obese by Maximizing Health: The Ultimate Knowledge Translation Gap

Elizabeth Dean,[1] Constantina Lomi,[2] Selma Bruno,[3] Hamzeh Awad,[4] and Grainne O'Donoghue[5]

[1] *Department of Physical Therapy, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada V6T 1Z3*
[2] *Department of Physiotherapy, Akmi Metropolitan College, 15125 Athens, Greece*
[3] *Departamento de Fisioterapia, Universidade Federal do Rio Grande do Norte, 59072-970 Natal, RN, Brazil*
[4] *Department of Prevention and Care of Diabetes, Faculty of Medicine, Dresden University of Technology and Ludwig-Maximilian University, 80336 Munich, Germany*
[5] *Department of Physiotherapy, School of Public Health, Physiotherapy, and Population Science, University College Dublin, Dublin 4, Ireland*

Correspondence should be addressed to Elizabeth Dean, elizabeth.dean@ubc.ca

Received 17 December 2010; Accepted 11 January 2011

Academic Editor: Kazuko Masuo

In accordance with the WHO definition of health, this article examines the alarming discord between the epidemiology of hypertension, type 2 diabetes mellitus (T2DM), and obesity and the low profile of noninvasive (nondrug) compared with invasive (drug) interventions with respect to their prevention, reversal and management. Herein lies the ultimate knowledge translation gap and challenge in 21st century health care. Although lifestyle modification has long appeared in guidelines for medically managing these conditions, this evidence-based strategy is seldom implemented as rigorously as drug prescription. Biomedicine focuses largely on reducing signs and symptoms; the effects of the problem rather than the problem. This article highlights the evidence-based rationale supporting prioritizing the underlying causes and contributing factors for hypertension and T2DM, and, in turn, obesity. We argue that a primary focus on maximizing health could eliminate all three conditions, at best, or, at worst, minimize their severity, complications, and medication needs. To enable such knowledge translation and maximizing health outcome, the health care community needs to practice as an integrated team, and address barriers to effecting maximal health in all patients. Addressing the ultimate knowledge translation gap, by aligning the health care paradigm to 21st century needs, would constitute a major advance.

1. Introduction

In accordance with the WHO definition of health and its conceptualization of health and disability (International Classification of Functioning, Disease, and Health) [1, 2], this article examines the alarming discord between the epidemiology of hypertension, type 2 diabetes mellitus, and obesity and the low profile of exploiting noninvasive interventions compared with invasive interventions (drugs) with respect to their prevention and reversal as well as management. Since the last half of the 20th century, lifestyle-related conditions have been among the leading causes of morbidity and premature death in middle-income and low-income countries as well as high-income countries (paralleling economic development in the former) [3, 4]. Lifestyle-related conditions include hypertension, type 2 diabetes mellitus, obesity as well as ischemic heart disease, smoking-related conditions, stroke, and many cancers [5]. On examining the causes and contributing factors to these conditions, some common lifestyle behaviors have been unequivocally implicated. The lifestyle behaviors that are associated with or contribute to common lifestyle-related

Table 1: Major modifiable risk factors for chronic lifestyle-related conditions.

Risk factor	Cardiovascular (ischemic heart disease & hypertension) and peripheral vascular disease	Chronic obstructive lung disease	Stroke	Type 2 diabetes mellitus	Cancer
Smoking	X	X	X	X	X (↑ risk of all-cause cancer*)
Physical inactivity	X		X	X	X
Obesity	X		X	X	X
Nutrition	X		X	X	X
High blood pressure	X		X	X	
Dietary fat†/blood lipids	X		X	X	X
Elevated glucose levels	X		X	X	X
Alcohol‡	X		?	X	X

* Smoking is not only related to cancer of the nose, mouth, airways, and lungs, but smoking also increases the risk of all-cause cancer.
† Partially saturated, saturated, and trans fats are the most injurious to health.
‡ Alcohol can be protective in moderate quantities, red wine in particular.
Sources: references [10–12].

conditions are shown in Table 1. This evidence supports that lifestyle-related conditions are largely multifactorial rather than resulting from one cause. When an individual is diagnosed with a lifestyle-related condition, the probability that he or she has more than one unhealthy lifestyle behavior is high, for example, smokers tend to exercise less; people who watch television for many hours daily tend to be overweight compared with those who watch television less; those who are not physically active tend to eat less healthfully [6–8]. Collectively, Western lifestyle behaviors have been predicted to limit life expectancy of this generation of children as well as contribute to many years of living with one or more chronic lifestyle-related conditions [9]. Although the relationship between lifestyle and chronic conditions has been well established, addressing lifestyle and behavior change has lagged being fully integrated into contemporary health care practice.

The general purpose of this article is to enable health care practitioners to better address the ultimate knowledge translation gap in their practices, that is, the link between lifestyle behavior choices and conditions such as hypertension, type 2 diabetes mellitus, and obesity. Specifically, we identify the common pathway that may lead to hypertension and type 2 diabetes mellitus in people who are obese. We argue that addressing this common pathway in routine practice through effective multiple health behavior change can be integrated readily and has several benefits; first, potential causes rather than simply the signs and/or symptoms are addressed. Addressing the causes helps maximize the individual's health overall given the etiological commonalities of these conditions which are also related to ischemic heart disease and some cancers, and helps to minimize the potential for iatrogenic effects of the conventional biomedical management of these conditions, as well as cascade iatrogenesis (treating the side effects of the treatment for the side effects of biomedical intervention). In turn, addressing the etiological and/or contributing lifestyle-related behaviors helps to maximize health-related quality of life and, in the event the individual becomes ill or disabled, helps to maximize their medical and surgical outcomes. The cost of not addressing the potential causes of lifestyle-related conditions as a priority is unsustainable and not best practice, given the evidence and the documented effect sizes of healthy living on health-related outcomes. Finally, the barriers as well as the facilitators to multiple health behavior change being a universally accepted clinical competency across the health care professions are presented.

2. The Common Pathway: Lifestyle-Related Behaviors

A paradigm shift has occurred in health care priorities over the past 60 years, that is, from acute infectious disease where an individual would tend to have one offending microorganism to lifestyle-related conditions that tend to be multifactorial [13, 14]. A reductionistic model provides a lens that looks for a problem usually a sign or symptom that can be targeted by one or more drugs. This model had some utility in the era of acute infectious disease; however, its applicability to the complexity of chronic lifestyle-related conditions appears limited given the increasing prevalence of hypertension, type 2 diabetes mellitus, and obesity. Through the lens of a noninvasive practitioner who exploits nondrug and nonsurgical interventions, the signs and symptoms of chronic lifestyle-related conditions are viewed largely as effects, and these need to be remediated by modifying the causes or contributing factors related to lifestyle. Medication does not always ensure effective control of blood pressure or blood sugar when left to real-world nonlaboratory contingencies. Further, a patient may believe that medication can control blood pressure or blood sugar better than they can and that this will offset the effect of poor lifestyle choices.

New terms such as obesogenic and diabetogenic have emerged in the common vernacular to describe Western society. Since World War II, economic growth has been associated with the evolution of convenience foods and the fast food industry (associated with mass-produced food products that are high in fat and sugar, hence, calories, and salt, preservatives, flavor enhances, colorants, and other additives). Packaged and easily prepared foods are associated with less nutritional value and additives to enhance shelf life and appearance. Good nutrition including a range of micro and macro nutrients is needed for optimal health and wellbeing, healing and repair, immunity, as well as energy. The Western diet is suboptimal nutritionally and has been described as monotonous and unbalanced. Compared with dietary regimes such as Mediterranean and Asian diets, the typical Western diet contributes to the high prevalence of ischemic heart disease, hypertension, stroke, and cancer as well as type 2 diabetes mellitus, and overweight and obesity [4, 14]. Further, some authorities have argued that lobbyists have influenced the nutrition guidelines that in previous years endorsed excessive saturated fat, sugar, meat consumption, and refined carbohydrates [15–17]. In turn, it is adherence to these guidelines that has contributed to lifestyle-related conditions in recent decades.

An individual who is obese with diagnoses of hypertension and type 2 diabetes mellitus often has a profile reflecting prolonged unhealthy lifestyle practices, potentially since childhood, which eventually become preferences. As a child, he or she may have been exposed to a diet higher than recommended in salt, sugar, refined foods, and fat (particularly saturated fat) which developed personal preferences early in life. In addition, comparable to smoking, children mimic the activity patterns of their families particularly their guardians or parents [18]. Similarly, other behaviors are likely to be mimicked, for example, hours of daily television viewing (often associated with snacking calorie-dense nonnutritious foods), or computer or video game use. Evidence over the past decade shows that the effects of sedentary living are distinct from low levels of physical activity [19, 20]. Prolonged periods of being sedentary are associated with health risk even if an individual exercises aerobically the recommended three times a week at a moderate intensity for 30 minutes. Like obesity, hypertension and type 2 diabetes mellitus develop over many years with prolonged exposure to factors that adversely affect vascular resistance and glucose metabolism, specifically, insulin sensitivity and resistance. Conversely, assuming healthy dietary habits (the Dash diet and diabetic diet which share common elements), less sitting coupled with regular daily physical activity, along with smoking cessation would do much to eliminate high blood pressure and type 2 diabetes mellitus in many patients, or at least reduce their manifestations and in turn their dire consequences.

Finally, systemic low-level inflammation has been identified as a common denominator in the chronic lifestyle-related conditions. Such inflammation has been associated with the Western diet and inactivity [21, 22]. Maximizing healthy lifestyle choices needs to be a focus of healthy societies to reduce the injurious effects of chronic inflammation even if considered low grade.

3. Effectiveness of Multiple Health Behavior Change

Health promotion practice needs to be integrated into the practices of contemporary health care professionals given the prevalence of lifestyle-related conditions and their being the leading causes of morbidity, disability, and premature death [23]. Based on the substantial body of evidence supporting the effectiveness of healthy living including not smoking, optimal weight and nutrition, and regular physical activity, new paradigms of practice are being called for that promote healthy living as a primary intervention. Recently, a paradigm of practice aligned with epidemiological need and the body of knowledge supporting the effectiveness of noninvasive interventions has been advanced for physical therapists in the 21st century [24]. Physical therapists are the quintessential established noninvasive health care professionals that need to take a lead in advancing the exploitation of noninvasive interventions in the prevention, reversal, and management of chronic lifestyle-related conditions. They serve as an example of a key health care profession capable of practicing shoulder to shoulder with physicians and surgeons to promote the best noninvasive approaches for a given patient.

The integration of health promotion into the practices of health professionals would help bridge the ultimate knowledge translation gap between the knowledge and power of healthy living, and the prevalence of lifestyle-related conditions. Health promotion practice, however, may be undervalued in that its outcomes are more challenging to identify than ill health outcomes. Health promotion practice raises the question of how much behavior change is needed to translate into better health. Studies are now addressing this critical question. In sum, not much change is needed. Excessive blood pressure can decrease with small amounts of weight loss [25] with commensurate reduction in health risk. In a recent study of over 23,000 people between 35 and 65 years old, Ford and colleagues [26] reported that over an eight-year period, people who did not smoke, had a body mass index of less than 30, were physically active for a minimum of 3.5 hours a week, and followed healthy nutritional principles, had a 78% lower risk of developing a chronic condition. Specifically, the risk of type 2 diabetes mellitus was reduced by 93%, myocardial infarction by 81%, stroke by 50%, and cancer by 36%. Even if not all four health factors were present, risk of developing a chronic lifestyle-related condition decreased commensurate with an increase in the number of positive lifestyle factors. Not only can few drugs replicate these effect sizes, but the absence of side effects, and the cost effectiveness of healthy living, not to mention ethical issues, are compelling reasons for exploiting healthy living maximally and minimizing ill health so that those individuals who really need this expensive care can receive it in a timely manner with the potential for the best outcomes. This warrants being done systematically

and always in conjunction with medical interventions as outcomes overall will likely be superior.

4. Integrating Multiple Health Behavior Change as a Priority into Practice

That the physician can assume full responsibility for holistic patient management is neither realistic nor feasible. The healthcare environment has changed radically since the era of infectious disease when there was a clear microorganism and a well-defined pharmacologic intervention that could be simply identified and managed. Infectious conditions tend to have similar profiles on presentations. Lifestyle-related conditions including those that affect the vasculature however fit this model less well. Their etiologies and manifestations are complex and multisystemic, and patients present differently despite some commonalities in the etiological lifestyle contributing factors. The etiologic health behaviors that underlie the causative factors need to be teased out systematically to address them maximally in every individual, including children who are exhibiting the risk factors of lifestyle-related conditions (e.g., high blood pressure, abnormal cholesterol, triglycerides, and blood glucose, and excess body weight and abnormal mass distribution, and deconditioning) [27]. In mainstream health care practice this century, vital signs have become reflective of lifestyle-related conditions. In adults, healthy blood pressure is ideally below 120/80 mm Hg [28], body mass index between 18.5 and 24.9 [29], and waist to hip ratio less than 0.85 for women and 0.90 for men [30]. To maximize such outcomes, the current healthcare environment calls for an integrated interprofesssional approach [31] to improve the effectiveness and efficiency of care.

Of the established health care professions, physical therapy is the leading noninvasive health care profession [32]. For almost 100 years, physical therapy has been associated with noninvasive interventions, specifically, health education and exercise to promote health, prevent disease, and manage conditions. The quintessential clinical competency in the 21st century of health care providers including physical therapists has been described as effecting multiple health behavior change [32, 33]. Changes in diet and physical activity levels can have profound effects on health outcomes such as reducing blood pressure and reducing blood sugar within days or weeks, and reducing weight over time, see recent reviews [32, 33]. The success of these simple interventions rests with the quality of the education from the relevant health care providers, as well as patient adherence and systematic followup. This suggests that health assessment and health education warrant being primary clinical competencies of health care practitioners in the 21st century regardless of the patient's primary complaint or problem. Although physicians are primarily qualified as invasive practitioners specializing in the optimal use of drugs and surgery, it behooves them to practice alongside noninvasive practitioners to best address a patient's health issues and maximize the effects of drugs or surgery. Physicians need to know when to refer to other health care practitioners; this is a collegial synergistic approach that effects the best outcome, short and long term, for the patient.

Although health education and lifestyle-related changes are mentioned in established guidelines for the management of all three conditions, namely, hypertension, type 2 diabetes mellitus, and obesity, seldom are they addressed as one entity having a common pathway which is highly modifiable through health behavior change. The literature on health behavior change, however, remains largely to be integrated into mainstream health care [34].

Western foods often have high sodium or salt content. In addition, foods high in sodium are typically associated with convenience and suboptimal nutrition, hence, are obesogenic and diabetogenic. In addition, the benefits of the Dash diet to stop hypertension [35, 36] have been well known for almost two decades, it supports the general health benefits associated with dietary regimens that are high in multigrains, vegetables, and are low in fat and sugar. Such a dietary regimen is optimal for the health of people in general, not only those with hypertension [37, 38]. The wide range of unhealthy food options despite the public's knowledge about healthy lifestyles adds to the challenge of promoting healthful eating. One prime example is salt consumption. An overriding simple solution is restricting added salt to foods. A one-third reduction of salt intake by the average American (from 3400 mg to 2300 mg daily) would reduce cases of hypertension, the second leading causes of death in the United States, by 11 million, and lower health care costs by $17.8 billion [39].

Smoking tobacco is associated with the inhalation of nicotine, a well-known vasoconstrictor, thus, smokers are prone to hypertension, ischemic heart disease, and stroke which has been well documented for many years [40]. Smokers also have poorer health behaviors than nonsmokers including poorer diets and inactivity [41]. In North America, smoking reduction over the past 40 years largely paralleled strict legislative controls on the selling and marketing of tobacco products, and increased taxation. More recently, tobacco smoking has been restricted in many countries with national policies and city by-laws prohibiting smoking in public places. Canada has been a leader in this area [42, 43]. At the clinical level, even brief advice by a health care provider helps smokers eventually quit [44].

The lack of physical activity has been described as the most critical disease of the past and present centuries in high-income countries [45]. Inactivity has not only been directly associated with hypertension, type 2 diabetes mellitus, and obesity, but it doubles their risks.

Given the interrelationships among lifestyle behaviors and the triad of hypertension, type 2 diabetes mellitus, and overweight and obesity, a reductionistic biomedical approach (a specific medication is prescribed for hypertension or type 2 diabetes mellitus) will likely be suboptimal in addressing their common pathway, and effecting lifelong health and wellbeing. In addition, the patient may be less likely to appreciate the common pathway if conditions are compartmentalized in this manner.

The health care practitioners of the 21st century need to have clinical competencies related to multiple health

behavior change. They need the capacity to motivate people to sustain lifelong health behavior change [34, 46], to assess readiness to change and gauge health behavior change strategies to a person's needs at a given time [47], to engage the family and take advantage of social contagion effects of positive health behaviors [48], and serve as a role model with positive attitudes toward maximal health [49]. In fact, patients are receptive to advice from health care professionals that they perceive as supportive and nonjudgmental [50, 51].

To change the course of lifestyle-related conditions, effective interprofessional team work is needed. The composition of the team that needed in the 21st century extends beyond the traditional team of physician, nurse, and pharmacist. It needs to include those who specialize in noninvasive, that is, nondrug and nonsurgical, interventions, including physical therapists, nutritionists, and counselors.

A new approach in contemporary health care is improved sharing of skills, expertise, and competencies. In addition, such an approach includes triaging patients to balance the need for noninvasive and invasive strategies for prevention, reversal, and management. The goal is to wean a patient off medications as much as possible after healthy living has had an opportunity to have a maximal effect.

Many authorities would concur that health care costs reflect doctor and hospital care, and the cost of medication [52]. This model of care is not sustainable and raises some serious ethical questions given that the evidence supports that healthy living [26] can reduce the risk of type 2 diabetes mellitus by 93%, ischemic heart disease by 73%, stroke by 50%, and cancer by 30%.

Maximizing health promotion in daily medical practice has the potential for increasing the threshold for chronic lifestyle-related conditions and reducing their rate of progression. If the end of life is viewed as the convergence of these two points, the end of life could be shifted such that premature death is offset with reduced end of life morbidity and disability (Figure 1). Health behaviors and outcomes can easily be tracked over time to provide both the practitioner and the patient with feedback about the patient's health behaviors and where the practitioner needs to focus further or refer the patient to another profession. An example of an insert to a chart to track health behavior change and outcomes appears in Table 2. Such a log enables the practitioner to target specific lifestyle changes needed and log lifestyle recommendations more effectively, engage other health care professionals, or both.

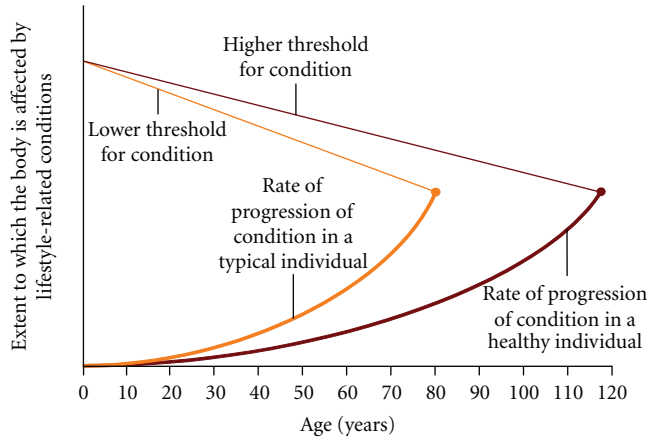


Figure 1: Theoretical relationship between the threshold of lifestyle-related conditions and their rate of progression over the life cycle. Horizontal axis: age. Vertical axis: extent to which the body is affected by lifestyle-related conditions. Top light line: threshold for chronic conditions with average Western lifestyle. Lower light line: rate of progression of chronic conditions with average Western lifestyle. Top dark line: threshold for chronic conditions with a healthy lifestyle. Lower dark line: rate of progression of chronic conditions with a healthy lifestyle.

5. Revisiting Conservative Approaches: Ethical Issues

Access to high-tech medicine and drugs are equated with quality health care. From the noninvasive practitioner's perspective, one would argue that the exploitation of healthy living would help minimize the need for biomedical intervention and, if needed, would reduce the level of intervention required and enhance outcomes. In recent decades, much attention has been given to ethical practice, specifically, the right treatment for the right condition for the right patient at the right time. However, what such a philosophy does not address is "what is the right treatment?" Some base this on the results of studies that have been rated as being of high quality and published in a reputable peer-reviewed journal with preferably a high impact factor. Often, however, a limitation of such studies is the lack of healthy control groups or stratification of the data in the analysis to examine the impact of good health on the outcomes of interest. It is likely that in many published studies, if this was done, that good health would trump the outcomes of drug intervention. Thus, on ethical grounds, studies related to the prevention, reversal, and management of chronic lifestyle-related conditions, need to include a healthy control group whenever feasible and appropriate, or analyze the data stratified-based indices of good health and health behaviors.

In a civil society, no patient should be denied treatment when needed. However, the invasive versus noninvasive balance needs to be addressed to establish the best treatment for a given patient. Most health care professionals would embrace the Hippocratic tenets of "first do no harm" and "the function of protecting and developing health must rank even above that of restoring it when it is impaired"; however, the practice of these tenets remains to be fully integrated into team-based health care practice. Some authorities have argued that health care is being influenced by corporate interests that are focused on the creation of disorders for which unique and expensive drugs are needed [53]. The power of pharmaceutical companies in directing an illness care versus health care agenda could seriously undermine the outcomes of noninvasive practitioners, for example, given their outcomes require long-term motivation, engagement, participation, commitment by the patient to effect lifelong health, and systematic followups.

Table 2: Monitoring multiple health behavior change over time: short-form template for assessing and evaluating behaviors associated with chronic lifestyle-related conditions.

Lifestyle choices and behaviors	Initial assessment date	Followup date	Followup date
Smoking status			
Nonsmoker or continuing not to smoke			
Smoking (cigarettes per day)			
Nutritional Status			
Processed foods (e.g., deli meats)			
Convenience foods (fast food)			
Soda pop (cans)			
For items below see daily serving size guide			
Vegetables			
Fruit			
Whole grains			
Meat (type)			
Fish (type)			
Milk (specify whole milk or fat reduced)			
Cheese			
Added sugar			
Added salt			
Saturated fat (animal fat, butter)			
Unsaturated fat (vegetable oils)			
Servings of mayo, prepared relishes, cats-up, gravy, margarine			
Body composition			
Weight			
Height			
Body mass index (weight in kg/height in m^2)			
Waist girth			
Hip girth			
Waist-to-hip ratio			
Activity status: sedentary activity, physical activity, and structured exercise			
Sedentary activity (daily hours television watching or in front of a computer screen)			
General physical activity (general walking and getting around, taking public transportation)			
Structured exercise (e.g., yoga, tai chi, aerobic exercise such as walking, swimming, jogging, cycling, and strengthening with weights or bands)			
Type-intensity-duration-frequency—for how long overall (weeks or months)			
Type-intensity-duration-frequency—for how long overall (weeks or months)			
Type-intensity-duration-frequency—for how long overall (weeks or months)			

Finally, a physician who fails to prescribe an established medication to a patient for a given problem would come under professional scrutiny, with the potential for discipline, if the patient had an untoward event. Paradoxically, practitioners who fail to prescribe evidence-based noninvasive interventions such as health education and exercise that can prevent, in some cases reverse as well as manage chronic lifestyle-related conditions, such as hypertension and type 2 diabetes mellitus (as well as obesity), and are associated with lifelong benefits, appear not to be held to a comparable standard of accountability. This needs to change. Noninvasive practitioners who exploit health education and exercise need to be accountable for exploiting these interventions particularly in the interest of being responsive to current global health priorities. Such an approach would help augment the medical outcomes of

physicians. This approach is philosophically consistent with both the wise tenets of Hippocrates for doing no harm and protecting health, to which most health care professionals would aspire, and health care based on the highest level of evidence.

6. Conclusion

Although lifestyle-related conditions such as hypertension, type 2 diabetes mellitus, and obesity have clinical distinctions, they share a common etiological pathway which contributes to their frequent coexistence. By addressing the common pathway through intensive targeted lifestyle behavior change, the reduced "signal-to-noise" in their patients' presentations would expedite their diagnoses, target their medications better, and achieve improved health outcomes with their patients. In turn, the long-term health of patients would be maximized, health care costs would be reduced, as well as the social burden of these conditions on families, communities and countries. This will best be achieved with a shoulder-to-shoulder relationship of invasive care practitioners (physicians) with noninvasive care practitioners (counselors, nutritionists, and physical therapists) to establish the optimal lifestyle program for a patient (and potentially the family) with a view to minimize need for or reliance on medication and the need for surgery in some cases.

References

[1] World Health Organization, "Definition of Health," 1984, http://www.who.int/about/definition.

[2] World Health Organization, "International Classification of Functioning, Disability and Health," 2002, http://www.sustainable-design.ie/arch/ICIDH-2PFDec-2000.pdf.

[3] World Health Organization, "Integrating prevention into health care. Fact sheet 172," 2010, http://www.who.int/mediacentre/factsheets/fs172/en/.

[4] R. Beaglehole and D. Yach, "Globalisation and the prevention and control of non-communicable disease: the neglected chronic diseases of adults," *Lancet*, vol. 362, no. 9387, pp. 903–908, 2003.

[5] World Health Organization, "Priority noncommunicable diseases and conditions," 2010, http://www.wpro.who.int/NR/rdonlyres/E72A001F-E6E1-4AB7-B33C-1C77F4FEF8FC/0/13_Chapter8.

[6] M. L. Neuhouser, D. L. Miller, A. R. Kristal, M. J. Barnett, and L. J. Cheskin, "Diet and exercise habits of patients with diabetes, dyslipidemia, cardiovascular disease or hypertension," *Journal of the American College of Nutrition*, vol. 21, no. 5, pp. 394–401, 2002.

[7] A. F. Subar, L. C. Harlan, and M. E. Mattson, "Food and nutrient intake differences between smokers and non-smokers in the US," *American Journal of Public Health*, vol. 80, no. 11, pp. 1323–1329, 1990.

[8] S. J. Sherman, J. S. Rose, K. Koch, C. C. Presson, and L. Chassin, "Implicit and explicit attitudes toward cigarette smoking: the effects of context and motivation," *Journal of Social and Clinical Psychology*, vol. 22, no. 1, pp. 13–39, 2003.

[9] S. J. Olshansky, D. J. Passaro, R. C. Hershow et al., "A potential decline in life expectancy in the United States in the 21st century," *New England Journal of Medicine*, vol. 352, no. 11, pp. 1138–1145, 2005.

[10] The Heart and Stroke Foundation of Canada, 2010, http://www.heartandstroke.com/site/c.ikIQLcMWJtE/b.3479403/k.BF78/Health_Information.htm.

[11] J. C. Bradberry, "Peripheral arterial disease: pathophysiology, risk factors, and role of antithrombotic therapy," *Journal of the American Pharmacists Association*, vol. 44, no. 2, supplement 1, pp. S37–S44, 2004.

[12] N. Charkoudian and M. J. Joyner, "Physiologic considerations for exercise performance in women," *Clinics in Chest Medicine*, vol. 25, no. 2, pp. 247–255, 2004.

[13] P. M. Lantz, J. S. House, J. M. Lepkowski, D. R. Williams, R. P. Mero, and J. Chen, "Socioeconomic factors, health behaviors, and mortality: results from a nationally representative prospective study of US adults," *Journal of the American Medical Association*, vol. 279, no. 21, pp. 1703–1708, 1998.

[14] A. H. Mokdad, E. S. Ford, B. A. Bowman et al., "Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001," *Journal of the American Medical Association*, vol. 289, no. 1, pp. 76–79, 2003.

[15] M. Nestle, "Food lobbies, the food pyramid, and U.S. nutrition policy," *International Journal of Health Services*, vol. 23, no. 3, pp. 483–496, 1993.

[16] O. Dyer, "US government rejects WHO's attempts to improve diet," *British Medical Journal*, vol. 328, no. 7433, p. 185, 2004.

[17] M. Nestle, "The ironic politics of obesity," *Science*, vol. 299, no. 5608, p. 781, 2003.

[18] S. S. Gidding, "Preventive pediatric cardiology. Tobacco, cholesterol, obesity, and physical activity," *Pediatric Clinics of North America*, vol. 46, no. 2, pp. 253–262, 1999.

[19] G. N. Healy, D. W. Dunstan, J. Salmon et al., "Breaks in sedentary time. Beneficial associations with metabolic risk," *Diabetes Care*, vol. 31, pp. 661–666, 2008.

[20] A. A. Thorp, G. N. Healy, N. Owen et al., "Deleterious associations of sitting time and television viewing time with cardiometabolic risk biomarkers," *Diabetes Care*, vol. 33, no. 2, pp. 327–334, 2010.

[21] H. Bruunsgaard, "Physical activity and modulation of systemic low-level inflammation," *Journal of Leukocyte Biology*, vol. 78, no. 4, pp. 819–835, 2005.

[22] A. P. Simopoulos, "Evolutionary aspects of diet, the omega-6/omega-3 ratio and genetic variation: nutritional implications for chronic diseases," *Biomedicine and Pharmacotherapy*, vol. 60, no. 9, pp. 502–507, 2006.

[23] J. P. Alegrante, J. C. Perterson, C. Boutin-Foster, G. Ogedegbe, and M. E. Charleson, "Multiple health-risk behavior in a chronic disease population: what behaviors do people choose to change?" *Preventive Medicine*, vol. 46, pp. 247–251, 2008.

[24] E. Dean, "Physical therapy practice in the 21st century: a new evidence-informed paradigm and implications," *Physiotherapy Theory and Practice*, vol. 25, no. 5-6, pp. 327–462, 2009.

[25] F. V. Costa, "Non-pharmacological treatment of hypertension in women," *Journal of Hypertension*, vol. 20, no. 2, pp. S57–S61, 2002.

[26] E. S. Ford, M. M. Bergmann, J. Kröger, A. Schienkiewitz, C. Weikert, and H. Boeing, "Healthy living is the best revenge: findings from the European prospective investigation into cancer and nutrition-potsdam study," *Archives of Internal Medicine*, vol. 169, no. 15, pp. 1355–1362, 2009.

[27] G. S. Berenson, S. R. Srinivasan, W. Bao, W. P. Newman 3rd, R. E. Tracy, and W. A. Wattigney, "Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults," *New England Journal of Medicine*, vol. 338, no. 23, pp. 1650–1656, 1998.

[28] American Heart Association Recommendations. High blood pressure, 2010, http://www.americanheart.org/presenter.jhtml?identifier=4623.

[29] Health Canada. Body mass index, 2010, http://www.hc-sc.gc.ca/fn-an/nutrition/weights-poids/guide-ldadult/bmi_chart_java-graph_imc_java-eng.php.

[30] S. Yusuf, S. Hawken, S. Ôunpuu et al., "Obesity and the risk of myocardial infarction in 27 000 participants from 52 countries: a case-control study," *Lancet*, vol. 366, no. 9497, pp. 1640–1649, 2005.

[31] P. G. Clark, "What is interprofessional health?" *Journal of Interprofessional Care*, vol. 7, pp. 219–220, 1993.

[32] E. Dean, "Physical therapy in the 21st century—part 2: evidence-based practice within the context of evidence-informed practice," *Physiotherapy Theory and Practice*, vol. 25, no. 5-6, pp. 354–368, 2009.

[33] E. Dean, "Physical therapy in the 21st century—part 1: toward practice informed by epidemiology and the crisis of lifestyle conditions," *Physiotherapy Theory and Practice*, vol. 25, no. 5-6, pp. 330–353, 2009.

[34] T. V. Achterberg, G. G. J. Huisma-De Waal, N. A. B. Ketelaar, R. A. Oostendorp, J. E. Jacobs, and H. C. H. Wolldersheim, "How to promote healthy behaviours in patients? An overviewof evidence for behaviour change techniques," *Health Promotion International*. In press.

[35] L. J. Appel, T. J. Moore, E. Obarzanek et al., "A clinical trial of the effects of dietary patterns on blood pressure," *New England Journal of Medicine*, vol. 336, no. 16, pp. 1117–1124, 1997.

[36] F. M. Sacks, E. Obarzanek, M. M. Windhauser et al., "Rationale and design of the Dietary Approaches to Stop Hypertension trial (DASH): a multicenter controlled-feeding study of dietary patterns to lower blood pressure," *Annals of Epidemiology*, vol. 5, no. 2, pp. 108–118, 1995.

[37] United States Department of Health and Human Services, Consumer Information Center. The food guide pyramid, 2010, http://www.usda.gov/.

[38] Health Canada. Canada's Food Guide, 2010, http://www.hc-sc.gc.ca/fn-an/food-guide-aliment/indexeng.php.

[39] Report of the Institute of Medicine of the National Academy of Sciences. IOM report declares high blood pressure a neglected disease, calls for strategies to change Americans' lifestyles and diets to curb hypertension, 2010.

[40] J. E. Fielding, "Smoking: health effects and control," *New England Journal of Medicine*, vol. 313, no. 8, pp. 491–498, 1985.

[41] T. L. Conway and T. A. Cronan, "Smoking, exercise, and physical fitness," *Preventive Medicine*, vol. 21, no. 6, pp. 723–734, 1992.

[42] M. Asbridge, "Public place restrictions on smoking in Canada: assessing the role of the state, media, science and public health advocacy," *Social Science and Medicine*, vol. 58, no. 1, pp. 13–24, 2004.

[43] J. Drope and S. Glantz, "British Columbia capital regional district 100% smokefree bylaw: a successful public health campaign despite industry opposition," *Tobacco Control*, vol. 12, no. 3, pp. 264–268, 2003.

[44] M. E. Bodner and E. Dean, "Advice as a smoking cessation strategy: a systematic review and implications for physical therapists," *Physiotherapy Theory and Practice*, vol. 25, no. 5-6, pp. 369–407, 2009.

[45] World Health Organization. Physical inactivity leading cause of disease and disability, 2010, http://www.who.int/mediacentre/news/releases/release23/en/index.html.

[46] N. C. H. Stott and R. M. Pill, "'Advise yes, dictate no'. Patients' views on health promotion in the consultation," *Family Practice*, vol. 7, no. 2, pp. 125–131, 1990.

[47] J. O. Prochaska and C. C. DiClemente, "Transtheoretical therapy: towards a more integrative model of change," *Psychother*, vol. 19, pp. 276–288, 1982.

[48] N. A. Christakis and J. H. Fowler, "The spread of obesity in a large social network over 32 years," *New England Journal of Medicine*, vol. 357, no. 4, pp. 370–379, 2007.

[49] M. Danzinger, "Tight white-coat syndrome: physician heal thyself," 2006, http://www.medscape.com/viewarticle/531752.

[50] R. E. Glasgow, L. M. Klesges, D. A. Dzewaltowski, S. S. Bull, and P. Estabrooks, "The future of health behavior change research: what is needed to improve translation of research into health promotion practice?" *Annals of Behavioral Medicine*, vol. 27, no. 1, pp. 3–12, 2004.

[51] M. W. Kreuter, S. G. Chheda, and F. C. Bull, "How does physician advice influence patient behavior? Evidence for a priming effect," *Archives of Family Medicine*, vol. 9, no. 5, pp. 426–433, 2000.

[52] S. Woolhandler, T. Campbell, and D. U. Himmelstein, "Costs of health care administration in the United States and Canada," *New England Journal of Medicine*, vol. 349, no. 8, pp. 768–775, 2003.

[53] R. Moynihan and A. Cassels, *Selling Sickness. How the World's Biggest Pharmaceutical Companies are Turning us all into Patients*, Greystone Books, Toronto, Canada, 2005.

SAGE-Hindawi Access to Research
International Journal of Hypertension
Volume 2011, Article ID 391762, 8 pages
doi:10.4061/2011/391762

Review Article

Insulin Resistance, Obesity, Hypertension, and Renal Sodium Transport

Shoko Horita, George Seki, Hideomi Yamada, Masashi Suzuki, Kazuhiko Koike, and Toshiro Fujita

Department of Internal Medicine, Faculty of Medicine, The University of Tokyo 7-3-1, Hongo, Bunkyo, Tokyo 113-8655, Japan

Correspondence should be addressed to George Seki, georgeseki-tky@umin.ac.jp

Received 14 January 2011; Accepted 16 February 2011

Academic Editor: Kazuko Masuo

Sodium transport through various nephron segments is quite important in regulating sodium reabsorption and blood pressure. Among several regulators of this process, insulin acts on almost all the nephron segments and is a strong enhancer of sodium reabsorption. Sodium-proton exchanger type 3 (NHE3) is a main regulator of sodium reabsorption in the luminal side of proximal tubule. In the basolateral side of the proximal tubule, sodium-bicarbonate cotransporter (NBCe1) mediates sodium and bicarbonate exit from tubular cells. In the distal nephron and the connecting tubule, epithelial sodium channel (ENaC) is of great importance to sodium reabsorption. NHE3, NBCe1, and ENaC are all regulated by insulin. Recently with-no-lysine (WNK) kinases, responsible for familial hypertension, stimulating sodium reabsorption in the distal nephron, have been found to be also regulated by insulin. We will discuss the regulation of renal sodium transport by insulin and its roles in the pathogenesis of hypertension in insulin resistance.

1. Introduction

Obesity is frequently accompanied with hypertension [1]. Obesity is, at the same time, closely related to hyperinsulinemia and insulin resistance [2]. While the precise mechanism of hypertension in insulin resistance remains to be clarified, the activation of sympathetic nerve system, the disorders dysregulation of central nerve system including leptin, and the activation of renin-angiotensin system are generally thought to be involved [1]. Although insulin has powerful stimulatory effects on renal sodium transport, it remains controversial whether hyperinsulinemia itself is a cause of hypertension.

Acute studies suggest that hyperinsulinemia may cause sodium retention and increased sympathetic activity, which will be an important cause of hypertension [3]. On the other hand, hyperinsulinemia due to insulinoma or chronic insulin infusion into animals do not significantly elevate blood pressure [4, 5]. Moreover, insulin itself has vasodilatory actions [6], which is dependent on nitric oxide [7]. Thus, the relationship between hyperinsulinemia and hypertension is not obvious.

However, the influence of insulin on blood pressure may be altered in insulin resistance. For example, the insulin-induced vasodilation is impaired due to defects in PI3-kinase signaling in insulin resistance [8, 9]. Moreover, several recent data suggest that the insulin-induced enhancement of renal sodium reabsorption is preserved or even enhanced in insulin resistance [10–12]. For example, Rocchini et al. showed that, in obese subjects with insulin resistance, urinary sodium excretion was decreased by insulin similarly as in nonobese subjects [11]. These considerations support a significant role of insulin-stimulated renal sodium transport in the pathogenesis of hypertension in insulin resistance. This review will focus mainly on the regulation of sodium reabsorption along the nephron segments by insulin and its roles in the blood pressure control. Figure 1 shows the main sodium transporters and regulators discussed in this review.

2. Insulin Acting Sites upon Nephron

It has been known for a long time, that insulin acts upon the whole nephron. Bourdeau et al. showed, using radioisotope technique that insulin is accumulated in the proximal tubule

[13]. Nakamura et al. showed that insulin binds upon various segments of rabbit nephron, among which it binds strongest upon thick ascending limb of Henle's loop and distal convoluted tubule [14]. In rat nephron, Butlen et al. showed that insulin is accumulated strongest in the proximal tubule, second in the pars recta and distal convoluted tubule [15]. The way that insulin arrives at the nephron seems to be by two ways: one is by glomerular clearance, and the other is peritubular clearance [16]. The former is by glomerular filtration and subsequent reabsorption from tubular cells by endocytosis, the latter is diffusion from peritubular capillaries and subsequent binding to the receptor.

3. Insulin and Renal Proximal Absorption

Insulin uptake in the renal proximal tubule has been reported on animals such as rabbits [13], rats [17], and dogs [18]. Importantly, insulin has been known to enhance sodium reabsorption in the proximal tubule [19]. Insulin stimulates not only sodium but also volume absorption in the rabbit proximal convoluted tubule. Regarding these stimulatory effects, insulin acts only from the basolateral side of the tubule, not from the luminal side [20]. Proximal tubules reabsorb about seventy percents of total Na filtered from glomeruli. Though important regulatory mechanisms exist afterwards in the Henle's loop, distal tubule and connecting tubule, the stimulation of Na reabsorption from proximal tubules may well contribute to the increase of total fluid volume in the individual, leading to hypertension.

Gesek and Schoolwerth proved that insulin directly increases the Na^+-H^+ exchanger type 3 (NHE3) activity in proximal tubules of rats [21]. This is important because NHE3 plays a major role in apical sodium entry in proximal tubules. Although the signaling pathway of insulin-mediated NHE3 activation remains unclear, Akt is known to play a critical role in the phosphoinositide 3-kinase- (PI3K-) mediated translocation of NHE3 into the apical membranes of proximal tubular cells [22–24]. The PI3K pathway has also chronic and posttranscriptional effects on the re-gulation of NHE3 mRNA in the proximal tubule cell [20, 25, 26].

It has been shown that Na-K-ATPase is also a target of insulin, contributing to the increase of Na reabsorption [27, 28]. Feraille et al. have showed that, in rat proximal convoluted tubule, insulin stimulates Na-K-ATPase activity [29]. Insulin is also known to stimulate the basolateral electrogenic Na-HCO_3 cotransporter (NBCe1), which plays a major role in sodium and bicarbonate exit from proximal tubular cells [30]. Therefore, insulin stimulates all the transporters involved in Na absorption from proximal tubules.

4. Insulin and Other Renal Tubules

4.1. Henle's Loop. Kirchner reported that insulin enhances chloride reabsorption in the Henle's loop of volume-expanded rats [31]. This showed a possibility that insulin may stimulate NaCl reabsorption in Henle's loop. Later, in rabbit kidney, it was shown that insulin directly stimulates NaCl reabsorption in Henle's loop [32]. Moreover, it was suggested that Na-K-2Cl cotransporter (NKCC2) and Na-K-ATPase are also involved in this stimulation [33]. Tsimaratos et al. have clarified that C-peptide, the cleavage product of proinsulin, stimulates Na-K-ATPase in rat thick ascending limb, which is mediated via protein kinase C (PKC) α pathway [34]. They also showed that C-peptide activates PKCα, which then stimulates the phosphorylation of Na-K-ATPase α-subunit.

As about twenty percents of Na reabsorption is accomplished at Henle's loop, stimulation of Na reabsorption here should have a substantial impact on whole-body Na homeostasis.

4.2. Distal Tubule and Connecting Tubule. In late tubule, including distal and connecting tubules, it is widely known that insulin stimulates the activity of amiloride-sensitive epithelial sodium channel (ENaC) [35]. A study using kidney-derived cell line has shown that the activation of ENaC by insulin results from an increase of ENaC channel density at the membrane [36]. Moreover, insulin is known to stimulate Na-K-ATPase in this segment [37, 38]. Consistent with these findings, DeFronzo et al. found that hyperinsulinemia and hyperglycemia enhance sodium reabsorption from distal tubule [19]. Some studies showed that insulin stimulates sodium transport via a signaling cascade involving PI3K, 3-phosphoinositide-dependent protein kinase (PDK1), and serum/glucocorticoid-kinase 1 (Sgk1) [39, 40]. In distal tubule, there are other transporters and kinases that are affected by insulin, such as with-no-lysine (WNK) kinases and sodium-chloride cotransporter (NCC), which we will discuss later.

Distal and connecting tubules regulate only about ten percents of total Na reabsorption in the nephron, but this process cannot be ignored as the final regulation of Na reabsorption.

5. IRS1/2, Hyperinsulinemia, Insulin Resistance, and Hypertension

Insulin receptor substrate (IRS) 1 was originally found through an attempt to find out the signal transduction system of insulin [41, 42]. $IRS1^{-/-}$ mice, however, survived with only a mild insulin resistance, which led to the identification of IRS2 [43]. The structures of IRS1 and IRS2 are quite similar to each other [44], but the signaling pathway is different [45]. IRS1 and IRS2 knockout mice develop mental retardation and insulin resistance [46, 47]. IRS-1 and IRS-2 differ in the tissue expression, the mechanism of insulin resistance, and the association of β-cell hyperplasia [48]. Some IRSs have been found later but IRS1 and IRS2 are the most important among the IRS family.

Our group compared the effects of insulin on proximal tubule absorption in wild-type, $IRS1^{-/-}$ and $IRS2^{-/-}$ mice [49]. In wild-type mice, insulin significantly stimulated Na-coupled HCO_3^- absorption from proximal tubule. In $IRS1^{-/-}$ mice, the stimulation of HCO_3^- absorption by insulin was preserved, but it was significantly attenuated in $IRS2^{-/-}$ mice. Moreover, the Akt phosphorylation induced

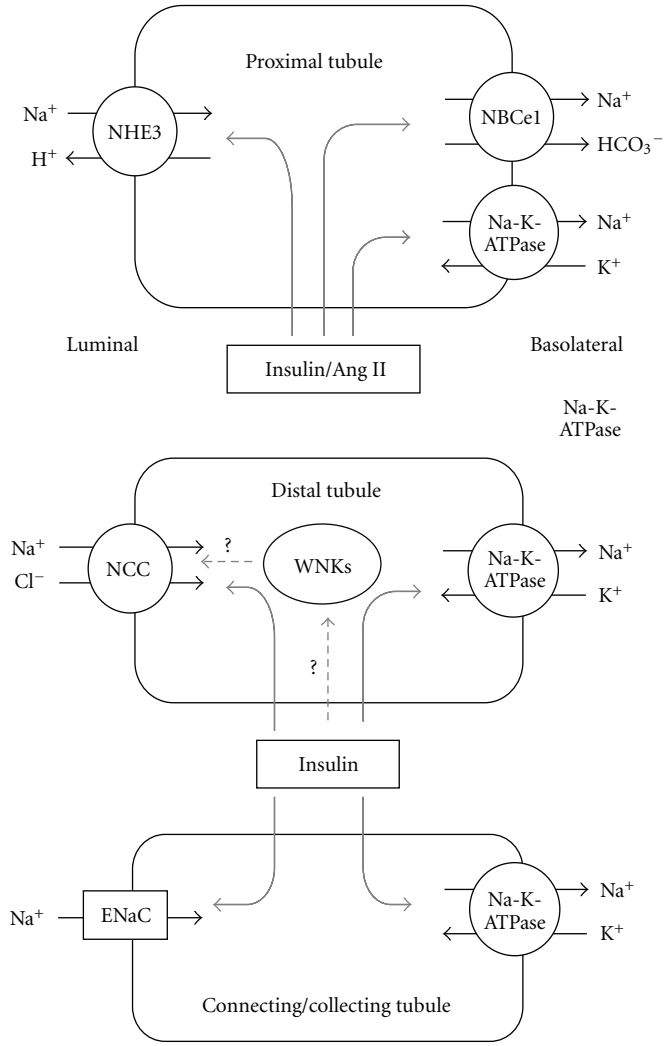


Figure 1: The main sodium transporters and regulators in the proximal tubule and distal and connecting/collecting tubules. In the proximal tubule, insulin and Ang II stimulate NHE3 at the luminal side, NBCe1, and Na-K-ATPase at the basolateral side. In the distal and connecting/collecting tubules, insulin stimulates ENaC and NCC in the luminal side, Na-K-ATPase at the basolateral side. Insulin may also indirectly stimulate NCC via WNK kinases.

by insulin stimulation, which mimicked the effect of insulin on proximal absorption, was preserved in IRS1$^{-/-}$ mice but significantly attenuated in IRS2$^{-/-}$ mice. Consistent with a major role of IRS2 in the insulin-mediated transport stimulation in proximal tubules, the tyrosine phosphorylation of IRS2 by insulin was more prominent than that of IRS1. Importantly, signaling defects specific to IRS1 has been often reported in insulin resistance [50–53]. Thus, sodium retention through IRS1-independent way, facilitated by hyperinsulinemia, could be an important factor in the pathogenesis of hypertension in insulin resistance.

6. Tumor Necrosis Factor (TNF) α and Renal Sodium Absorption

TNFα is a pleiotropic 157-amino acid peptide cytokine. It is committed in various physiological reactions, such as inflammation, proliferation, cell differentiation, and cell death including cell apoptosis [54, 55]. TNFα binds to TNF receptor (TNFR), which has two subtypes, called TNFR1 and TNFR2.

It has been proposed for a long that TNFα causes insulin resistance [56, 57]. Uysal et al. reported that mice lacking TNFα function do not develop obesity-induced insulin resistance [58]. However, TNFα alone may be insufficient to induce insulin resistance [59].

Interestingly, there are controversial papers about the effect of TNFα on sodium reabsorption. In C2BBe1 cells, derived from human intestinal epithelial cell line, TNFα was reported to reduce NHE3 expression via transcriptional regulation [60, 61]. TNFα seems to reduce Sp1/Sp3 complex to bind to NHE3 promoter DNA via cAMP/PKA way. Relatively high concentrations, though within the physiological levels, of TNFα are also known to increase urine volume and

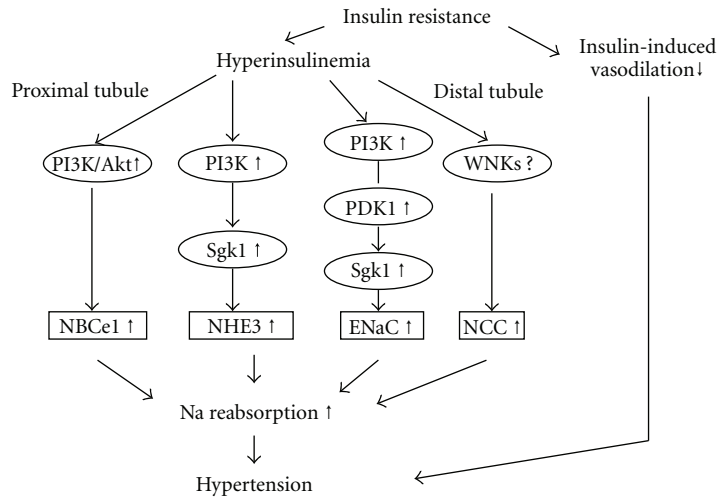


Figure 2: Mechanism of hypertension in insulin resistance. In insulin resistance, insulin-induced vasodilation is impaired. However, insulin induced sodium reabsorption through various nephron segments seems to be preserved or enhanced.

sodium excretion [62]. On the contrary, TNFα was reported to enhance sodium absorption from distal tubule in diabetic rats [63, 64]. The stimulation of sodium uptake by TNFα was blocked by amiloride, an inhibitor of ENaC, and PD98059, an inhibitor of ERK. It seems that TNFα acts on sodium status in a biphasic way: toward sodium excretion at high concentrations [65] and sodium retention at low concentrations. The effect of TNFα on renal sodium reabsorption in the nondiabetic condition, however, remains to be clarified.

7. Angiotensin II and Insulin Resistance

Angiotensin II (Ang II) is important for its potent ability to raise blood pressure. In addition to the vascular effects, Ang II stimulates sodium absorption from the proximal tubule, acting on several transporters carrying sodium [66]. Renin-angiotensin system (RAS) is activated in insulin-resistant state [67, 68]. RAS activation, on the other hand, has been related to impaired insulin signaling and systemic insulin resistance in various tissues and organs [69]. RAS and insulin resistance are, therefore, believed to be closely related. Moreover, numerous clinical evidences with RAS inhibitors, such as ACE inhibitors and ARBs, show that the inhibition of RAS contributes to amelioration of insulin resistance, prevention of hypertension, and damage of tissues and organs.

Interestingly, Ang II is known to regulate proximal tubule transport in a biphasic way: stimulation by low (picomolar to nanomolar) concentrations and inhibition by high (nanomolar to micromolar) concentrations. Studies using Ang II type 1A receptor (AT1A) KO mice revealed that these effects of Ang II are mediated by AT1A [70, 71]. Interestingly, the ERK pathway mediates the stimulatory effect but not the inhibitory effect of Ang II in proximal tubules [72]. It is unknown whether the stimulatory effect of Ang II on proximal tubule transport is enhanced in insulin resistance.

On the other hand, hyperglycemic state was shown to stimulate Ang II expression in the proximal tubule derived cells [73]. This is mediated by p44/42 MAPK signal transduction system. Taken together, Ang II might act to enhance sodium reabsorption from proximal tubule in both acute and chronic phases of insulin resistance.

8. Kidney and WNK, Hypertension, and Insulin

WNK kinase was originally found as a kind of serine-threonine kinase with an atypical lysine placement [74]. Notably, mutations in WNK kinases cause Gordon's syndrome (pseudohypoaldosteronism type II (PHAII) or familial hyperkalemic hypertension (FHH)) [75]. This finding has led to investigating the regulation of WNK kinases and their effects on renal transporters, such as NCC (sodium chloride cotransporter) and NKCC (sodium-potassium-chloride cotransporter), in the context of blood pressure homeostasis.

WNKs have five subtypes: WNK1, WNK2, WNK3, and WNK4, and a transcriptional variant of WNK1, KS-WNK1 [76]. In the distal tubule cells, NCC reabsorbs sodium and chloride at the apical membrane. WNK4 reduces NCC amount at the plasma membrane at least in some conditions [75, 77–80]. On the other hand, WNK4 is reported to enhance the NCC activity through its phosphorylation [81]. WNK1 does not affect NCC activity itself but suppresses WNK4 activity [78, 79]. KS-WNK1, which does not have kinase domain of WNK1, inhibits the WNK1 action on WNK4 [82, 83]. WNK3 stimulates NCC activity in its active form, but exerts a negative effect in its inactive form [84, 85]. In contrast to these distinct effects of individual WNKs on NCC, Heise et al. recently showed that WNKs 1, 3, and 4 all stimulate ENaC through serum glucocorticoid-induced kinase (SGK) 1, and that these stimulatory effects of WNKs are mediated by their N-terminal sequences without kinase activity [86]. These results suggest that WNKs regulate NCC and ENaC through different mechanisms.

Table 1: Effects of insulin on renal transporters, channels, or regulators.

	Transporter/channel	Effects of insulin
Proximal	NBCe1	Stimulation
	NHE	Stimulation
	Na-K-ATPase	Stimulation
Henle	NKCC	Stimulation
	Na-K-ATPase	Stimulation
Distal	ENaC	Stimulation
	NCC	Stimulation
	Na-K-ATPase	Stimulation
	WNK4	?
	WNK1	?
CNT	ENaC	Stimulation

Recently, there are some reports suggesting that insulin has influence on the activity of WNKs, which may have a role in the pathogenesis of salt-sensitive hypertension. For WNK1, Vitari et al. showed that WNK1 is a substrate of protein kinase B/Akt, a serine-threonine kinase known to be downstream of insulin signaling. This finding suggests that insulin may affect blood pressure by regulating WNK1 [87]. For WNK4, Sohara et al. have revealed that the WNK4 mutation (R1185C) induces excess phosphorylation of WNK4 S1190, which is a target phosphorylation site by insulin. They have also clarified that the phosphorylation of WNK4 S1190-OSR1/SPAK-NCC cascade is increased in the mice with hyperinsulinemia. These findings suggest that insulin regulates Na reabsorption from the distal tubule through WNKs and is involved in the pathogenesis of salt-sensitive hypertension [88]. Ellison et al. showed that the WNK4-NCC pathway as well as the abundance of WNK4 was altered in the rat model of insulin resistance [89]. Huang and Kuo reported that insulin reduced the renal cortical WNK4 expression [90]. This would indirectly enhance NCC and ENaC [91]. Now, the interaction between WNK kinases and insulin is intensively investigated, so it is expected that, in the near future, the regulatory system of insulin and distal to connecting tubules will be much more clarified.

Table 1 is a summary of insulin action on the regulators of sodium transport in the nephron segment. Insulin acts mostly as an enhancer of sodium reabsorption. The effects of insulin on WNKs require further investigations. Figure 2 is a scheme about how insulin triggers the signal transduction downstream and leads to hypertension.

9. Conclusion

We have discussed the renal actions of insulin. Sodium transport along nephron segments is a key for regulating blood pressure and sodium metabolism, with great influence on cardiovascular management. There are several regulators along each segment of the nephron. Among them, insulin and its signal transduction system have outstanding features and important roles from the view of hypertension associated with insulin resistance. Moreover, WNKs seem to be important mediators of insulin actions on the distal nephron.

References

[1] J. E. Hall, D. A. Hildebrandt, and J. Kuo, "Obesity hypertension: role of leptin and sympathetic nervous system," *American Journal of Hypertension*, vol. 14, no. 6, pp. 103S–115S, 2001.

[2] B. B. Kahn and J. S. Flier, "Obesity and insulin resistance," *Journal of Clinical Investigation*, vol. 106, no. 4, pp. 473–481, 2000.

[3] G. M. Reaven and B. B. Hoffman, "A role for insulin in the aetiology and course of hypertension?" *The Lancet*, vol. 2, no. 8556, pp. 435–437, 1987.

[4] N. Tsutsu, K. Nunoi, T. Kodama, R. Nomiyama, M. Iwase, and M. Fujishima, "Lack of association between blood pressure and insulin in patients with insulinoma," *Journal of Hypertension*, vol. 8, no. 5, pp. 479–482, 1990.

[5] J. E. Hall, "Hyperinsulinemia: a link between obesity and hypertension?" *Kidney International*, vol. 43, no. 6, pp. 1402–1417, 1993.

[6] K. Hayashi, K. Fujiwara, K. Oka, T. Nagahama, H. Matsuda, and T. Saruta, "Effects of insulin on rat renal microvessels: studies in the isolated perfused hydronephrotic kidney," *Kidney International*, vol. 51, no. 5, pp. 1507–1513, 1997.

[7] H. O. Steinberg, G. Brechtel, A. Johnson, N. Fineberg, and A. D. Baron, "Insulin-mediated skeletal muscle vasodilation is nitric oxide dependent. A novel action of insulin to increase nitric oxide release," *Journal of Clinical Investigation*, vol. 94, no. 3, pp. 1172–1179, 1994.

[8] Z. Y. Jiang, Y. W. Lin, A. Clemont et al., "Characterization of selective resistance to insulin signaling in the vasculature of obese Zucker (fa/fa) rats," *Journal of Clinical Investigation*, vol. 104, no. 4, pp. 447–457, 1999.

[9] R. Li, H. Zhang, W. Wang et al., "Vascular insulin resistance in prehypertensive rats: role of PI3-kinase/Akt/eNOS signaling," *European Journal of Pharmacology*, vol. 628, no. 1–3, pp. 140–147, 2010.

[10] D. Finch, G. Davis, J. Bower, and K. Kirchner, "Effect of insulin on renal sodium handling in hypertensive rats," *Hypertension*, vol. 15, no. 5, pp. 514–518, 1990.

[11] A. P. Rocchini, V. Katch, D. Kveselis et al., "Insulin and renal sodium retention in obese adolescents," *Hypertension*, vol. 14, no. 4, pp. 367–374, 1989.

[12] L. A. Sechi, "Mechanisms of insulin resistance in rat models of hypertension and their relationships with salt sensitivity," *Journal of Hypertension*, vol. 17, no. 9, pp. 1229–1237, 1999.

[13] J. E. Bourdeau, E. R. Y. Chen, and F. A. Carone, "Insulin uptake in the renal proximal tubule," *American Journal of Physiology*, vol. 225, no. 6, pp. 1399–1404, 1973.

[14] R. Nakamura, D. S. Emmanouel, and A. I. Katz, "Insulin binding sites in various segments of the rabbit nephron," *Journal of Clinical Investigation*, vol. 72, no. 1, pp. 388–392, 1983.

[15] D. Butlen, S. Vadrot, S. Roseau, and F. Morel, "Insulin receptors along the rat nephron: [125I] insulin binding in microdissected glomeruli and tubules," *Pflugers Archiv European Journal of Physiology*, vol. 412, no. 6, pp. 604–612, 1988.

[16] R. Rabkin, M. P. Ryan, and W. C. Duckworth, "The renal metabolism of insulin," *Diabetologia*, vol. 27, no. 3, pp. 351–357, 1984.

[17] M. A. Cortney, L. L. Sawin, and D. D. Weiss, "Renal tubular protein absorption in the rat," *Journal of Clinical Investigation*, vol. 49, no. 1, pp. 1–4, 1970.

[18] R. Rabkin, N. M. Simon, S. Steiner, and J. A. Colwell, "Effect of renal disease on renal uptake and excretion of insulin in man," *The New England Journal of Medicine*, vol. 282, no. 4, pp. 182–187, 1970.

[19] R. A. DeFronzo, C. R. Cooke, and R. Andres, "The effect of insulin on renal handling of sodium, potassium, calcium, and phosphate in man," *Journal of Clinical Investigation*, vol. 55, no. 4, pp. 845–855, 1975.

[20] M. Baum, "Insulin stimulates volume absorption in the rabbit proximal convoluted tubule," *Journal of Clinical Investigation*, vol. 79, no. 4, pp. 1104–1109, 1987.

[21] F. A. Gesek and A. C. Schoolwerth, "Insulin increases Na^+-H^+ exchange activity in proximal tubules from normotensive and hypertensive rats," *American Journal of Physiology*, vol. 260, no. 5, pp. F695–F703, 1991.

[22] W. Lee-Kwon, D. C. Johns, B. Cha et al., "Constitutively active phosphatidylinositol 3-kinase and AKT are sufficient to stimulate the epithelial Na^+/H^+ exchanger 3," *Journal of Biological Chemistry*, vol. 276, no. 33, pp. 31296–31304, 2001.

[23] W. Lee-Kwon, K. Kawano, J. W. Choi, J. H. Kim, and M. Donowitz, "Lysophosphatidic acid stimulates brush border Na^+/H^+ exchanger 3 (NHE3) activity by increasing its exocytosis by an NHE3 kinase A regulatory protein-dependent mechanism," *Journal of Biological Chemistry*, vol. 278, no. 19, pp. 16494–16501, 2003.

[24] H. Shiue, M. W. Musch, Y. Wang, E. B. Chang, and J. R. Turner, "Akt2 phosphorylates ezrin to trigger NHE3 translocation and activation," *Journal of Biological Chemistry*, vol. 280, no. 2, pp. 1688–1695, 2005.

[25] J. Klisic, M. C. Hu, V. Nief et al., "Insulin activates Na^+/H^+ exchanger 3: biphasic response and glucocorticoid dependence," *American Journal of Physiology*, vol. 283, no. 3, pp. F532–F539, 2002.

[26] D. G. Fuster, I. A. Bobulescu, J. Zhang, J. Wade, and O. W. Moe, "Characterization of the regulation of renal Na^+/H^+ exchanger NHE3 by insulin," *American Journal of Physiology*, vol. 292, no. 2, pp. F577–F585, 2007.

[27] Z. Talor, D. S. Emmanouel, and A. I. Katz, "Insulin (INS) stimulates Na-K-ATPase activity of basolateral (BL) renal tubular membranes," *Kidney International*, vol. 21, supplement 1, p. 266, 1982.

[28] C. Rivera, H. Santos-Reyes, and M. Martinez-Maldonado, "Response of dog renal Na,K-ATPase to insulin in vitro," *Renal Physiology*, vol. 1, no. 2, pp. 74–83, 1978.

[29] E. Feraille, M. L. Carranza, M. Rousselot, and H. Favre, "Insulin enhances sodium sensitivity of Na-K-ATPase in isolated rat proximal convoluted tubule," *American Journal of Physiology* , vol. 267, no. 1, pp. F55–F62, 1994.

[30] O. S. Ruiz, YI. Y. Qiu, L. R. Cardoso, and J. A. L. Arruda, "Regulation of the renal Na-HCO_3 cotransporter: IX. Modulation by insulin, epidermal growth factor and carbachol," *Regulatory Peptides*, vol. 77, no. 1–3, pp. 155–161, 1998.

[31] K. A. Kirchner, "Insulin increases loop segment chloride reabsorption in the euglycemic rat," *American Journal of Physiology*, vol. 255, no. 6, pp. F1206–F1213, 1988.

[32] O. Ito, Y. Kondo, N. Takahashi et al., "Insulin stimulates NaCl transport in isolated perfused MTAL of Henle's loop of rabbit kidney," *American Journal of Physiology*, vol. 267, no. 2, pp. F265–F270, 1994.

[33] N. Takahashi, O. Ito, and K. Abe, "Tubular effects of insulin," *Hypertension Research*, vol. 19, no. 1, pp. S41–S45, 1996.

[34] M. Tsimaratos, F. Roger, D. Chabardès et al., "C-peptide stimulates Na^+,K^+-ATPase activity via PKC alpha in rat medullary thick ascending limb," *Diabetologia*, vol. 46, no. 1, pp. 124–131, 2003.

[35] J. Loffing and C. Korbmacher, "Regulated sodium transport in the renal connecting tubule (CNT) via the epithelial sodium channel (ENaC)," *Pflugers Archiv*, vol. 458, no. 1, pp. 111–135, 2009.

[36] B. L. Blazer-Yost, X. Liu, and S. I. Helman, "Hormonal regulation of eNaCs: insulin and aldosterone," *American Journal of Physiology*, vol. 274, no. 5, pp. C1373–C1379, 1998.

[37] E. Feraille, M. Rousselot, R. Rajerison, and H. Favre, "Effect of insulin on Na^+,K^+-ATPase in rat collecting duct," *Journal of Physiology*, vol. 488, no. 1, pp. 171–180, 1995.

[38] A. V. Chibalin, M. V. Kovalenko, J. W. Ryder, E. Féraille, H. Wallberg-Henriksson, and J. R. Zierath, "Insulin- and glucose-induced phosphorylation of the Na^+,K^+-adeno-sine triphosphatase α-subunits in rat skeletal mescle," *Endocrinology*, vol. 142, no. 8, pp. 3474–3482, 2001.

[39] IL. H. Lee, C. R. Campbell, D. I. Cook, and A. Dinudom, "Regulation of epithelial Na^+ channels by aldosterone: role of Sgk1," *Clinical and Experimental Pharmacology and Physiology*, vol. 35, no. 2, pp. 235–241, 2008.

[40] J. Loffing, S. Y. Flores, and O. Staub, "Sgk kinases and their role in epithelial transport," *Annual Review of Physiology*, vol. 68, pp. 461–490, 2006.

[41] M. F. White, R. Maron, and C. R. Kahn, "Insulin rapidly stimulates tyrosine phosphorylation of a M(r)-185,000 protein in intact cells," *Nature*, vol. 318, no. 6042, pp. 183–186, 1985.

[42] X. J. Sun, P. Rothenberg, C. R. Kahn et al., "Structure of the insulin receptor substrate IRS-1 defines a unique signal transduction protein," *Nature*, vol. 352, no. 6330, pp. 73–77, 1991.

[43] X. J. Sun, L. M. Wang, Y. Zhang et al., "Role of IRS-2 in insulin and cytokine signalling," *Nature*, vol. 377, no. 6545, pp. 173–177, 1995.

[44] M. F. White, "The IRS-signalling system: a network of docking proteins that mediate insulin action," *Molecular and Cellular Biochemistry*, vol. 182, no. 1-2, pp. 3–11, 1998.

[45] J. C. Brüning, J. Winnay, B. Cheatham, and C. R. Kahn, "Differential signaling by insulin receptor substrate 1 (IRS-1) and IRS- 2 in IRS-1-deficient cells," *Molecular and Cellular Biology*, vol. 17, no. 3, pp. 1513–1521, 1997.

[46] E. Araki, M. A. Lipes, M. E. Patti et al., "Alternative pathway of insulin signalling in mice with targeted disruption of the IRS-1 gene," *Nature*, vol. 372, no. 6502, pp. 186–190, 1994.

[47] N. Kubota, K. Tobe, Y. Terauchi et al., "Disruption of insulin receptor substrate 2 causes type 2 diabetes because of liver insulin resistance and lack of compensatory β-cell hyperplasia," *Diabetes*, vol. 49, no. 11, pp. 1880–1889, 2000.

[48] Y. Kido, D. J. Burks, D. Withers et al., "Tissue-specific insulin resistance in mice with mutations in the insulin receptor, IRS-1, and IRS-2," *Journal of Clinical Investigation*, vol. 105, no. 2, pp. 199–205, 2000.

[49] Y. Zheng, H. Yamada, K. Sakamoto et al., "Roles of insulin receptor substrates in insulin-induced stimulation of renal proximal bicarbonate absorption," *Journal of the American Society of Nephrology*, vol. 16, no. 8, pp. 2288–2295, 2005.

[50] L. J. Goodyear, F. Giorgino, L. A. Sherman, J. Carey, R. J. Smith, and G. L. Dohm, "Insulin receptor phosphorylation, insulin receptor substrate-1 phosphorylation, and phosphatidylinositol 3-kinase activity are decreased in intact skeletal muscle strips from obese subjects," *Journal of Clinical Investigation*, vol. 95, no. 5, pp. 2195–2204, 1995.

[51] J. E. Friedman, T. Ishizuka, J. Shao, L. Huston, T. Highman, and P. Catalano, "Impaired glucose transport and insulin receptor tyrosine phosphorylation in skeletal muscle from obese women with gestational diabetes," *Diabetes*, vol. 48, no. 9, pp. 1807–1814, 1999.

[52] C. M. Rondinone, L. M. Wang, P. Lonnroth, C. Wesslau, J. H. Pierce, and U. Smith, "Insulin receptor substrate (IRS) 1 is reduced and IRS-2 is the main docking protein for phosphatidylinositol 3-kinase in adipocytes from subjects with non-insulin-dependent diabetes mellitus," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 94, no. 8, pp. 4171–4175, 1997.

[53] E. Carvalho, P. A. Jansson, M. Axelsen et al., "Low cellular IRS 1 gene and protein expression predict insulin resistance and NIDDM," *FASEB Journal*, vol. 13, no. 15, pp. 2173–2178, 1999.

[54] N. M. Al-Rasheed, G. B. Willars, and N. J. Brunskill, "C-peptide signals via Gα to protect against TNF-α-mediated apoptosis of opossum kidney proximal tubular cells," *Journal of the American Society of Nephrology*, vol. 17, no. 4, pp. 986–995, 2006.

[55] H. Wajant, K. Pfizenmaier, and P. Scheurich, "Tumor necrosis factor signaling," *Cell Death and Differentiation*, vol. 10, no. 1, pp. 45–65, 2003.

[56] P. Peraldi and B. Spiegelman, "TNF-α and insulin resistance: summary and future prospects," *Molecular and Cellular Biochemistry*, vol. 182, no. 1-2, pp. 169–175, 1998.

[57] G. S. Hotamisligil, "The role of TNFα and TNF receptors in obesity and insulin resistance," *Journal of Internal Medicine*, vol. 245, no. 6, pp. 621–625, 1999.

[58] K. T. Uysal, S. M. Wiesbrock, M. W. Marino, and G. S. Hotamisligil, "Protection from obesity-induced insulin resistance in mice lacking TNF- α function," *Nature*, vol. 389, no. 6651, pp. 610–614, 1997.

[59] S. E. Shoelson, J. Lee, and A. B. Goldfine, "Inflammation and insulin resistance," *Journal of Clinical Investigation*, vol. 116, no. 7, pp. 1793–1801, 2006.

[60] MD. R. Amin, J. Malakooti, R. Sandoval, P. K. Dudeja, and K. Ramaswamy, "IFN-γ and TNF-α regulate human NHE3 gene expression by modulating the Sp family transcription factors in human intestinal epithelial cell line C2BBe1," *American Journal of Physiology*, vol. 291, no. 5, pp. C887–C896, 2006.

[61] M. D. R. Amin, P. K. Dudeja, K. Ramaswamy, and J. Malakooti, "Involvement of Sp1 and Sp3 in differential regulation of human NHE3 promoter activity by sodium butyrate and IFN-γ/TNF-α," *American Journal of Physiology*, vol. 293, no. 1, pp. G374–G382, 2007.

[62] M. Shahid, J. Francis, and D. S. A. Majid, "Tumor necrosis factor-α induces renal vasoconstriction as well as natriuresis in mice," *American Journal of Physiology*, vol. 295, no. 6, pp. F1836–F1844, 2008.

[63] K. DiPetrillo, B. Coutermarsh, and F. A. Gesek, "Urinary tumor necrosis factor contributes to sodium retention and renal hypertrophy during diabetes," *American Journal of Physiology*, vol. 284, no. 1, pp. F113–F121, 2003.

[64] K. DiPetrillo, B. Coutermarsh, N. Soucy, J. Hwa, and F. Gesek, "Tumor necrosis factor induces sodium retention in diabetic rats through sequential effects on distal tubule cells," *Kidney International*, vol. 65, no. 5, pp. 1676–1683, 2004.

[65] C. Schmidt, K. Höcherl, F. Schweda, A. Kurtz, and M. Bucher, "Regulation of renal sodium transporters during severe inflammation," *Journal of the American Society of Nephrology*, vol. 18, no. 4, pp. 1072–1083, 2007.

[66] A. D. M. Riquier-Brison, P. K. K. Leong, K. Pihakaski-Maunsbach, and A. A. McDonough, "Angiotensin II stimulates trafficking of NHE3, NaPi2, and associated proteins into the proximal tubule microvilli," *American Journal of Physiology*, vol. 298, no. 1, pp. F177–F186, 2010.

[67] F. A. El-Atat, S. N. Stas, S. I. Mcfarlane, and J. R. Sowers, "The relationship between hyperinsulinemia, hypertension and progressive renal disease," *Journal of the American Society of Nephrology*, vol. 15, no. 11, pp. 2816–2827, 2004.

[68] L. A. Velloso, F. Folli, L. Perego, and M. J. A. Saad, "The multi-faceted cross-talk between the insulin and angiotensin II signaling systems," *Diabetes/Metabolism Research and Reviews*, vol. 22, no. 2, pp. 98–107, 2006.

[69] G. Lastra, S. Dhuper, M. S. Johnson, and J. R. Sowers, "Salt, aldosterone, and insulin resistance: impact on the cardiovascular system," *Nature Reviews Cardiology*, vol. 7, no. 10, pp. 577–584, 2010.

[70] S. Horita, Y. Zheng, C. Hara et al., "Biphasic regulation of Na^+-HCO_3^- cotransporter by angiotensin II type 1A receptor," *Hypertension*, vol. 40, no. 5, pp. 707–712, 2002.

[71] Y. Zheng, S. Horita, C. Hara et al., "Biphasic regulation of renal proximal bicarbonate absorption by luminal AT receptor," *Journal of the American Society of Nephrology*, vol. 14, no. 5, pp. 1116–1122, 2003.

[72] Y. Li, H. Yamada, Y. Kita et al., "Roles of ERK and cPLA in the angiotensin II-mediated biphasic regulation of Na^+-HCO_3^- transport," *Journal of the American Society of Nephrology*, vol. 19, no. 2, pp. 252–259, 2008.

[73] S. L. Zhang, X. Chen, T. J. Hsieh et al., "Hyperglycemia induces insulin resistance on angiotensinogen gene expression in diabetic rat kidney proximal tubular cells," *Journal of Endocrinology*, vol. 172, no. 2, pp. 333–344, 2002.

[74] B. E. Xu, J. M. English, J. L. Wilsbacher, S. Stippec, E. J. Goldsmith, and M. H. Cobb, "WNK1, a novel mammalian serine/threonine protein kinase lacking the catalytic lysine in subdomain II," *Journal of Biological Chemistry*, vol. 275, no. 22, pp. 16795–16801, 2000.

[75] F. H. Wilson, S. Disse-Nicodème, K. A. Choate et al., "Human hypertension caused by mutations in WNK kinases," *Science*, vol. 293, no. 5532, pp. 1107–1112, 2001.

[76] J. A. McCormick, C. L. Yang, and D. H. Ellison, "WNK kinases and renal sodium transport in health and disease: an integrated view," *Hypertension*, vol. 51, no. 3, pp. 588–596, 2008.

[77] M. E. Safar and H. S. Boudier, "Vascular development, pulse pressure, and the mechanisms of hypertension," *Hypertension*, vol. 46, no. 1, pp. 205–209, 2005.

[78] C. L. Yang, J. Angell, R. Mitchell, and D. H. Ellison, "WNK kinases regulate thiazide-sensitive Na-Cl cotransport," *Journal of Clinical Investigation*, vol. 111, no. 7, pp. 1039–1045, 2003.

[79] A. P. Golbang, G. Cope, A. Hamad et al., "Regulation of the expression of the Na/Cl cotransporter by WNK4 and WNK1: evidence that accelerated dynamin-dependent endocytosis is not involved," *American Journal of Physiology*, vol. 291, no. 6, pp. F1369–F1376, 2006.

[80] H. Cai, V. Cebotaru, Y. H. Wang et al., "WNK4 kinase regulates surface expression of the human sodium chloride cotransporter in mammalian cells," *Kidney International*, vol. 69, no. 12, pp. 2162–2170, 2006.

[81] A. Ohta, T. Rai, N. Yui et al., "Targeted disruption of the Wnk4 gene decreases phosphorylation of Na-Cl cotransporter, increases Na excretion and lowers blood pressure," *Human Molecular Genetics*, vol. 18, no. 20, pp. 3978–3986, 2009.

[82] C. L. Yang, X. Zhu, Z. Wang, A. R. Subramanya, and D. H. Ellison, "Mechanisms of WNK1 and WNK4 interaction in the regulation of thiazide-sensitive NaCl cotransport," *Journal of Clinical Investigation*, vol. 115, no. 5, pp. 1379–1387, 2005.

[83] A. R. Subramanya, C. L. Yang, X. Zhu, and D. H. Ellison, "Dominant-negative regulation of WNK1 by its kidney-specific kinase-defective isoform," *American Journal of Physiology*, vol. 290, no. 3, pp. F619–F624, 2006.

[84] J. Rinehart, K. T. Kahle, P. De Los Heros et al., "WNK3 kinase is a positive regulator of NKCC2 and NCC, renal cation-Cl cotransporters required for normal blood pressure homeostasis," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 102, no. 46, pp. 16777–16782, 2005.

[85] C. L. Yang, X. Zhu, and D. H. Ellison, "The thiazide-sensitive Na-Cl cotransporter is regulated by a WNK kinase signaling complex," *Journal of Clinical Investigation*, vol. 117, no. 11, pp. 3403–3411, 2007.

[86] C. J. Heise, B.-E. Xu, S. L. Deaton et al., "Serum and Glucocorticoid-induced Kinase (SGK) 1 and the epithelial sodium channel are regulated by multiple with no lysine (WNK) family members," *Journal of Biological Chemistry*, vol. 285, no. 33, pp. 25161–25167, 2010.

[87] A. C. Vitari, M. Deak, B. J. Collins et al., "WNK1, the kinase mutated in an inherited high-blood-pressure syndrome, is a novel PKB (protein kinase B)/Akt substrate," *Biochemical Journal*, vol. 378, no. 1, pp. 257–268, 2004.

[88] E. Sohara, T. Rai, A. Ohta, e. Ohta, S. Sasaki, and S. Uchida, "Novel Insulin-WNK4-NCC phosphorylation cascade is involved in pathogenesis of PHA II caused by WNK4 R1185C mutation," in *Proceedings of the 42nd Annual Meeting of American Society of Nephrology*, p. F-FC279, San Diego, Calif, USA, November 2009.

[89] D. H. Ellison, T. T. Oyama, C. L. Yang, S. Rogers, D. r. Beard, and R. Komers, "Altered WNK4/NCC signaling in a rat model of insulin resistance," in *Proceedings of the 42nd Annual Meeting of American Society of Nephrology*, p. SA-FC432, November 2009.

[90] C. L. Huang and E. Kuo, "Mechanisms of Disease: WNK-ing at the mechanism of salt-sensitive hypertension," *Nature Clinical Practice Nephrology*, vol. 3, no. 11, pp. 623–630, 2007.

[91] E. J. Hoorn, N. Van Der Lubbe, and R. Zietse, "The renal WNK kinase pathway: a new link to hypertension," *Nephrology Dialysis Transplantation*, vol. 24, no. 4, pp. 1074–1077, 2009.

SAGE-Hindawi Access to Research
International Journal of Hypertension
Volume 2011, Article ID 738689, 8 pages
doi:10.4061/2011/738689

Research Article

Circadian Variations in Blood Pressure, Heart Rate, and HR-BP Cross-Correlation Coefficient during Progression of Diabetes Mellitus in Rat

Chikodi N. Anigbogu,[1,2] Daniel T. Williams,[2] David R. Brown,[2] Dennis L. Silcox,[2] Richard O. Speakman,[2] Laura C. Brown,[2] Dennis G. Karounos,[3] and David C. Randall[2]

[1] *Department of Physiology, College of Medicine, University of Lagos, 12003 Lagos, Nigeria*
[2] *Department of Physiology, College of Medicine University of Kentucky, Lexington, KY 40536-0298, USA*
[3] *Lexington VA Medical Center and Department of Internal Medicine, College of Medicine University of Kentucky, Lexington, KY 40536-0298, USA*

Correspondence should be addressed to David C. Randall, randall@uky.edu

Received 16 January 2011; Accepted 10 February 2011

Academic Editor: Kazuko Masuo

Circadian changes in cardiovascular function during the progression of diabetes mellitus in the diabetes prone rat (BBDP) ($n = 8$) were studied. Age-matched diabetes-resistant rats (BBDR) served as controls. BP was recorded via telemetry in contiguous 4 hr time periods over 24 hours starting with 12 midnight to 4 am as period zero (P0). Prior to onset of diabetes BP was high at P0, peaked at P2, and then fell again at P3; BP and heart rate (HR) then increased gradually at P4 and leveled off at P5, thereby exhibiting a bipodal rhythm. These patterns changed during long-term diabetes. The cross-correlation coefficient of BP and HR was not significantly different across groups at onset, but it fell significantly at 9 months of duration of diabetes (BBDP: 0.39 ± 0.06; BBDR: 0.65 ± 0.03; $P < .05$). These results show that changes in circadian cardiovascular rhythms in diabetes mellitus became significant at the late stage of the disease.

1. Introduction

Circadian variations in most bodily functions have been recognized. The circadian variation enables the organism, system, and individual organs to maximize efficiency by ensuring optimal performance with minimal energy expenditure. The diurnal variation in blood pressure rhythm has been demonstrated in man [1–3] and various mammalian species [4–6]. Some variations in the circadian blood pressure patterns have been attributed to endocrine influences [7, 8] while others are thought to be of neural origin [9]. Blood pressure and heart rate are thought to vary in different ways, with diurnal changes in weather, time of day, and temperature. Circadian rhythm involves changes in autonomic function controlled by the hypothalamus and influenced by the higher brain centers. Therefore variation in circadian rhythm may also be an indicator of autonomic changes. Vinik and Erbas [10] have stressed the importance of recognizing and treating autonomic neuropathy in diabetes, but early detection of autonomic neuropathy is difficult with current assessment techniques. The search for more sensitive, less invasive, and less stressful markers of autonomic and cardiovascular dysfunction is still imperative.

Young et al. [11] have reported that the heart possesses an internal circadian clock, which is associated with gene expression, metabolism, and contractile performance. They reported loss of synchronization in the phases of these circadian rhythms in streptozotocin-induced diabetes in rats. Loss of circadian rhythm of blood pressure following acute stroke has been reported in human patients [12–14]. Diabetes mellitus is known to produce autonomic neuropathy, which results in functional and anatomical changes in the autonomic and cardiovascular system [15]. Clinical studies have used beat-to-beat variation of heart rate during deep

breathing and during the Valsalva maneuver to show the altered parasympathetic nervous control of the heart in diabetes [16, 17]. Other experimental studies have been carried out in streptozotocin- or alloxan-treated rats [11, 18]. The autonomic nervous system plays an important role in the regulation of cardiovascular function in health and disease [19]. However the effect of the development of diabetes and diabetic neuropathy on regulation of cardiovascular function and the circadian variability of blood pressure and heart rate has not been convincingly elucidated. The development of an animal model of spontaneous autoimmune diabetes mellitus, the BBDP rat, provides a good opportunity for the study of the phenomenological changes in autonomic and cardiovascular function and the circadian variations in these parameters during the progression of type 1 diabetes mellitus.

This study was designed to investigate the circadian variations in blood pressure, heart rate, and blood pressure and heart rate cross-correlation (xcorr) in BBDP rats. We posit that the circadian rhythm of blood pressure, heart rate, and heart rate-blood pressure cross-correlation in diabetic rats will differ from those of the control (i.e., diabetes-resistant) rats.

2. Materials and Methods

2.1. Animals. Male, genetically diabetes-prone (BBDP) ($n = 8$) and diabetes-resistant (BBDR) ($n = 8$) rats obtained from the Biomedical Models Inc. (Rutland MA) were used in the study. The experiments were performed in accordance with the National Institutes of Health guidelines for care and use of experimental animals [20] and were approved by the Institutional Animal Care and Use Committee of the University Of Kentucky College Of Medicine. These BBDP rats spontaneously develop an autoimmune, abrupt onset type 1 diabetes mellitus between 50–120 days of age. The diabetes is characterized by polydipsia, polyurea, and hyperglycemia. The rats were obtained from the vendor at 31–45 days of age. They were housed in an isolated room where the temperature was controlled at 72 degrees Fahrenheit (22°C), 56% humidity, and a 12/12-hour light/dark cycle. The rats were fed on standard rat chow (Harlan Teklad 2018, Madison, WI, USA) and had access to water *ad libitum*. The diabetic animals were weighed each morning, and blood glucose was measured. Briefly a drop of blood from the saphenous vein was placed on the reagent strip of the One-Touch Ultra glucometer (LifeScan Inc., Milpitas, CA, USA) and read within 5 seconds.

2.2. Surgery. All procedures were appropriate for rodent survival surgery. The rats were anaesthetized with sodium pentobarbital (65 mg/kg, IP). The abdominal aorta was accessed via a laparotomy. The sensory element of a Data Sciences International (DSI) probe (model TA11PA-C40) was placed into the aorta via a puncture such that the tip pointed towards the heart. The catheter containing the sensitive element of the probe was secured in place with surgical glue. The body of the probe that contains the sensor, transmitter, and battery was secured to the interior abdominal wall with sutures. The incision was closed and the rat monitored until it roused from the anesthetic.

Table 1: Demographic and laboratory variables (MEAN ± SD) of diabetic rats (BBDP) and resistant rats (BBDR) at onset of diabetes.

Variable	BBDP	BBDR
Age at onset (weeks)	9	9
Numbers (16)	8	8
Weight (g)	280 ± 25	320 ± 12*
Blood sugar (mg%)	347 ± 48	87 ± 5.4*

*$P < .05$.

2.3. Experimental Protocol. The body weight and the blood glucose level were monitored each morning at about 9 am. The day the animal first showed a morning blood glucose level above 250 mg/dL was taken as onset of diabetes mellitus and designated "day 0." The diabetic age was calculated from this point, which occurred at about 65 days of age. The diabetic rats were maintained on an insulin dose schedule developed by the breeder. This involved giving Protamine-Zinc Insulin (PZI) 0.9 U/100 g/day, subcutaneously. The dose was increased or reduced by 0.2 units per day, depending on weight gain or loss and plasma glucose level. Blood pressure was monitored continuously throughout the period or in some cases continuously for two-week intervals each month. The latter arrangement or rotation helps increase the number of animals monitored and also prolongs battery life of the telemeter, as the telemetry unit is switched off.

2.4. Data Acquisition and Analysis. The telemetry data were obtained using the PhysioTel RPC 1 receiver. The received signal was fed into a DSI Data Exchange Matrix to which was connected an ambient pressure reference (APR 1). The output from the matrix was fed, via a Dataquest PCI card, into the Pentium IV computer-based workstation running a Dataquest A.R.T system software program. The output from this computer was cross-fed into an analog-output Data Exchange Matrix. The analog output of the DEM was passed through a BNC-2110 A-D converter (National Instruments) into an analysis and output computer for further processing or display. The data stream was analyzed using an in-house developed computer program (ViiSoftware, Lexington) running on a Pentium IV based computer. Heart rate (HR) was computed from the pulsatile BP signal. For data analysis the 24-hour day was divided into six 4-hour periods starting from 12 : 00 midnight (P0, P1, P2, P3, P4, and P5). The blood pressure and heart rate were plotted to reveal any diurnal variations and cyclic variations. The cross-correlation coefficient between heart rate and blood pressure was computed [21]. Data are presented as mean ± SEM unless specifically noted otherwise. Two-factor between group analysis of variance (ANOVA) was applied to the strains (BBDP and BBDR). One-way ANOVA was used for individual changes and appropriate t-tests applied. Significance was taken as $P < .05$.

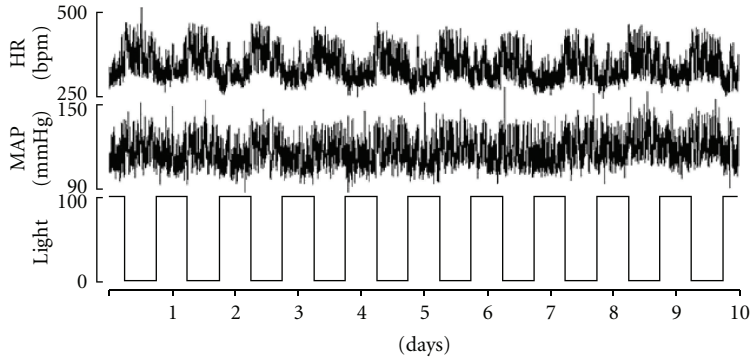


Figure 1: Compressed recording showing heart rate and blood pressure variations with the light and dark cycles in BBDP rats, over ten days. Note the circadian pattern with increased HR and BP over the dark periods, typical of nocturnal animals.

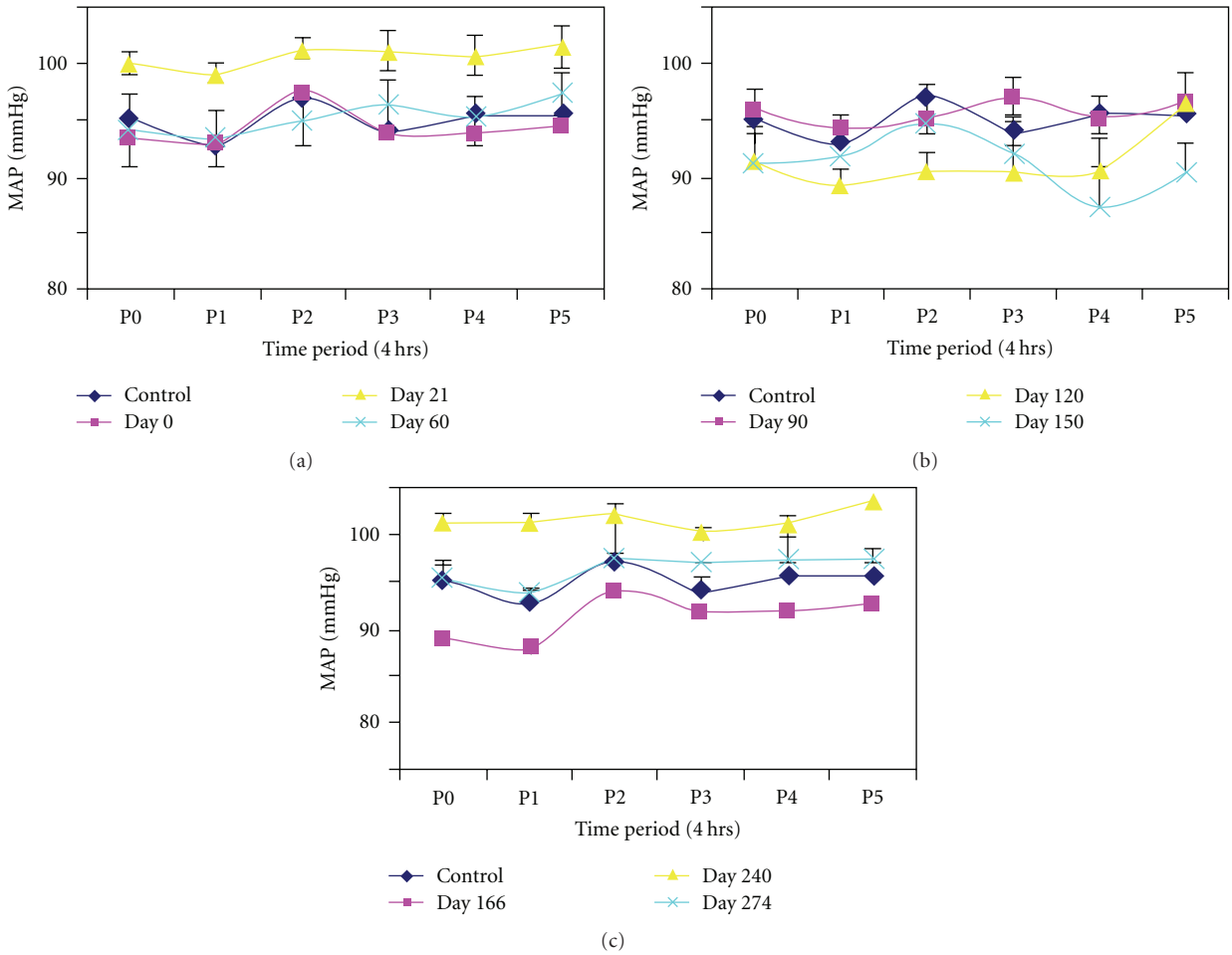


Figure 2: Circadian variations in blood pressure in six diurnal periods (P0–P5) at (a) 0, 21, 60 days, (b) 90–150 days, (c) 166–274 days of diabetes duration. Values are mean ± S.E.M.

3. Results

Table 1 shows the parameters of the spontaneously diabetic rats (BBDP) at the onset of diabetes and the age-matched diabetes-resistant control rats (BBDR). The diabetes-prone rats had a slightly, but significantly, lower body weight than the control rats. As expected, the diabetic rats had a significantly higher blood glucose level. We report elsewhere [22] that, aside from the consistent between-group difference in absolute weight, both groups exhibited similar growth patterns during the study period. Likewise, we reported [22] that baseline mean arterial pressure (MAP) did not differ between groups and that HR was minimally, but significantly, lower in the diabetic animals versus the controls for the first 6 months

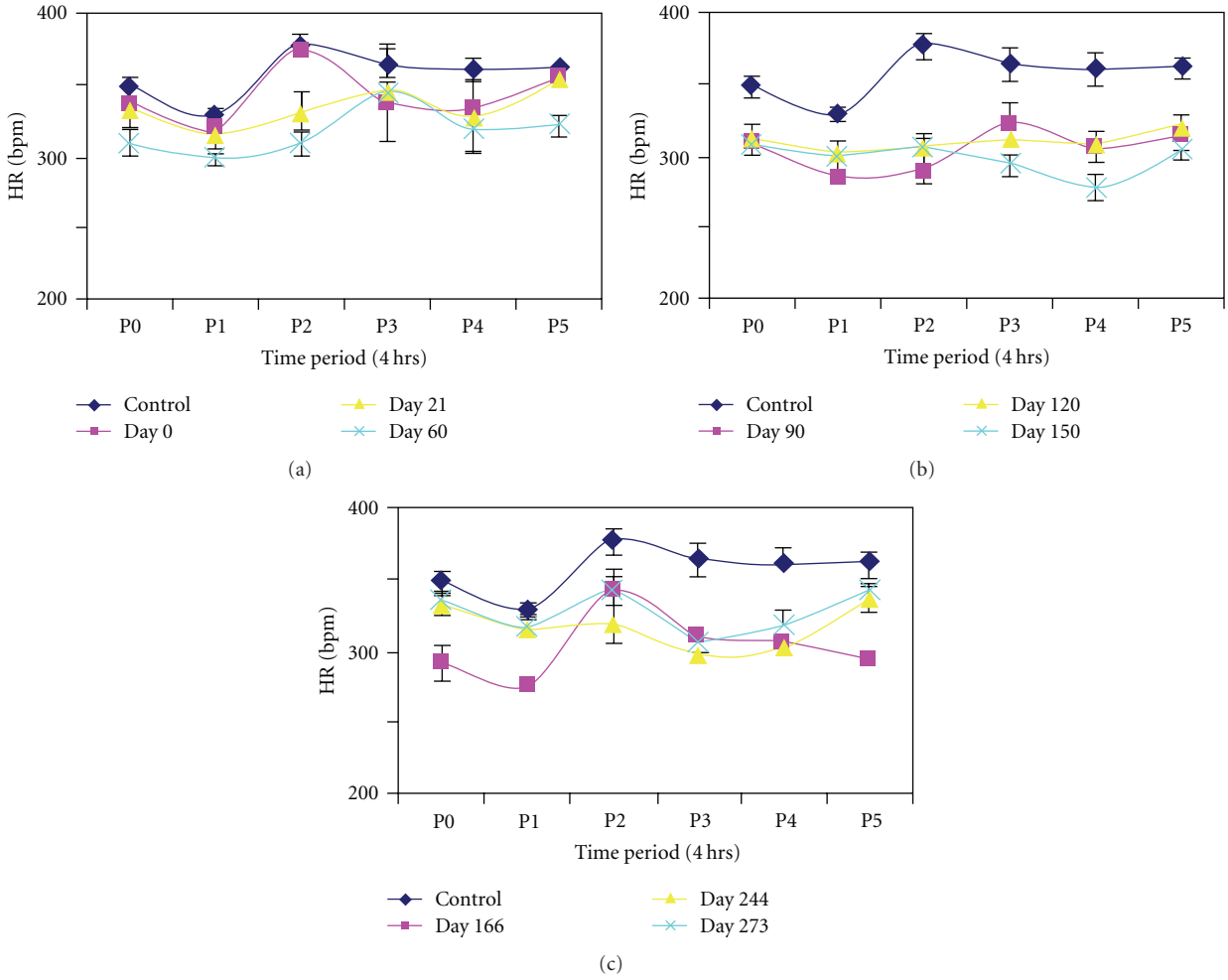


Figure 3: Circadian variations in heart rate (HR) in six diurnal (4 hour) periods (P0–P5) at (a) 0–60 days, (b) 90–150 days, (c)166–274 days after diabetic conversion. Values are means ± SEM. Note the near consistent relationships with changes in arterial pressure findings (Figure 2) in terms of fluctuations.

after the BBDP became diabetic. One diabetic rat died about day 120 of diabetic duration and another at day 244.

3.1. Circadian Changes in BP and HR in BBDP and BBDR Rats. Figure 1 shows ten days of mean arterial pressure (MAP), HR, and light/dark cycles for a diabetes-resistant animal. The circadian variations in blood pressure and heart rate are demonstrably out of phase with the light/dark rhythm (i.e., lowest MAP and HR during light on), as would be expected for an animal that is most active during the dark. Panels a, b, and c of Figure 2 graph MAP recorded for the time periods P0 (12 midnight–4 am), P1 (4 am–8 am), P2 (8 am–12 noon), P3 (12–4 pm), P4 (4 pm–8 pm), and P5 (8 pm–12 midnight) in the BBDP rats at the indicated days following their becoming diabetic. Each point is an across-rats average, in turn derived from a beat-by-beat average over the four-hour recordings for each time period for each subject. The results show that prior to conversion (top-left panel) to the diabetic state (i.e., control, dark blue) blood pressure was high at P0, was lower at P1, and rose to a peak at P2 and then fell again at P3. Thereafter MAP increased gradually at P4 and leveled off at P5. A similar circadian pattern was recorded for the onset of diabetes at day 0 (Panel a, maroon) and again at Day 21 (yellow). By Day 60 (light blue) the peak diurnal blood pressure was shifted to period P3 (12–4 pm) while the night time peak increased (P5; 97.4 ± 5.2 mmHg). The circadian BP rhythms for diabetic duration 3–5 months are shown in Figure 2(b) (top-right panel). The diurnal peak of BP remained at P3 at 90 days (maroon) and 120 days (yellow) while the nighttime peak was still at P5. At 150 days (light blue) peak diurnal BP was at P2; however BP at P4 fell below the early morning dip at P1. The pattern of circadian changes in BP appeared to normalize later in diabetes, but the amplitudes of the changes are greatly reduced especially in the P3 to P4 period (Figure 2(c)).

The diabetes-resistant rats BBDR showed no appreciable shifts in the diurnal peak period over the study period.

Circadian changes in heart rate (Figure 3) followed a pattern similar to that of mean arterial pressure. Prior to conversion and at day 0 heart rate was high at P0 followed

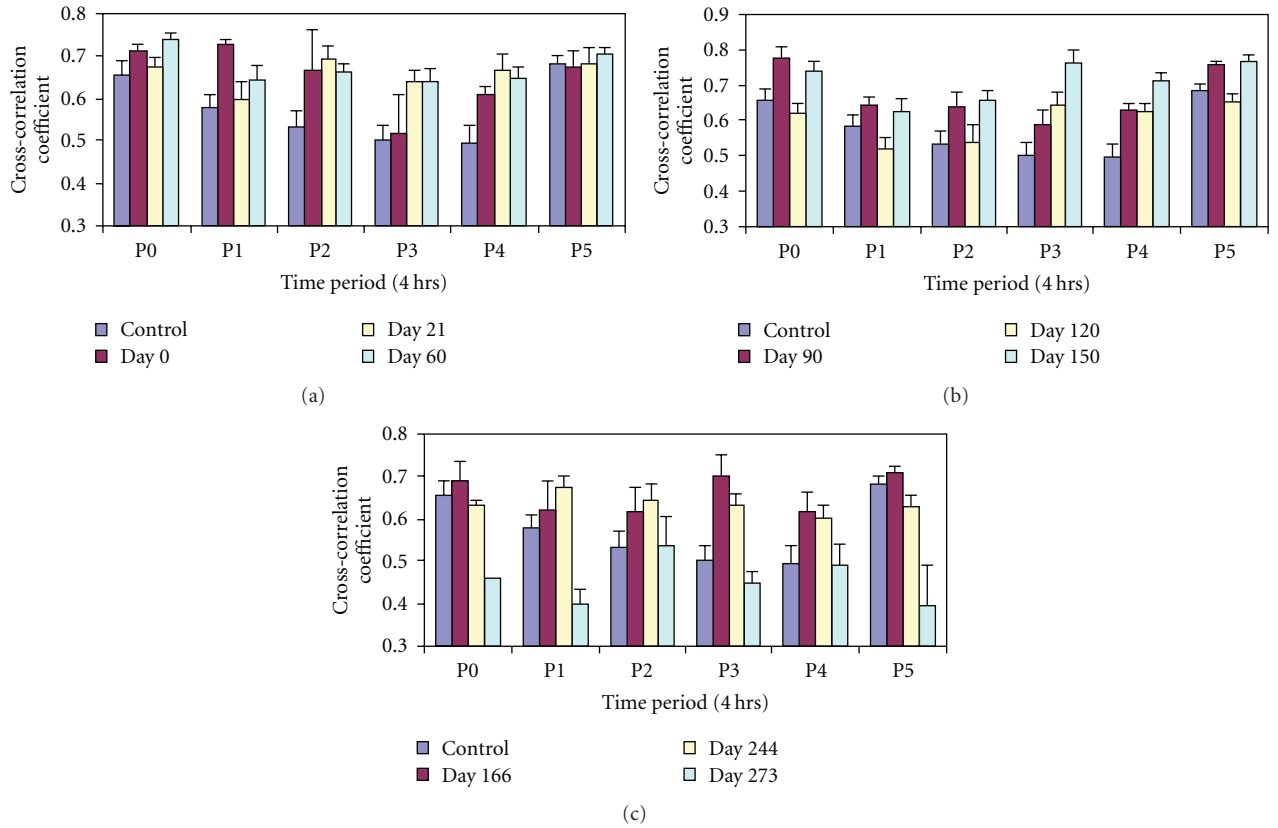


Figure 4: Graph showing circadian variations of cross-correlation coefficients (Xcorr) of blood pressure and heart rate in six periods P0–P5 at (a) 0–60 days (b) 90–150 (c) 166–273 days of diabetic conversion. The prediabetic control values were taken from n14 to n1 days. Values are mean ± SEM. $^*P < .05$.

by a dip at P1 and increasing to a peak at P2 (Figure 3(a), top-left). However from day 21 to day 90 the peak shifted to midafternoon at P3. Beyond Day 150 there was a return to normal pattern with a dip at P1 and peak at P2, another dip at P3, and gradual rise to P4 and P5 in the night (Figures 3(b) and 3(c)).

3.2. Circadian Changes in Cross Correlation Coefficient in Diabetes. The cross-correlation coefficient of heart rate and blood pressure [21] in the diabetic animals in the six time periods looks "parabolic" with P0 and P5 having the highest values (P0: 0.65 ± 0.031; P5: 0.68 ± 0.019), while the periods P3 and P4 had the lowest values (0.49 ± 0.036, 0.50 ± 0.04, resp.) in the control recording (Figure 4(a)). The cross-correlation coefficient was elevated relative to control at P1 and P2 at the onset of diabetes (i.e., day 0, maroon). By days 21 and 60 there was a midday peak at P2 with dips at P1 and P3 showing a change in pattern. The late diurnal coefficient showed little or no change from P3 to P5 at diabetic age 120–150 days (Figure 4(b)). With an increase in diabetic age the amplitude of the variation in cross-correlation coefficient across the 24-hour day was reduced by day 244, but overall values remained high. However, by the 9th month the cross-correlation coefficient fell significantly with a peak at P2 and lowest dip at P5 (0.39 ± 0.06) (Figure 4(c)) suggesting impairment or degeneration of integrative functions. In contrast the nondiabetic control rats maintained a higher cross-correlation coefficient and did not manifest a dip at P5 (BBDR: 0.65 ± 0.03, $P < .05$ versus BBDP, 0.39 ± 0.06).

Figure 5 shows the effect of diabetic age on the circadian cross-correlation coefficient in the diabetic rats. Note that, in the pre-conversion period (i.e., n14 to n1), there was considerable daily fluctuation in the cross-correlation coefficient (0.46 to 0.69). After conversion the range of the daily fluctuation narrowed, and by day 21 all the periods had converged (0.6 to 0.67); thereafter (day 60 to day166) the cross-correlation coefficient again showed a wide circadian fluctuation which was sometimes higher than the pre-conversion values. Around day 244 a reduction in the diurnal range was noticeable. This reduction was steady and continued as the cross-correlation coefficient started to decline by day 273. The nondiabetic rats showed less fluctuation in their cross-correlation coefficients. The graph shows that apart from the daily rhythm, there is also a long-term periodic cycle of about one-month duration exhibited by this parameter. This fairly regular pattern was diminished later (from day 180) in the diabetes.

The lead/lag times of the cross-correlation between HR and BP in the circadian period of the diabetic rats are shown in Figure 6. The negative values of the Lead/Lag plot indicate that heart rate changes led blood pressure changes by

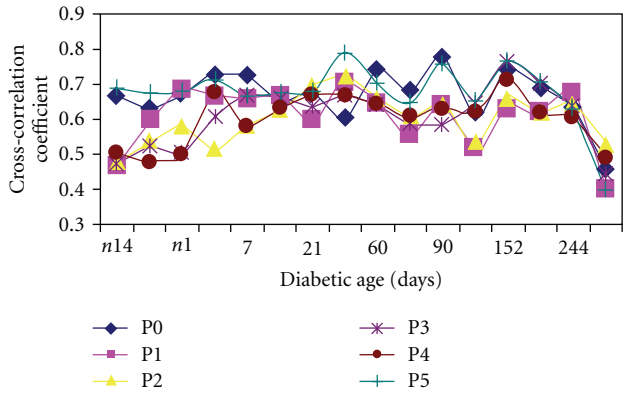


Figure 5: Graph showing longitudinal effect of diabetic age on cross-correlation coefficient of BP and HR in the 6 diurnal periods over the 9-month period. Values are means ± SD. ($n = 8$). Note the wide differences before onset of diabetes and the fall and convergence towards the last stage (273 days).

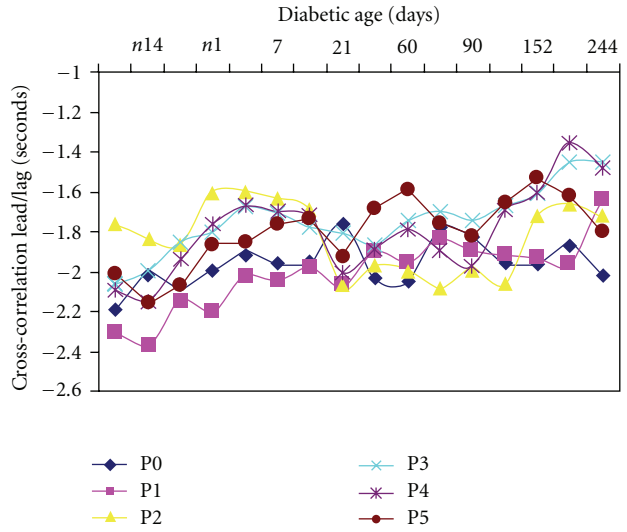


Figure 6: Changes in circadian rhythms of cross correlation lead/lag time of HR and BP in BBDP rats over the nine months diabetic period. Values are mean ± SEM. ($n = 8$). Note the gradual reduction in the lead/lag times with duration of diabetes.

the indicated value (in sec.). In the pre conversion period the values for the night and early morning periods (P0, P1, P4, and P5) were generally higher (−2.0 to −2.3 sec) while those for midday (P2 and P3) were lower (−1.6 to −2.0 sec). However about day 21 in the postconversion period there was a change in the trend with the continued reduction of the nighttime lead values, especially between Day 21 and Day 90. There was gradual reduction in the lead/lag time for the various periods as the diabetes progressed; however, by day 244 the diurnal circadian variation was significant with P0 (nighttime) having the highest lead (−2.0 ± 0.06 sec) while P3 (afternoon) had the lowest (1.45 ± 0.07 sec). When the changes were aggregated (Figures 7(a) and 7(b)) the average cross-correlation coefficients of the peak (Figure 7(a)) and nadir (Figure 7(b)) showed less fluctuation in the control diabetic-resistant rats suggesting that the between group differences are not primarily due to maturation.

4. Discussion

Results from this study in an animal model of spontaneous type 1 diabetes mellitus are associated with changes in resting circadian cardiovascular and autonomic functions. The heart is said to possess a fully functional internal clock [23]. It is also established that central suprachiasmatic nucleus and related structures act as circadian pacemakers for the whole body [24, 25]. The interplay of the central and peripheral oscillators enables the organism to adjust the activities of its organs to maximize efficiency while functioning optimally in a changing environment. Our results show that at the onset of diabetes up to the 3rd diabetic week blood pressure had two peaks at midnight/morning, and midafternoon, interlaced with a dip in the morning and followed by another dip late afternoon. This gave way to a gradual rise through the evening and late night. In this longitudinal study a phase shift was seen by the 2nd diabetic month in which the diurnal blood pressure peak shifted from midafternoon to late afternoon (P3). This new pattern was sustained to the third and fourth months of the duration of diabetes. The prediabetic pattern of blood pressure changes was displayed beyond the fifth month, but the amplitude of the rhythm was reduced. Similar circadian rhythm behavior was demonstrated in heart rate by the diabetic rats. The cross-correlation coefficient of heart rate and blood pressure showed wide circadian variation in the pre-conversion period, and the amplitude of the rhythm reduced in the postconversion period and showed little or no fluctuation in the late afternoon-night section during the third to the fifth diabetic month. A sharp fall in the cross-correlation coefficient followed in the 9-10th month with reduction of the diurnal range. Our results suggest that there is also a seasonal rhythm of oscillation in cross-correlation coefficient with a periodicity of about sixty days. This rhythm also diminished late in the study.

The lead time of the peak lead/lag plot of the cross-correlation coefficient was negative throughout the study showing that heart rate change was leading blood pressure change [21]. This value diminished with diabetic age but did not overturn, suggesting that sympathetic efferent control of the cardiovascular system was maintained, but with reduction in effectiveness [21]. The diurnal rhythm showed that the heart rate lead over blood pressure was longer in the morning period (P1) before and at onset of diabetes. This lead became reduced in most periods as the diabetes progressed.

The combination of the spontaneously diabetic rat model and telemetry has proven advantageous for this long-term longitudinal study of the circadian cardiovascular and autonomic function in diabetes. Our findings are consonant with earlier reports of time-dependent alterations in heart rate, circadian variation, pulse pressure, and cardiac autonomic control in streptozotocin- (STZ-) treated rats [18, 26, 27]. Young et al. [11] have also reported alteration of internal circadian clock in the heart of STZ-treated rats. The former

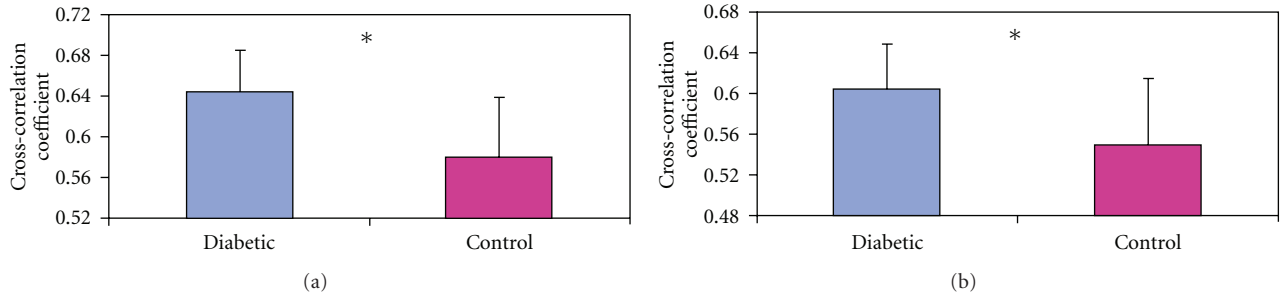


Figure 7: Bar charts showing average overall cross-correlation coefficients of blood pressure and heart rate in diabetes-prone (BBDP) and diabetes-resistant (BBDR) control rats. These are aggregate results averaged over 9 months. (a) shows the average peak Xcorr while (b) shows the average nadir Xcorr values. Values are means ± SEM. ($n = 8$ in each group). $^*P < .05$.

were acute studies or intermittent-duration studies lasting one day, 8 weeks, and ten weeks, respectively, and some used indwelling arterial cannula for blood pressure measurement. To the best of our knowledge the present study is unique because we not only measured continuous prediabetic data, but we also recorded during the diabetic conversion period and, thereafter, continuous, long-term cardiovascular function. Our observations reveal that there is yet another rhythmic long-term variation of cardiovascular function. This rhythm has a periodicity of about sixty days which is not obvious in diabetes-resistant rats. The mechanisms underlying the reported changes in cardiovascular function were thought to be in the heart and/or neuroendocrine control. It has been recognized that STZ-induced alterations of the circadian clock of the heart may be independent of diabetes development [11]. Our results do not show a dramatic change in heart rate at onset of diabetes. This is in contrast with the severe bradycardia of about 20% [18] and 30% [28] in earlier reports that used STZ. Other reports on isolated cardiac preparations have associated STZ diabetes with depression of basal spontaneous pacemaker rate [29–31], which was not affected by nadolol or atropine [31, 32]. These findings indicated that the recorded changes were not mediated by endogenous neurotransmitter release. It was thought that changes in electrophysiological properties of the sinoatrial (SA) node of the heart, such as maximum diastolic potential, threshold, or slope of diastolic depolarization, were responsible [18].

It is not certain how these factors affect circadian rhythm in vivo. Our results show bipodal peaks in circadian rhythms over 24 hours. This may be due to central effect(s) on cardiovascular system via the autonomic nervous system.

We have applied computational cross-correlation coefficient analysis of the changes in heart rate and blood pressure to the circadian rhythm and the long-term variability of heart rate and blood pressure in these animals. This method has been shown to be advantageous for investigating dynamic arterial blood pressure and heart rate control [21, 33]. This method revealed different changes in circadian rhythms at different times in the development of diabetes. In the control period the circadian rhythm consisted of a unipodal curve with a peak in the night and a dip in the midday. Immediately at conversion to diabetes the circadian rhythm showed a sustained peak of the cross-correlation coefficient into the mornings. However by the second month the relationship changed to a bipodal curve with peaks in the night and midday and dips in the morning and afternoon. These observations point to changes in autonomic cardiovascular control. This pattern was maintained through the 8th month when the peaks were flattened. The cross-correlation coefficient remained positive indicating [21] that sympathetic control was maintained, though with fluctuations. Thus it can be surmised that in this period permanent damage to autonomic regulatory mechanisms may not have occurred, but some destabilization of the resting tone may be in place. In the ninth month we observed a significant reduction in cross-correlation coefficient and a phase shift in the peaks and dips with the nighttime having the lowest dip, and this did not occur in the diabetes-resistant rats. This may mark the beginning of irreversible impairment of autonomic and cardiovascular function.

In classic blood pressure driven changes as in baroreflex tests, haemorrhage and postural change, BP change is followed reflexly by a compensatory change in HR yielding a negative cross-correlation with BP leading HR. While this is true for volume expansion, compartment reduction via vasoconstriction or vasodilation, this appears not to hold true for euvolemic and nonbaroreflex adjustments [34].

In conclusion, our observations show that in the development of diabetes the circadian cardiovascular rhythms show slight alterations, though these changes only became significant at the late stage of the disease. This is consistent with impairment of integration and/or functional autonomic capacity in prolonged diabetes mellitus.

Acknowledgment

This paper was supported by NIH Grant RO1 NS039774 to the University of Kentucky.

References

[1] M. Middeke and J. Schrader, "Nocturnal blood pressure in normotensive subjects and those with white coat, primary, and secondary hypertension," *British Medical Journal*, vol. 308, no. 6929, pp. 630–632, 1994.

[2] D. Sander and J. Klingelhöfer, "Changes of circadian blood pressure patterns after hemodynamic and thromboembolic brain infarction," *Stroke*, vol. 25, no. 9, pp. 1730–1737, 1994.

[3] I. Edery, "Circadian rhythms in a nutshell," *Physiological Genomics*, vol. 3, pp. 59–74, 2000.

[4] K. Sato, F. Chatani, and S. Sato, "Circadian and short-term variabilities in blood pressure and heart rate measured by telemetry in rabbits and rats," *Journal of the Autonomic Nervous System*, vol. 54, no. 3, pp. 235–246, 1995.

[5] M. Mishina, T. Watanabe, S. Matsuoka et al., "Diurnal variations of blood pressure in dogs," *Journal of Veterinary Medical Science*, vol. 61, no. 6, pp. 643–647, 1999.

[6] V. Gross, A. F. Milia, R. Plehm, T. Inagami, and F. C. Luft, "Long-term blood pressure telemetry in AT receptor-disrupted mice," *Journal of Hypertension*, vol. 18, no. 7, pp. 955–961, 2000.

[7] J. Widimsky Jr., M. Krsek, and J. Marek, "Altered circadian blood pressure rhythm in endocrine diseases," *Experimental and Clinical Cardiology*, vol. 1, pp. 108–112, 1996.

[8] M. Middeke, M. Kluglich, and H. Holzgreve, "Circadian blood pressure rhythm in primary and secondary hypertension," *Chronobiology International*, vol. 8, no. 6, pp. 451–459, 1991.

[9] D. P. F. Duarte, V. L. Silva, A. M. Jaguaribe, D. P. Gilmore, and C. P. Da Costa, "Circadian rhythms in blood pressure in free-ranging three-toed sloths (Bradypus variegatus)," *Brazilian Journal of Medical and Biological Research*, vol. 36, no. 2, pp. 273–278, 2003.

[10] A. I. Vinik and T. Erbas, "Recognizing and treating diabetic autonomic neuropathy," *Cleveland Clinic Journal of Medicine*, vol. 68, no. 11, pp. 928–944, 2001.

[11] M. E. Young, C. R. Wilson, P. Razeghi, P. H. Guthrie, and H. Taegtmeyer, "Alterations of the circadian clock in the heart by streptozotocin-induced diabetes," *Journal of Molecular and Cellular Cardiology*, vol. 34, no. 2, pp. 223–231, 2002.

[12] S. Jain, K. K. N. Namboodri, S. Kumari, and S. Prabhakar, "Loss of circadian rhythm of blood pressure following acute stroke," *BMC Neurology*, vol. 4, pp. 1–6, 2004.

[13] S. L. Dawson, S. N. Evans, B. N. Manktelow, M. D. Fotherby, T. G. Robinson, and J. F. Potter, "Diurnal blood pressure change varies with stroke subtype in the acute phase," *Stroke*, vol. 29, no. 8, pp. 1519–1524, 1998.

[14] J. T. Korpelainen, K. A. Sotaniemi, H. V. Huikuri, and V. V. Myllylä, "Circadian rhythm of heart rate variability is reversibly abolished in ischemic stroke," *Stroke*, vol. 28, no. 11, pp. 2150–2154, 1997.

[15] A. I. Vinik, R. E. Maser, B. D. Mitchell, and R. Freeman, "Diabetic autonomic neuropathy," *Diabetes Care*, vol. 26, no. 5, pp. 1553–1579, 2003.

[16] D. L. Eckberg, S. W. Harkins, J. M. Fritsch, G. E. Musgrave, and D. F. Gardner, "Baroreflex control of plasma norepinephrine and heart period in healthy in healthy subjects and diabetic patients," *The Journal of Clinical Investigation*, vol. 78, pp. 366–374, 1986.

[17] M. Lishner, S. Akselrod, V. Mor Avi, O. Oz, M. Divon, and M. Ravid, "Spectral analysis of heart rate fluctuations. A non-invasive, sensitive method for the early diagnosis of autonomic neuropathy in diabetes mellitus," *Journal of the Autonomic Nervous System*, vol. 19, no. 2, pp. 119–125, 1987.

[18] K. K. Hicks, E. Seifen, J. R. Stimers, and R. H. Kennedy, "Effects of streptozotocin-induced diabetes on heart rate, blood pressure and cardiac autonomic nervous control," *Journal of the Autonomic Nervous System*, vol. 69, no. 1, pp. 21–30, 1998.

[19] C. N. Anigbogu and S. A. Adigun, "Blood pressure, heart rate and autonomic reflexes in Plasmodium berghei malaria infection," *Nigerian Quarterly J of Hospital Medicine*, vol. 6, pp. 47–51, 1996.

[20] National Research Council, *Guide for the Care and Use of Laboratory Animals*, National Academy Press, Washington, DC, USA, 1996.

[21] B. R. Baldridge, D. E. Burgess, E. E. Zimmerman et al., "Heart rate-arterial blood pressure relationship in conscious rat before vs. after spinal cord transaction," *American Journal of Physiology*, vol. 283, pp. R748–R756, 2002.

[22] C. N. Anigbogu, R. O. Speakman, D. L. Silcox et al., "Extended longitudinal analysis of arterial blood pressure and heart rate in unanesthetized rats with type 1 diabetes mellitus and in age-matched controls," submitted to *American Journal of Physiology*.

[23] M. E. Young, P. Razeghi, and H. Taegtmeyer, "Clock genes in the heart: characterization and attenuation with hypertrophy," *Circulation Research*, vol. 88, no. 11, pp. 1142–1150, 2001.

[24] F. Damiola, N. Le Minli, N. Preitner, B. Kornmann, F. Fleury-Olela, and U. Schibler, "Restricted feeding uncouples circadian oscillators in peripheral tissues from the central pacemaker in the suprachiasmatic nucleus," *Genes and Development*, vol. 14, no. 23, pp. 2950–2961, 2000.

[25] S. Yamazaki, R. Numano, M. Abe et al., "Resetting central and peripheral circadian oscillators in transgenic rats," *Science*, vol. 288, no. 5466, pp. 682–685, 2000.

[26] R. T. Dowell, F. L. Atkins, and S. Love, "Integrative nature and time course of cardiovascular alterations in the diabetic rat," *The Journal of Clinical Investigation*, vol. 78, pp. 366–374, 1986.

[27] S. Ramanadham and T. E. Tenner Jr., "Chronic effects of streptozotocin diabetes on myocardial sensitivity in the rat," *Diabetologia*, vol. 29, no. 10, pp. 741–748, 1986.

[28] E. Dobrzynski, D. Montanari, J. Agata, J. Zhu, J. Chao, and L. Chao, "Adrenomedullin improves cardiac function and prevents renal damage in streptozotocin-induced diabetic rats," *American Journal of Physiology*, vol. 283, no. 6, pp. E1291–E1298, 2002.

[29] M. E. Young, C. R. Wilson, P. Razeghi, P. H. Guthrie, and H. Taegtmeyer, "Alterations of the circadian clock in the heart by streptozotocin-induced diabetes," *Journal of Molecular and Cellular Cardiology*, vol. 34, no. 2, pp. 223–231, 2002.

[30] N. Akiyama, K. Okumura, Y. Watanabe et al., "Altered acethlcholine and norepinephrine concentrations in diabetic rat hearts. Role of parasympathetic nervous system in diabetic cardiomyopathy," *Diabetes*, vol. 38, no. 2, pp. 231–236, 1989.

[31] X. Li, R. D. Tanz, and K. S. K. Chang, "Effect of age and methacholine on the rate and coronary flow of isolated hearts of diabetic rats," *British Journal of Pharmacology*, vol. 97, no. 4, pp. 1209–1217, 1989.

[32] K. A. Kimball, R. H. Kennedy, and E. Seifen, "Diabetes and the control of cardiac pacemaking activity," *The FASEB Journal*, vol. 5, article A1257, 1991.

[33] D. C. Randall, D. E. Burgess, E. E. Zimmerman et al., "BP and HR cross correlations in rat before vs after spinal cord transection," *The FASEB Journal*, vol. 15, article A1145, 2001.

[34] L. Brown, D. Brown, D. Randall, and C. Knapp, "Correlation of arterial pressure, heart rate and physical activity in rats," *Federation Proceedings*, vol. 46, article A1252, 1987.

SAGE-Hindawi Access to Research
International Journal of Hypertension
Volume 2011, Article ID 954757, 8 pages
doi:10.4061/2011/954757

Review Article

Ambulatory Blood Pressure Monitoring in Diabetes and Obesity—A Review

Kazuo Eguchi

Division of Cardiovascular Medicine, Department of Medicine, School of Medicine, Jichi Medical University, 3311-1 Yakushiji, Shimotsuke, Tochigi 329-0498, Japan

Correspondence should be addressed to Kazuo Eguchi, ke112@jichi.ac.jp

Received 11 January 2011; Accepted 20 January 2011

Academic Editor: Kazuko Masuo

Diabetes mellitus and obesity are both related to the risk of cardiovascular disease and sudden death. In hypertensive guidelines, diabetes and obesity, especially abdominal obesity, are regarded as high-risk factors. Ambulatory blood pressure monitoring (ABPM) is an established method for the management of hypertension. However, ABPM is not a standard tool for the management of hypertension in diabetes and obesity. In this paper, recent data on the use of ABPM in diabetes and obesity will be discussed. In patients with diabetes, the ambulatory BP level has been shown to be better than clinic BP in predicting cardiovascular events. A riser pattern has been associated with increased risk of cardiovascular disease. White-coat hypertension and masked hypertension in diabetics constitute a moderate risk. A nondipping pattern is very common in obese hypertensive patients. In this paper, we will summarize the findings on the use of ABPM in patients with diabetes and obesity.

1. Introduction

There have been increasing numbers of diabetic and obese patients in recent years. Hypertension coexisting with diabetes and obesity has a major impact on cardiovascular prognosis. Patients with diabetes and obesity usually have other risk factors, such as dyslipidemia, sleep apnea syndrome, and metabolic syndrome. Strict control of BP has been recommended in these patients. The ACCORD trial proved that aggressive BP control has no such benefit on cardiovascular prognosis in patients with diabetes [1], but a new target level of BP in diabetes has not yet been established in response to these findings. Therefore, individualized control of BP is becoming more important in this post-ACCORD era. In this paper, we summarized the data on ABPM in diabetes and obesity.

2. Ambulatory Blood Pressure Monitoring in Diabetes

Diabetes itself is classified as a high-risk factor for cardiovascular disease, and when hypertension coexists with diabetes, not only is the cardiovascular risk magnified, but cardiovascular target organ damages such as silent cerebral infarcts (SCIs) and left ventricular hypertrophy (LVH) may progress. This is why the target level of blood pressure in diabetes is set as low as 130/80 mmHg. In a seminal paper by de la Sierra et al. based on findings from 42,947 patients included in the Spanish Society of Hypertension, ABPM registry has shown that diabetes was associated with nondipping status [2].

In clinical practice, it is sometimes very hard to identify the true blood pressure level when the BP variability is very large. In such cases, 24-hour BP monitoring (ABPM) is useful for the assessment of the actual blood pressure level and the prediction of cardiovascular prognosis. In patients with diabetes, the guidelines of the International Diabetes Federation (IDF) recommend that 24-hour ambulatory monitoring (ABPM) be used if so-called white coat hypertension is suspected, and it is limited in case of suspected white-coat hypertension [3]. On the other hand, there are no recommendations in regard to ABPM in the guidelines of the Japanese Society of Hypertension [4] or the American Diabetes Association [5]. This is largely because the data on the use of ABPM in diabetes, while gradually increasing (including in our own studies), currently remains insufficient.

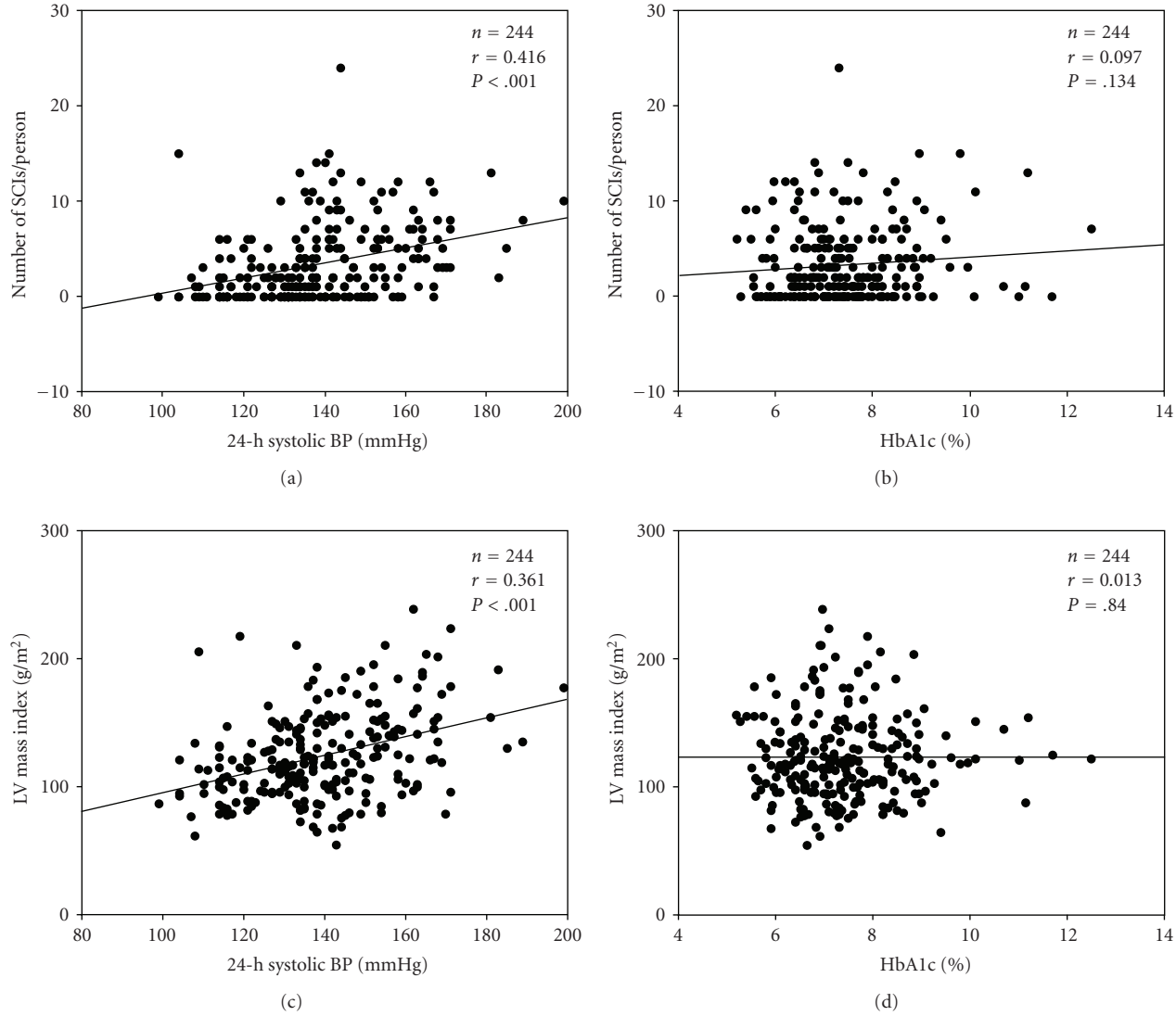


Figure 1: (a) and (b) represent 24-hour systolic blood pressure (BP), glycosylated hemoglobin (HbA1c), and number of silent cerebral infarcts (SCIs). (c) and (d) represent 24-hour systolic BP, HbA1c, and left ventricular (LV) mass index (adopted from [8]).

3. Glucose Control and Ambulatory Blood Pressure Control: Which Is More Important in Preventing Cardiovascular Events in Diabetic Patients?

Appropriate blood glucose control is a central part of the management of diabetes. Tight blood glucose control can lower not only microvascular complications, but also the risk of macrovascular disease. A prospective study in patients with type 2 diabetes reported an association between the degree of hyperglycemia and increased risk of stroke [6]. However, the United Kingdom Prospective Diabetes Study (UKPDS) reported that tight control of BP was more effective than tight control of blood glucose in the prevention of stroke [7, 8]. Thus there has been some controversy about whether BP level or glycemic control is more strongly associated with future cerebrovascular events.

At present, there are few reports comparing the effects of ambulatory BP and glycemic factors on target organ damage in diabetic patients. We performed a cross-sectional analysis to investigate factors associated with target organ damage (SCI, LVH, and albuminuria) in 244 type 2 diabetics [9]. The mean age was 65.4 years, and the study group included 122 men and 122 women. As shown in Figures 1(a) and 1(b), 24-h systolic BP was significantly correlated with the number of SCIs ($r = 0.416$, $P < .001$), but the average hemoglobin A1c level was not ($r = 0.097$, $P = .134$). Similarly, as shown in Figures 1(c) and 1(d), 24-h systolic BP was positively correlated with the LV mass index ($r = 0.361$, $P < .001$), but the hemoglobin A1c level was not positively correlated with the LV mass index ($r = 0.013$, $P = .84$). Then the subjects were divided into 4 groups according to the median values of ambulatory BP and hemoglobin A1c. As shown in Figure 2, the prevalence of SCI, multiple SCI and

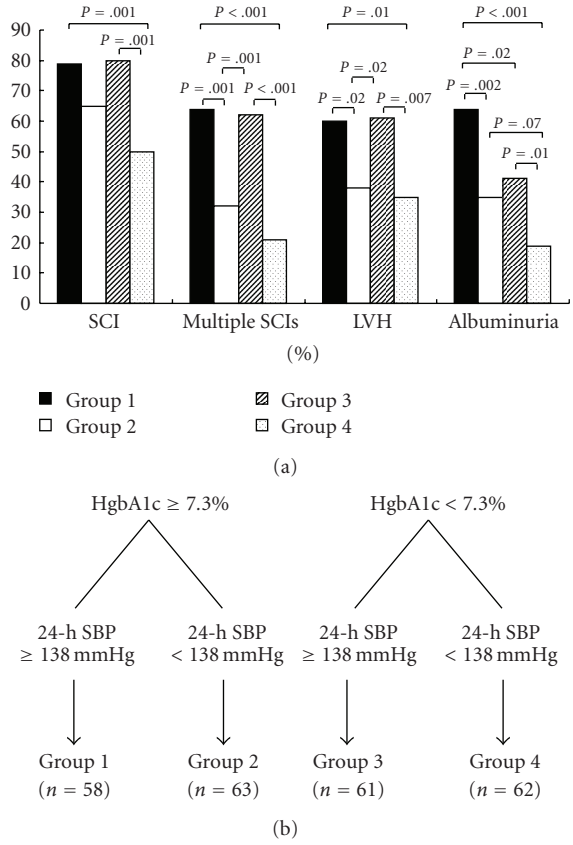


Figure 2: (a) Prevalence of hypertensive target organ damage in each group. SCI = silent cerebral infarct; multiple SCIs = three or more lesions; LVH = left ventricular hypertrophy; *P*-values noted above bars (adopted from [8]). (b) Classification of the subjects based on the median values of ambulatory systolic blood pressure (SBP) and glycosylated hemoglobin (HbA1c).

LVH were higher in Groups 1 and 3 (with high ambulatory BP) than in Group 2 (high HbA1c and normal 24-h BP) or 4 (normal HbA1c and normal 24-h BP). Group 1 had the highest value of albuminuria among the four groups. In multiple regression analyses, 24-h systolic BP, age, and duration of hypertension were significantly correlated with the number of SCIs. On the other hand, 24-h SBP and male sex were significantly correlated with LVMI. We performed the same analysis for albuminuria, and found that 24-h systolic BP was most strongly correlated with the presence of albuminuria. Ambulatory BP control was shown to be more closely associated with target organ damage of the brain, heart, and kidney than glycemic control, and it is possible that ambulatory BP control is effective in preventing future risk of cardiovascular disease in patients with diabetes.

4. Ambulatory Blood Pressure More Useful Than Clinic BP for the Management of Diabetic Patients?

The effectiveness of ABPM in the management of hypertension in diabeticpatients has not been conclusively established. Nonetheless, we have shown that ambulatory BP was superior to clinic BP in predicting cardiovascular prognosis in patients with diabetes [10] (Figure 3). This finding was in agreement with a previous report by Nakano et al. showing that increased 24-hour pulse pressure was significantly associated with cardiovascular events in diabetes [11]. In combination with the findings of masked hypertension in diabetes (described below) [12], these results lead us to advocate that all diabetic subjects should undergo ABPM at least once regardless of the presence of hypertension. Even in cases of resistant hypertension in diabetes, pseudoresistance, that is, apparent hypertension in the clinic but normal BP outside the clinic, is sometimes observed due to the white-coat effect [13].

5. Is the Circadian BP Rhythm Useful in Predicting Cardiovascular Prognosis in Patients with Diabetes?

In diabetes, an abnormal BP rhythm, that is, a non-dipper pattern, is frequently observed [2]. In patients with diabetes, nondipping pattern detected by a single ABPM study could be more reliable than nondiabetic patients as shown by Cuspidi et al. [14]. There have been several papers on circadian BP rhythm and CV prognosis in patients with diabetes. Nakano et al. performed ABPM in 325 patients with type 2 diabetes who they followed for 4 years to look at the effect of the riser pattern, an abnormal BP rhythm in which the average nighttime BP exceeds the average daytime BP, on future CV events [15]. Circadian BP rhythm was assessed by the COSINOR (an acronym formed from cosine and vector) method. A total of 288 patients were successfully followed, consisting of 201 dippers (*N* group) and 87 risers (*R* group). There were no differences in baseline gender, HbA1c, rate of smokers, lipids, or electrolytes, but the age, rate of hypertension, and rate of diabetic complications were higher in the *R* group than in the *N* group. During the follow-up period, fatal and nonfatal CV events (cerebrovascular, cardiovascular, peripheral vascular, and renovascular) occurred in 20 cases of the *N* group and 56 cases of the *R* group. Unadjusted survival and event-free survival were evaluated by Kaplan-Meier methods, and the *R* group had a significantly higher number of events than the *N* group (Log-rank $P < .001$, Figure 4). In multivariable analyses, after adjusting for various covariates, a riser pattern and age were significant predictors for both fatal and nonfatal events. Therefore, in type 2 DM, a riser pattern has been shown to be associated with fatal and nonfatal vascular events. In agreement with these results, we found that a riser pattern was associated with a 150% increase in the risk of CV disease even after adjusting for other covariates based on our data of diabetes and CV prognosis [10]. Therefore, for the prevention of CV disease in the context of diabetes, physicians should recognize that patients are at high risk when an abnormal circadian rhythm of BP is observed.

Lurbe et al. studied 75 young patients with type 1 diabetes who had had a normal BP for more than 5 years and were free from albuminuria at baseline. ABPM was

Table 1: *P*-values for the comparisons of 4 groups in Figure 6.

	SCI	Multiple SCI
WCHT versus SHT	0.122	0.010
WCHT versus WCHT + DM	0.160	0.047
WCHT versus SHT + DM	<0.001	<0.001
SHT versus WCHT + DM	0.856	1.000
SHT versus SHT + DM	<0.001	<0.001
WCHT + DM versus SHT + DM	0.001	0.001

WCHT = white coat hypertension; SHT = sustained hypertension; WCHT + DM = white coat hypertension + diabetes mellitus; SHT + DM = sustained hypertension + diabetes mellitus. *P*-values for SCI (multiple SCI) were calculated by chi-square test.

performed at baseline and 2 years later and the status of albuminuria was assessed [16]. Fourteen patients developed albuminuria, while the remaining 61 subjects did not. In the patients who developed albuminuria, nocturnal BP increased from 109.9 ± 11.3 to 114.9 ± 11.7 mmHg (P = .01), but in patients who did not develop albuminuria, nocturnal BP did not change (106.0 ± 8.8 versus 106.4 ± 14.8 mmHg). The negative predictive value for the progression for albuminuria was 91% when the night/day ratio of BP was less than 0.9. Patients with a night/day ratio of BP ≤ 0.9 showed a 70% reduction of albuminuria (95% CI 44–110, P = .01, Figure 5) compared to those with a ratio >0.9. Therefore, even in normotensive diabetes, the importance of a nondipping pattern was confirmed in this study.

6. White-Coat Hypertension in Diabetes

The effects of white-coat hypertension in diabetes have not been fully studied. We performed ABPM and brain MRI in 360 patients with hypertension, diabetes, or both. SCI, a risk factor for future stroke, was evaluated by brain MRI [17]. Among the four groups, SCI was most frequently seen in diabetic patients with sustained hypertension (defined as both high clinic BP and high ambulatory BP) and was least frequently observed in nondiabetic patients with white-coat hypertension. On the other hand, the frequency of SCI was similar between nondiabetic patients with sustained HT and diabetic patients with WCH (Figure 6) Table 1 [18]. White-coat hypertension has been considered a low-risk factor for CV events; however, when coexistent with diabetes, white-coat hypertension does have an impact via so-called white-coat syndrome [19].

In our follow-up study on the above-described cohort, the CV prognosis of diabetic WCH was much better than in the diabetic SHT group (Figure 7) [20]. However, because the number of normotensive diabetics was relatively small, we could not compare the risk of CV events between diabetic WCH and diabetic normotensives. On the other hand, Kramer et al. performed a cross-sectional study which investigated the effect of white-coat HT in diabetes on the impact of microvessel disease [21]. They studied 319 type 2 diabetics who were normotensive or who had white-coat hypertension. Normotension was defined as office BP < 140/90 mmHg and average daytime BP < 135/85 mmHg, and white-coat HT as office BP ≥ 140/90 mmHg and average daytime BP < 135/85 mmHg. Diabetic nephropathy (DN: defined by 24-hour urinary albumin excretion) and diabetic retinopathy (DR: classification of the Global Diabetic Retinopathy Group) were assessed. The results showed that 46 patients with type 2 DM were classified as having white-coat hypertension (14.4%), and 117 subjects were defined as normotensive (36.6%). 24-hour SBP was higher in the WCH group than in the normotensive group (average 24-hour BP: 124.7 ± 6.7 versus 121.0 ± 8.5 mmHg, P = .01; average daytime BP: 126.6 ± 7.2 versus 123.2 ± 8.2 mmHg, P = .01). Of note, WCH was associated with the risk of overt albuminuria (odds ratio: 4.9, 95% CI 1.3–18.7, P = .01). In the multivariable analysis, WCH was associated with overt albuminuria (odds ratio: 2.0; 95% CI 1.3–3.2, P = .02) and nonproliferative and proliferative retinopathy (odds ratio, 2.7, 95% CI 1.2–6.6, P = .02). The authors concluded that WCH with type 2 DM was associated with an increased risk of diabetic retinopathy and nephropathy. Therefore, the combination of WCH and type 2 DM constitutes some level of risk for CV events and may require some treatment.

7. Masked HT in DM

Masked hypertension (MHT), a state office BP is normal range, but out-of-office BP is high and has been shown to be associated with future risk of CV events. However, the prevalence and clinical significance of MHT in patients with DM have not been fully investigated. We assessed the association of MHT (defined as a clinic BP < 140/90 mmHg and daytime ambulatory BP > 135/85 mmHg) with micro- and macrovascular end organ damage in 81 clinically normotensive Japanese diabetics [12]. The prevalence of SCI and albuminuria was evaluated, and the left ventricular mass (LVM) was determined. Among the 81 patients, the 38 (46.9%) who were classified as having MHT showed significantly more SCIs (mean ± SEM: 2.5 ± 0.5 versus 1.1 ± 0.2, P = .017), and significantly higher incidence of albuminuria (39% versus 16%, P = .025), but no increase of LVMI compared to the true normotensive group. We concluded that the prevalence of MHT in this diabetic population was 47%, a surprisingly high result. Diabetic patients with MHT showed evidence of brain and kidney damage. Leitão et al. performed a similar study in 135 normotensive patients with type 2 diabetes [22]. Patients underwent urinary albumin excretion rate (UAER) measurement, echocardiography, and 24-h ambulatory blood pressure monitoring (ABPM). The definition of masked hypertension was the same as in our study. The prevalence of masked hypertension was 30% (n = 41). UAER and LV wall thickness were significantly higher in the group with masked hypertension than in the normotensives. After adjustments for covariates, all associations were sustained for daytime systolic blood pressure but not for office systolic blood pressure. Hence out-of-office monitoring of BP may be indicated even in diabetics whose BPs are normal in the clinic.

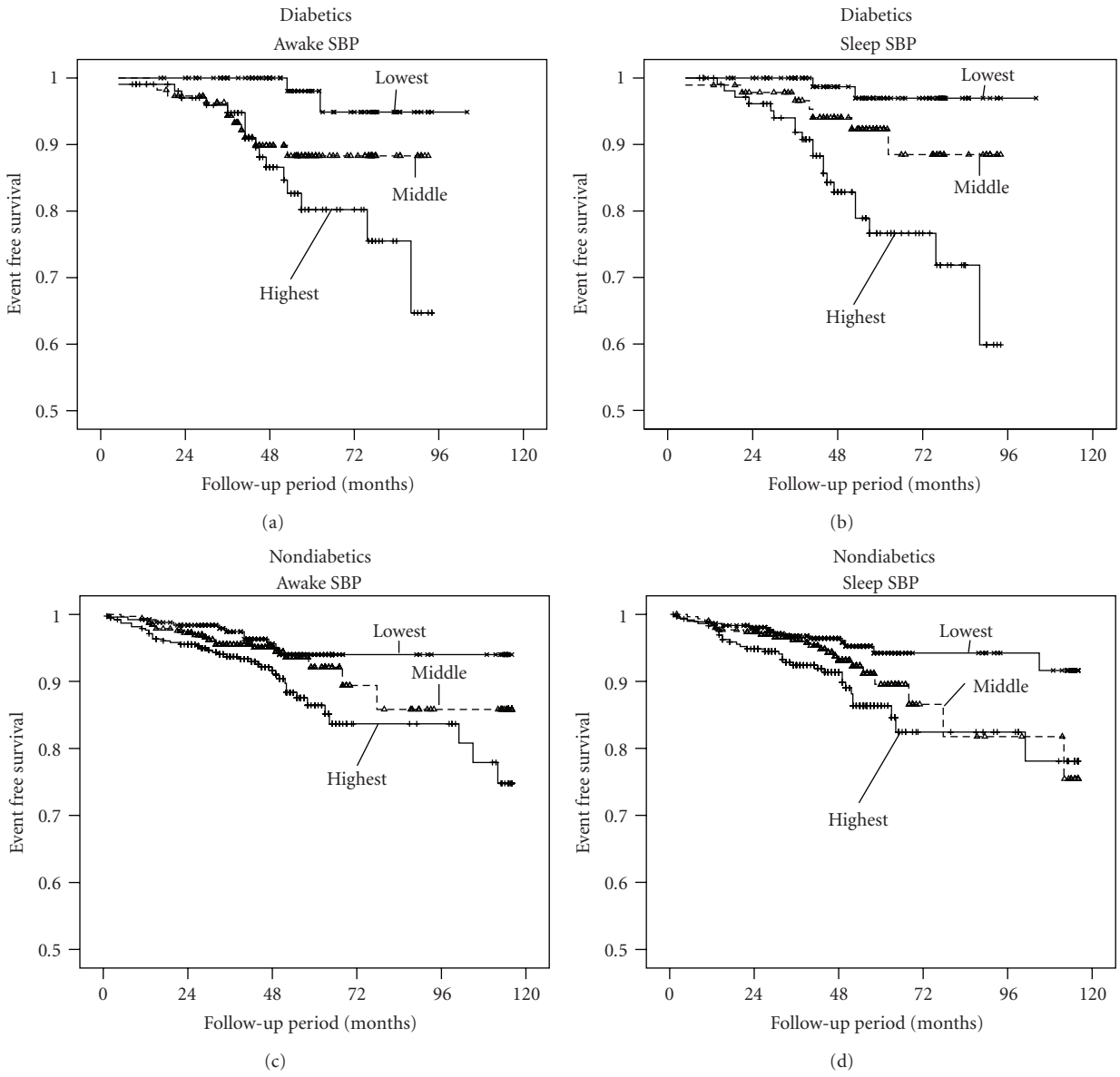


Figure 3: Event-free survival Kaplan-Meier curves for three categories of awake and sleep SBP. The log-rank statistic between the highest- and lowest-awake SBP is 11.2 ($P = .001$) for the diabetes and 8.4 ($P = .004$) for the non-diabetes group, while that between the middle- and lowest-awake SBP is 4.5 ($P = .03$) for the diabetes and 1.0 ($P = .32$) for the non-diabetes group. The log-rank statistic between the highest- and middle-awake SBP is 1.8 ($P = .19$) for the diabetes and 4.0 ($P = .046$) for the non-diabetes group. The log-rank statistic between the highest- and lowest-sleep SBP is 16.3 ($P < .001$) for the diabetes and 11.3 ($P = .001$) for the non-diabetes group, and that between the middle- and lowest-sleep SBP is 3.3 ($P = .07$) for the diabetes and 3.8 ($P = .05$) for the non-diabetes group. The log-rank statistic between the highest- and lowest-sleep SBP is 6.4 ($P = .01$) for the diabetes and 1.9 ($P = .17$) for the non-diabetes group. SBP indicates systolic blood pressure (adopted from [10]).

8. Ambulatory Blood Pressure Monitoring in the Obese

There has been conflicting evidence that obesity or overweight is associated with abnormal circadian rhythm of BP. Kotsis et al. demonstrated that normal nocturnal BP reduction was significantly decreased from normal weight to obese in 3,216 untreated hypertensive patients. The prevalence of nondippers was much greater in the obese than in the normal weight group (71.4% versus 41.1% in the normotensive and 72.7% versus 61.5% in the hypertensive subsets) [23]. In the Oman Family Study ($n = 1,124$), BMI was reported to be significantly associated with a nocturnal dipping pattern ($r = -0.23$) in a multivariate model among patients with metabolic syndrome [24]. In a data from the Spanish Society of Hypertension registry, obesity was one of the determinants of non-dipper pattern [2]. In contrast, Diamantopoulos et al. examined 226 (116 male and 110 female) overweight

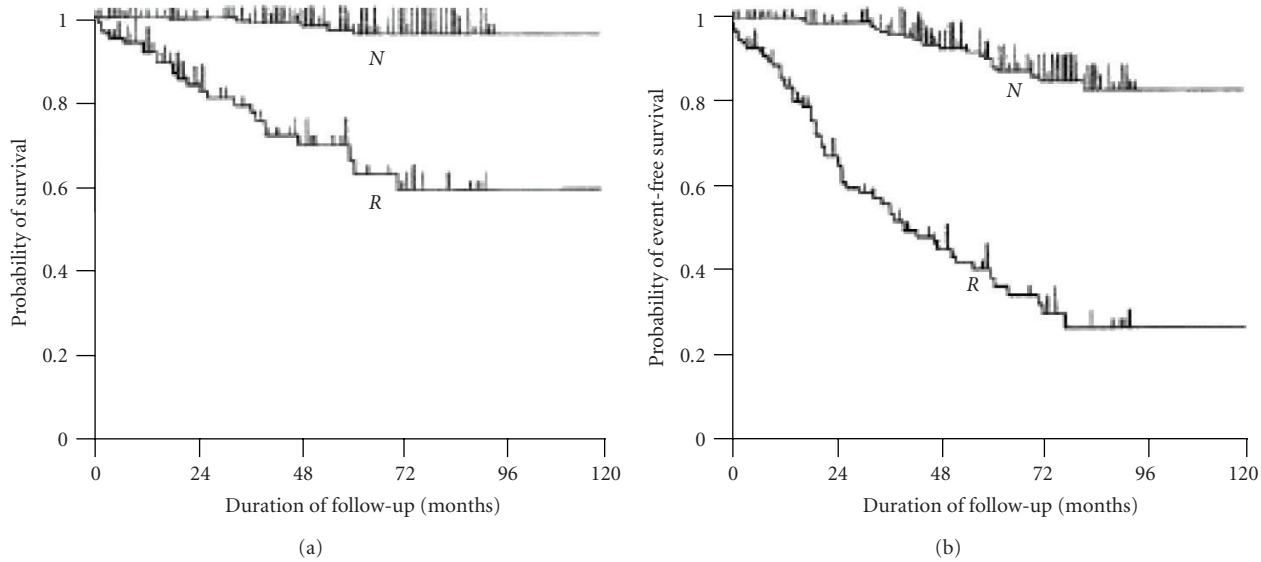


Figure 4: Survival curves (a) and event-free survival curves (b) of diabetic subjects with normal (N) and reversed circadian BP rhythm. The unadjusted relative risk for diabetic subjects with a reversed circadian BP rhythm was 20.6-fold higher than that of subjects with a normal rhythm ($P < .001$; Cox-Mantel's test) for survival curves (a), and 12.9-fold higher than that of subjects with a normal rhythm ($P < .001$; Cox-Mantel's test) for event-free survival curves (b) (adopted from [11]).

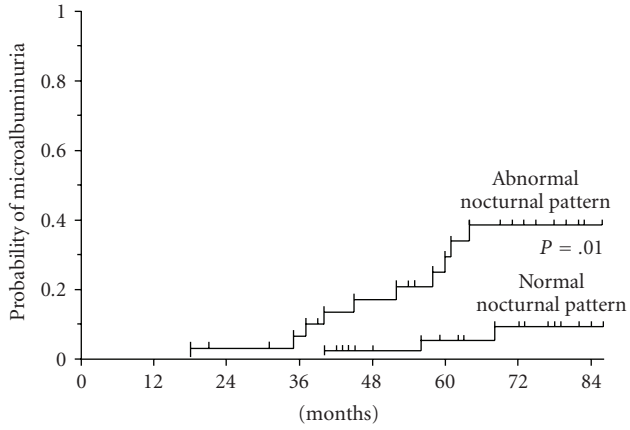


Figure 5: Kaplan-Meier curves showing the probability of microalbuminuria according to the pattern of daytime and nighttime systolic pressure. The probability of microalbuminuria differed significantly between the two groups ($P = .01$ by the log-rank test). The risk of microalbuminuria was 70% lower in the subjects with a normal nocturnal pattern (adopted from [16]).

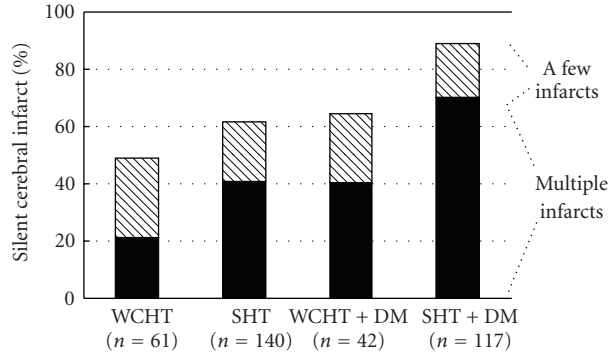


Figure 6: Prevalence of SCIs detected by brain MRI. Multiple SCIs are defined as ≥3 infarcts per person. The overall probability values for 4-group comparisons were determined by chi-square test as shown in Table 1 (adopted from [17]).

and obese subjects (BMI > 27 kg/m^2) with newly diagnosed essential hypertension. There were no significant differences in BMI between the dippers and nondippers [25]. Obese men had an increased heart rate and diastolic BP compared to normal and overweight men, but those were similar between the normal and obese women [26]. Such a gender difference could reflect some pathophysiological mechanism of BP and obese status. Because obesity is associated with many other factors, such as diabetes, Metabolic Syndrome (MS), and Sleep apnea syndrome, it is difficult to isolate any single component in human studies. Further studies will be needed to examine the relationship between obesity and dipping patterns.

9. Metabolic Syndrome and Circadian Rhythm of BP

There has been accumulating evidence that metabolic syndrome is associated with nondipping of BP. Hermida et al. studied 1770 nondiabetic untreated hypertensive patients, and performed ABPM for 48 hours [27]. They found that the prevalence of a nondipping profile was significantly higher in patients with MS (46.1% versus 37.5% in patients without MS, $P < .001$). The single most relevant factor in the

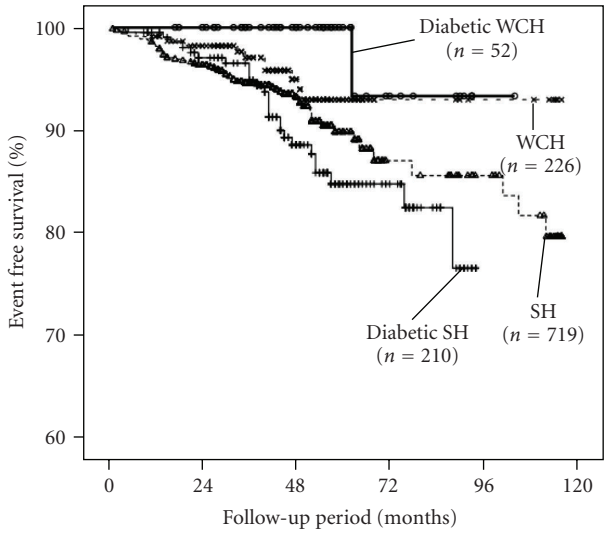


Figure 7: Curves for event-free survival without a cardiovascular event. The overall log-rank statistic for the 4-group comparison was 8.8 ($P = .032$). The log-rank statistics for the intergroup comparisons were 4.9 ($P = .028$; diabetic SH versus diabetic WCH), 2.08 ($P = .15$; diabetic SH versus SH), and 5.1 ($P = .024$; diabetic SH versus WCH). However, the value in the diabetic WCH group was not significantly different from that in the SH group ($\chi^2 = 3.0$, $P = .08$) or WCH group ($\chi^2 = 1.2$, $P = .28$) and that in the SH group was not significantly different from that in the WCH group ($\chi^2 = 2.2$, $P = .14$). SH, sustained hypertension; WCH, white-coat hypertension (Adopted from [20]).

definition of MS associated with nondipping was elevated waist circumference. There are other reports supporting the relationship between MS and a nondipping pattern [24, 28–30]. Additionally, nondipping status has been shown to be an independent predictor of glucose tolerance and several other metabolic abnormalities [31]. In contrast, other studies reported no difference in the ambulatory BP patterns between patients with and those without MS. With regard to the components of MS, glucose and abdominal obesity were two important components, but the number of components itself was also a determinant of the nondipping pattern. The common pathological states between MS and the nondipping status would be hyperinsulinemia and resultant sympathetic hyperactivity. However, it is not clear which component is the most important factor in determining nondipping status in the MS, because many factors which are related to nondipping patterns, such as abdominal obesity, diabetes, and sleep apnea syndrome, coexist in the same individuals. Further studies will be needed to clarify the relationship between MS and the nondipping pattern.

10. Conclusion

In patients with diabetes and obesity, ABPM should be performed at least once for the better risk stratification of hypertension. Early detection of nocturnal hypertension (in its most extreme form, a "riser pattern") is very important for preventing cardiovascular events. ABPM data are also effective to improve adherence to therapy. Further studies will be needed for the proper application of ABPM in such high-risk populations.

References

[1] W. C. Cushman, G. W. Evans, R. P. Byington et al., "Effects of intensive blood-pressure control in type 2 diabetes mellitus," *The New England Journal of Medicine*, vol. 362, no. 17, pp. 1575–1585, 2010.

[2] A. de la Sierra, J. Redon, J. R. Banegas et al., "Prevalence and factors associated with circadian blood pressure patterns in hypertensive patients," *Hypertension*, vol. 53, no. 3, pp. 466–472, 2009.

[3] P. Home, "Global guideline for type 2 diabetes: recommendations for standard, comprehensive, and minimal care," *Diabetic Medicine*, vol. 23, no. 6, pp. 579–593, 2006.

[4] T. Ogihara, K. Kikuchi, H. Matsuoka et al., "The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009)," *Hypertension Research*, vol. 32, no. 1, pp. 3–107, 2009.

[5] American Diabetes Association, "Diagnosis and classification of diabetes mellitus," *Diabetes Care*, vol. 34, supplement 1, pp. S62–S69, 2010.

[6] S. Lehto, T. Rönnemaa, K. Pyörälä, and M. Laakso, "Predictors of stroke in middle-aged patients with non-insulin-dependent diabetes," *Stroke*, vol. 27, no. 1, pp. 63–68, 1996.

[7] R. Turner, R. Holman, I. Stratton et al., "Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38," *British Medical Journal*, vol. 317, no. 7160, pp. 703–713, 1998.

[8] I. M. Stratton, A. I. Adler, H. A. W. Neil et al., "Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study," *British Medical Journal*, vol. 321, no. 7258, pp. 405–412, 2000.

[9] K. Eguchi, J. Ishikawa, S. Hoshide, S. Ishikawa, K. Shimada, and K. Kario, "Impact of blood pressure vs. glycemic factors on target organ damage in patients with type 2 diabetes mellitus," *Journal of Clinical Hypertension*, vol. 8, no. 6, pp. 404–410, 2006.

[10] K. Eguchi, T. G. Pickering, S. Hoshide et al., "Ambulatory blood pressure is a better marker than clinic blood pressure in predicting cardiovascular events in patients with/without type 2 diabetes," *American Journal of Hypertension*, vol. 21, no. 4, pp. 443–450, 2008.

[11] S. Nakano, K. Konishi, K. Furuya et al., "A prognostic role of mean 24-h pulse pressure level for cardiovascular events in type 2 diabetic subjects under 60 years of age," *Diabetes Care*, vol. 28, no. 1, pp. 95–100, 2005.

[12] K. Eguchi, J. Ishikawa, S. Hoshide, T. G. Pickering, K. Shimada, and K. Kario, "Masked hypertension in diabetes mellitus: a potential risk," *Journal of Clinical Hypertension*, vol. 9, no. 8, pp. 601–607, 2007.

[13] K. Eguchi, T. G. Pickering, and K. Kario, "Why is blood pressure so hard to control in patients with type 2 diabetes?" *Journal of the Cardiometabolic Syndrome*, vol. 2, no. 2, pp. 114–118, 2007.

[14] C. Cuspidi, S. Meani, L. Lonati et al., "Short-term reproducibility of a non-dipping pattern in type 2 diabetic hypertensive patients," *Journal of Hypertension*, vol. 24, no. 4, pp. 647–653, 2006.

[15] S. Nakano, M. Fukuda, F. Hotta et al., "Reversed circadian blood pressure rhythm is associated with occurrences of both fatal and nonfatal vascular events in NIDDM subjects," *Diabetes*, vol. 47, no. 9, pp. 1501–1506, 1998.

[16] E. Lurbe, J. Redon, A. Kesani et al., "Increase in nocturnal blood pressure and progression to microalbuminuria in type 1 diabetes," *The New England Journal of Medicine*, vol. 347, no. 11, pp. 797–805, 2002.

[17] K. Kario, T. G. Pickering, T. Matsuo, S. Hoshide, J. E. Schwartz, and K. Shimada, "Stroke prognosis and abnormal nocturnal blood pressure falls in older hypertensives," *Hypertension*, vol. 38, no. 4, pp. 852–857, 2001.

[18] K. Eguchi, K. Kario, and K. Shimada, "Greater impact of coexistence of hypertension and diabetes on silent cerebral infarcts," *Stroke*, vol. 34, no. 10, pp. 2471–2474, 2003.

[19] K. Kario and T. G. Pickering, "White-coat hypertension or white-coat hypertension syndrome: which is accompanied by target organ damage?" *Archives of Internal Medicine*, vol. 160, no. 22, pp. 3497–3498, 2000.

[20] K. Eguchi, S. Hoshide, J. Ishikawa et al., "Cardiovascular prognosis of sustained and white-coat hypertension in patients with type 2 diabetes mellitus," *Blood Pressure Monitoring*, vol. 13, no. 1, pp. 15–20, 2008.

[21] C. K. Kramer, C. B. Leitão, L. H. Canani, and J. L. Gross, "Impact of white-coat hypertension on microvascular complications in type 2 diabetes," *Diabetes Care*, vol. 31, no. 12, pp. 2233–2237, 2008.

[22] C. B. Leitão, L. H. Canani, C. K. Kramer, J. C. Boza, A. F. Pinotti, and J. L. Gross, "Masked hypertension, urinary albumin excretion rate, and echocardiographic parameters in putatively normotensive type 2 diabetic patients," *Diabetes Care*, vol. 30, no. 5, pp. 1255–1260, 2007.

[23] V. Kotsis, S. Stabouli, M. Bouldin, A. Low, S. Toumanidis, and N. Zakopoulos, "Impact of obesity on 24-hour ambulatory blood pressure and hypertension," *Hypertension*, vol. 45, no. 4, pp. 602–607, 2005.

[24] M. O. Hassan, D. Jaju, S. Albarwani et al., "Non-dipping blood pressure in the metabolic syndrome among Arabs of the Oman family study," *Obesity*, vol. 15, no. 10, pp. 2445–2453, 2007.

[25] E. J. Diamantopoulos, E. Andreadis, G. Tsourous et al., "Insulin resistance and blood pressure circadian variation in an obese hypertensive population," *Clinical and Experimental Hypertension*, vol. 28, no. 7, pp. 625–630, 2006.

[26] A. Kagan, H. Faibel, G. Ben-Arie, Z. Granevitze, and J. Rapoport, "Gender differences in ambulatory blood pressure monitoring profile in obese, overweight and normal subjects," *Journal of Human Hypertension*, vol. 21, no. 2, pp. 128–134, 2007.

[27] R. C. Hermida, L. Chayán, D. E. Ayala et al., "Association of metabolic syndrome and blood pressure nondipping profile in untreated hypertension," *American Journal of Hypertension*, vol. 22, no. 3, pp. 307–313, 2009.

[28] Z. Tartan, H. Uyarel, H. Kasikcioglu et al., "Metabolic syndrome as a predictor of non-dipping hypertension," *Tohoku Journal of Experimental Medicine*, vol. 210, no. 1, pp. 57–66, 2006.

[29] G. P. Vyssoulis, E. A. Karpanou, S. M. G. Kyvelou et al., "Nocturnal blood pressure fall and metabolic syndrome score in hypertensive patients," *Blood Pressure Monitoring*, vol. 12, no. 6, pp. 351–356, 2007.

[30] D. E. Ayala, R. C. Hermida, L. Chayán, A. Mojón, M. J. Fontao, and J. R. Fernández, "Circadian pattern of ambulatory blood pressure in untreated hypertensive tatients with and without metabolic syndrome," *Chronobiology International*, vol. 26, no. 6, pp. 1189–1205, 2009.

[31] O. Ukkola, R. L. Vasunta, and A. Y. Kesäniemi, "Non-dipping pattern in ambulatory blood pressure monitoring is associated with metabolic abnormalities in a random sample of middle-aged subjects," *Hypertension Research*, vol. 32, no. 11, pp. 1022–1027, 2009.

SAGE-Hindawi Access to Research
International Journal of Hypertension
Volume 2011, Article ID 398065, 6 pages
doi:10.4061/2011/398065

Research Article

Management of Hypertension and Diabetes in Obesity: Non-Pharmacological Measures

Joseph M. Pappachan,[1] Elias C. Chacko,[2] Ganesan Arunagirinathan,[3] and Rajagopalan Sriraman[4]

[1] *Department of Medicine, Grantham and District Hospital, NG31 8DG East Midlands, UK*
[2] *Department of Medicine, Singapore General Hospital, Singapore 169608*
[3] *Department of Diabetes and Endocrinology, The Royal Infirmary of Edinburgh, Edinburgh, UK*
[4] *Department of Diabetes and Endocrinology, Lincoln County Hospital, LN2 5QY East Midlands, UK*

Correspondence should be addressed to Joseph M. Pappachan, drpappachan@yahoo.co.in

Received 20 January 2011; Accepted 24 January 2011

Academic Editor: Kazuko Masuo

Obesity has become a global epidemic over the past few decades because of unhealthy dietary habits and reduced physical activity. Hypertension and diabetes are quite common among obese individuals and there is a linear relationship between the degree of obesity and these diseases. Lifestyle interventions like dietary modifications and regular exercise are still important and safe first-line measures for treatment. Recently, bariatric surgery has emerged as an important and very effective treatment option for obese individuals especially in those with comorbidities like hypertension and diabetes. Though there are few effective drugs for the management of obesity, their efficacy is only modest, and they should always be combined with lifestyle interventions for optimal benefit. In this paper we aim to outline the non-pharmacological measures for the management of hypertension and diabetes in obesity.

1. Introduction

Hypertension, diabetes mellitus and obesity together form 24% of the global risk for mortality [1]. Cardiovascular disorders related to these life-style diseases form the major cause of morbidity and mortality among the sufferers worldwide. Obesity has become a global epidemic in the past few decades. Among the adult US population, 33.8% are obese, and another 34.2% are overweight [2]. Obesity is a risk factor for many diseases of which hypertension and type 2 diabetes mellitus are the most important.

Obese individuals (those with body mass index (BMI) more than 30 kg/m^2) were found to have higher risk for diabetes mellitus (age-adjusted odds ratio (OR) = 3.66) and hypertension (age-adjusted OR = 3.72) compared to those with normal body weight [3]. Overweight individuals also had higher risk for diabetes and hypertension (age-adjusted OR = 1.59 and 1.88, resp.) and those with morbid obesity (BMI > 40 kg/m^2) had the highest risk (age-adjusted OR = 7.37 and 6.38, resp.) [3]. As there is a significant linear relationship between body weight and these two diseases, control of excess bodyweight is important for their prevention and treatment.

Over the past few decades, a lot of effective drugs have been developed for the treatment of hypertension and diabetes. However, the pharmacotherapy of obesity is still not very promising without lifestyle modification and/or surgical intervention. Therefore, we aim to discuss the treatment options without drugs for management of hypertension and diabetes in obesity through this paper.

2. Life-Style Interventions for Treatment of Hypertension and Diabetes in Obesity

2.1. Exercise for the Obese Hypertensive. The role of physical activity for treatment of hypertension is wellknown [4–6]. Aerobic exercise has shown to be associated with reduction

of systolic blood pressure (SBP) by 3.84 mm Hg and diastolic blood pressure (DBP) by 2.58 mm Hg in a meta-analysis examining large data from 54 randomized controlled trials [4]. More profound reduction of SBP (14.77 mm Hg) and DBP (5.63 mm Hg) has been observed in a recent study among obese patients after a 12-month regular exercise program along with dietary changes [7]. Significant reduction in body weight and cardiometabolic parameters like insulin resistance and hepatic fat also have been observed among the participants in this study.

Regular exercise along with dietary modifications has shown to be associated with significantly greater reduction in both SBP (4.5 mm Hg) and DBP (2.4 mm Hg) when compared with dietary adjustments alone among hypertensive patients [8]. Reduction in body weight was also higher among the former group. Weight loss has been found to be associated with a decrease in arterial stiffness [8, 9]. Better control of blood pressure among obese hypertensives following weight loss may be partly due to the reduction in arterial stiffness. Even minor reduction in the body weight has been associated with better control of hypertension and cardiovascular risk factors [10].

An average weight loss of 3.0 kg through lifestyle interventions corresponded 2.5 years later with a 30% reduction in combined cardiovascular events, poorly controlled blood pressure and the need to reinitiate antihypertensive medications [11]. Reductions in total body and abdominal fat, even without significant weight loss achieved through regular exercise, were found to be associated with improved SBP, DBP and cardiovascular risk factors [12]. Diet, Exercise, and Weight Loss Intervention Trial (DEW-IT) showed that exercise-incorporated lifestyle interventions can result in significantly better BP control among patients taking pharmacotherapy for hypertension [13].

2.2. Exercise for Diabetes in Obesity. Regular exercise improves glycemic control in all forms of diabetes. Insulin resistance is the major cause for hyperglycemia in obese diabetics and physical activity is one of the best ways to reduce insulin resistance [7, 14–16]. Physical activity improves insulin resistance through various mechanisms. Hepatic lipid accumulation is one of the primary mechanisms that drive obesity-related insulin resistance and type 2 diabetes, and exercise can reduce the free fatty acid-induced hepatic insulin resistance [14]. Reversal of hepatic insulin resistance is related to the reduction in central adiposity induced by exercise. Weight loss achieved by regular exercise was found to improve hepatic insulin sensitivity better than weight loss induced through calorie restriction [16]. Exercise can also reduce hepatic glucose production and augment insulin-mediated suppression of hepatic glucose output [14, 17].

Exercise increases skeletal muscle glucose uptake and utilization. This effect is mediated by an increase in expression of glucose transporter 4 (GLUT 4, an isoform of glucose transporter) in skeletal muscle [18]. Exercise also induces an increase in muscle insulin sensitivity [19]. Through these adaptations in the muscle, physical activity improves the peripheral glucose disposal and insulin resistance, and augments the glycemic control among obese individuals with diabetes.

Aerobic exercise has been demonstrated to improve the insulin sensitivity and reduce the glycemic load, without any significant change in energy intake, among obese men and women, and exercise may have a synergistic effect to reduce insulin resistance when combined with a low glycemic diet [15]. Despite the absence of weight loss, moderate-intensity exercise was associated with significant reductions in visceral obesity (an important determinant of insulin resistance) among obese individuals with type 2 diabetes [20].

Look AHEAD (Action for Health and Diabetes) is a US National Institutes of Health-funded long-term multicentric clinical trial studying the effect of an intensive lifestyle intervention on cardiovascular disease (CVD) morbidity and mortality in overweight/obese people with type 2 diabetes. Weight loss achieved by exercise and dietary changes among the intervention group resulted in better glycemic control and CVD risk factors [21]. Reduced medication use and lower therapeutic costs were the other benefits observed among this group after one year [22].

Diabetes Prevention Program (DPP) was a prospective multi-centre randomized clinical trial examining the diabetes incidence in overweight/obese adults managed with intensive lifestyle intervention or metformin or placebo. Exercise-incorporated lifestyle intervention reduced the incidence of type 2 diabetes by 58% and metformin by 31% when compared with placebo after 2.8 years of follow up [23]. Decreased diabetes risk by lifestyle intervention observed in the DPP trial was related to reductions of body weight, BMI, and central adiposity [24]. Follow up data from the trial has shown that the cumulative incidence of diabetes remained lowest in the lifestyle intervention group even after 10 years [25].

2.3. Dietary Measures for Hypertension Management in Obesity. The Dietary Approaches to Stop Hypertension (DASH) trial was a multicenter, randomized clinical trial that examined the effects of dietary patterns on blood pressure. This landmark study showed that a diet rich in fruits, vegetables and low-fat diary products along with reduced saturated and total fat lowered systolic blood pressure by 5.5 mm Hg and diastolic blood pressure by 3.0 mm Hg more than a control diet [26]. For overweight or obese persons, the addition of exercise and weight loss to the DASH diet resulted in even larger BP reductions and cardiac risk factors [8].

Dietary sodium restriction (to <3 grams/day) is an important component of management of any patient with hypertension. Overweight/obese hypertensives were found to have higher salt sensitivity in observational studies [27, 28]. Obese subjects were also found to have an enhanced rate of renal tubular sodium reabsorption [29]. Animal studies showed that obesity is associated with salt retention by the kidney through reduction of natriuresis (increased clearance of atrial natriuretic peptide by adipose cells), increased sympathetic activity and activation of renin angiotensin-aldosterone system (and high blood pressure as

a consequence) [30]. Hence, the beneficial effect of salt restriction would be more profound among obese hypertensives. A recent large population-based study reported from China adds evidence to this concept [31].

A long-term dietary intervention trial with a nutrient-fortified prepared meal plan (approximately 22% energy from fat, 58% from carbohydrate and 20% from protein) was found to be associated with better control of BP among obese/overweight hypertensives than with the usual care diet [32]. The dietary intervention group in this study also achieved better weight loss and improved cardiovascular risk factors. Combining a daily fish meal with a weight-loss diet has an additive effect on blood pressure among overweight hypertensives [33].

A systematic review to determine the long-term effects of weight loss on hypertension through dietary interventions versus pharmacologic treatment showed that the former approach resulted in greater weight loss and BP reductions than the latter [34]. The American Dietetic Association recommends the application of medical nutrition therapy (MNT) and lifestyle counseling as an integral component of the medical treatment for management of specific disease states and conditions (including hypertension and obesity) and should be the initial step in the management of these situations [35]. When pharmacotherapy becomes necessary for control, MNT may complement or enhance its therapeutic effectiveness, thereby reducing or eliminating the need for multiple medications.

Excess alcohol consumption is well known to raise the blood pressure in human beings. However, social drinking may not be very hazardous. According to the European Society of Hypertension and Cardiology recommendation, alcohol consumption in hypertensive subjects who drink alcohol should be limited to no more than 20 to 30 gm of ethanol per day for men and no more than 10 to 20 gm for women [36]. In obese hypertensives, low levels of drinking may help to reduce calorie consumption and thus may facilitate weight reduction.

Overall, weight reduction achieved through lifestyle interventions like dietary modification and regular exercise programs (at least 30 minutes/day on most days) help obese individuals with hypertension to obtain better BP control and reduce complications related to uncontrolled hypertension.

2.4. Dietary Measures to Treat Diabetes in Obesity. Nutritional intervention is of paramount importance in preventing diabetes, managing existing diabetes and preventing/slowing diabetic complications. Total calorie intake can be distributed as follows in a type 2 diabetic: 45–65% of total calorie intake as carbohydrate, 10–30% as proteins and less than 30% as total fat (<7% saturated fat) with <300 mg/day of cholesterol [37]. Total calorie intake must be appropriate to weight management goals of the individual. Macronutrient intake should be tailored according to the metabolic status of the patient (e.g., lipid profile). Similarly, there is no evidence-based recommendation for generalization of micronutrient supplements.

For obese diabetic, a weight losing diet containing either low-carbohydrate or low-fat calorie-restricted diet may be effective in the short term (up to 1 year) [37]. Standard weight loss diets provide 500–1,000 fewer calories than estimated to be necessary for weight maintenance. Up to 10% of weight loss can be achieved in 6 months with such diets. Lipid profiles, renal function and protein intake (in those with nephropathy) of patients on low-carbohydrate-diets should be monitored and adjustments of hypoglycemic drug therapy should be made to avoid the risk of hypoglycemia. Maintenance of weight loss after one year usually depends on the adherence to lifestyle interventions.

Intensive individualized dietary advice (according to the nutritional recommendations of the European Association for the Study of Diabetes) for six months has shown to reduce HbA1c by 0.4%, body weight by 1.3 Kg, BMI by 0.5 kg/M^2 and waist circumference by 1.6 cm when compared to controls, among overweight/obese diabetics on optimal medical treatment without adequate glycemic control [38].

A carbohydrate intake of 130 grams/day is recommended for patients as this provides adequate glucose for the central nervous system, without reliance on glucose production from ingested protein or fat, for its fuel needs [39]. Long-term metabolic effects of very-low-carbohydrate diets on brain are unclear (though brain may function even on lower carbohydrate diets) and such diets may result in imbalance of energy, fiber, vitamins and minerals, and may not be palatable.

3. Bariatric Surgery for Management of Obese Individuals with Hypertension and Diabetes

Few surgical procedures in the upper gastrointestinal tract, collectively termed as bariatric surgery, have emerged as important therapeutic options for management of obesity in the recent years. They are classified as purely restrictive (limiting the stomach volume) and primarily malabsorptive [40]. Restrictive procedures commonly used now are laparoscopic adjustable gastric banding and laparoscopic vertical sleeve gastrectomy. The main malabsorptive procedure in use now is Roux-en-Y gastric bypass.

Calorie restriction may be through three mechanisms in bariatric surgery: (1) mechanical limiting of volume of the gastric pouch and reduction of its outlet (2) modulation of satiety by postprandial induction of neuro-hormonal signals (e.g., peptide YY, an anorexiant) and (3) restriction of calorie intake spontaneously adopted by patients to limit the burden of postprandial dumping syndrome [41]. Weight loss is achieved mainly through restriction of calorie intake. Significant weight loss following the surgery usually results in improvement of diabetes and hypertension.

A recent meta-analysis that included 621 studies with 888 treatment arms and 135,246 patients has shown that the weight loss overall was 38.5 kg or 55.9% excess body weight loss [42]. Overall, 78.1% of diabetic patients had complete resolution and diabetes was improved or resolved in 86.6% of patients. Improvement of diabetes usually occurs days after surgery even before significant weight loss is achieved.

Apart from calorie restriction obtained through the procedure, improvement of insulin resistance and insulin sensitivity (mainly related to weight loss) also contributes to better glycemic control among obese diabetic patients undergoing bariatric surgery. Other proposed mechanisms are through release of gut hormones like glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide (the incretin effect) and increase in the beta-cell mass [41].

Hypertension was resolved in 61.7% and resolved or improved in 78.5% of patients undergoing bariatric procedures [43]. The improvement in hypertension is mainly related to weight loss. In general, one percent reduction in body weight will decrease systolic blood pressure by 1 mm Hg and diastolic blood pressure by 2 mm Hg [43]. Reduction in salt sensitivity and alteration of renal hemodynamics brought about by weight loss may be the contributing factors for improvement of hypertension following bariatric surgery. A 14 mm Hg reduction in SBP and 12 mm Hg reduction in DBP was observed among obese hypertensives undergoing bariatric surgery in a recent clinical trial [44]. Discontinuation/ reduction of dose of antihypertensive medication can be achieved in many patients following bariatric surgery.

A recent study showed the distinct advantages of bariatric surgery over lifestyle interventions for treatment of obesity and related diseases like hypertension and diabetes [44]. The mean weight loss at one year was 30% and 8% in the surgical and lifestyle intervention groups, respectively. Remission rates of type 2 diabetes and hypertension were significantly higher in the surgery group than in the lifestyle intervention group (70 versus 33% and 49 versus 23%).

Bariatric surgery is a relatively safe (perioperative mortality rate 0.3%) procedure with only a few adverse consequences (4.3%) [45]. The most frequent and severe adverse events in the immediate postprocedure period are anastomotic leaks, hemorrhage and thromboembolic events. Long-term hazards are vitamin deficiencies, malnutrition, osteoporosis, psychiatric disorders and a slightly higher risk of accidental death [41, 46]. However, a Swedish study showed significantly reduced 10-year mortality risk with bariatric surgery when compared to nonsurgical treatment of obesity, making this treatment option a promise for many [47].

The Scottish Intercollegiate Guidelines Network (SIGN) recommends that bariatric surgery may be considered for patients with all three of the following: (a) BMI of 35 or more, (b) one or more severe comorbidities that are expected to have a meaningful clinical improvement with weight reduction (e.g., severe mobility problems, arthritis, type 2 diabetes), and (c) evidence of completion of a structured weight management program that covered diet, physical activity, and psychological and drug interventions but did not result in significant and sustained improvement in co-morbidities [48]. The most recent Diabetes Surgery Summit consensus conference recommends bariatric surgery for type 2 diabetic patients with severe obesity (BMI > 35 kg/m^2) as well as in carefully selected, moderately obese patients (BMI: 30–35 kg/m^2) who are inadequately controlled by conventional medical and behavioral therapies [49].

4. Conclusions

Weight loss achieved through lifestyle interventions like dietary adjustments and regular physical activity are safe and moderately effective measures for management of hypertension and diabetes in obesity. They also help to reduce the treatment costs related to pharmacotherapy and also to reduce the pill burden. Even when drug therapy is considered, lifestyle interventions should continue, to obtain the desired effects of medications. Bariatric surgery is more effective than lifestyle interventions for treatment and is remarkably safe in selected patient groups. These non-pharmacological interventions should be the first-line management option and should also be combined with pharmacotherapy for scientific treatment of these diseases.

References

[1] World Health Organization, "Global health risks: mortality and burden of disease attributable to selected major risks," December 2010, http://www.who.int/healthinfo/global_burden_disease/GlobalHealthRisks_report_full.pdf.

[2] K. M. Flegal, M. D. Carroll, C. L. Ogden, and L. R. Curtin, "Prevalence and trends in obesity among US adults, 1999–2008," *Journal of the American Medical Association*, vol. 303, no. 3, pp. 235–241, 2010.

[3] A. H. Mokdad, E. S. Ford, B. A. Bowman et al., "Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001," *Journal of the American Medical Association*, vol. 289, no. 1, pp. 76–79, 2003.

[4] S. P. Whelton, A. Chin, X. Xin, and J. He, "Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials," *Annals of Internal Medicine*, vol. 136, no. 7, pp. 493–503, 2002.

[5] N. A. Khan, B. Hemmelgarn, R. J. Herman et al., "The 2009 Canadian hypertension education program recommendations for the management of hypertension: part 2—therapy," *Canadian Journal of Cardiology*, vol. 25, no. 5, pp. 287–298, 2009.

[6] J. Redon, R. Cifkova, S. Laurent et al., "The metabolic syndrome in hypertension: European society of hypertension position statement," *Journal of Hypertension*, vol. 26, no. 10, pp. 1891–1900, 2008.

[7] B. H. Goodpaster, J. P. DeLany, A. D. Otto et al., "Effects of diet and physical activity interventions on weight loss and cardiometabolic risk factors in severely obese adults: a randomized trial," *Journal of the American Medical Association*, vol. 304, no. 16, pp. 1795–1802, 2010.

[8] J. A. Blumenthal, M. A. Babyak, A. Hinderliter et al., "Effects of the DASH diet alone and in combination with exercise and weight loss on blood pressure and cardiovascular biomarkers in men and women with high blood pressure: the ENCORE study," *Archives of Internal Medicine*, vol. 170, no. 2, pp. 126–135, 2010.

[9] A. L. Dengo, E. A. Dennis, J. S. Orr et al., "Arterial destiffening with weight loss in overweight and obese middle-aged and older adults," *Hypertension*, vol. 55, no. 4, pp. 855–861, 2010.

[10] J. M. Pascual, E. Rodilla, J. A. Costa et al., "Body weight variation and control of cardiovascular risk factors in essential hypertension," *Blood Pressure*, vol. 18, no. 5, pp. 247–254, 2009.

[11] K. M. McTigue, R. Hess, and J. Ziouras, "Obesity in older adults: a systematic review of the evidence for diagnosis and treatment," *Obesity*, vol. 14, no. 9, pp. 1485–1497, 2006.

[12] K. J. Stewart, A. C. Bacher, K. Turner et al., "Exercise and risk factors associated with metabolic syndrome in older adults," *American Journal of Preventive Medicine*, vol. 28, no. 1, pp. 9–18, 2005.

[13] E. R. Miller 3rd, T. P. Erlinger, D. R. Young et al., "Results of the diet, exercise, and weight loss intervention trial (DEW-IT)," *Hypertension*, vol. 40, no. 5, pp. 612–618, 2002.

[14] J. M. Haus, T. P. J. Solomon, C. M. Marchetti, J. M. Edmison, F. González, and J. P. Kirwan, "Free fatty acid-induced hepatic insulin resistance is attenuated following lifestyle intervention in obese individuals with impaired glucose tolerance," *Journal of Clinical Endocrinology and Metabolism*, vol. 95, no. 1, pp. 323–327, 2010.

[15] J. P. Kirwan, H. Barkoukis, L. M. Brooks, C. M. Marchetti, B. P. Stetzer, and F. Gonzalez, "Exercise training and dietary glycemic load may have synergistic effects on insulin resistance in older obese adults," *Annals of Nutrition and Metabolism*, vol. 55, no. 4, pp. 326–333, 2009.

[16] R. H. Coker, R. H. Williams, S. E. Yeo et al., "The impact of exercise training compared to caloric restriction on hepatic and peripheral insulin resistance in obesity," *Journal of Clinical Endocrinology and Metabolism*, vol. 94, no. 11, pp. 4258–4266, 2009.

[17] J. P. Kirwan, T. P. J. Solomon, D. M. Wojta, M. A. Staten, and J. O. Holloszy, "Effects of 7 days of exercise training on insulin sensitivity and responsiveness in type 2 diabetes mellitus," *American Journal of Physiology—Endocrinology and Metabolism*, vol. 297, no. 1, pp. E151–E156, 2009.

[18] J. O. Holloszy, "A forty-year memoir of research on the regulation of glucose transport into muscle," *American Journal of Physiology—Endocrinology and Metabolism*, vol. 284, no. 3, pp. E453–E467, 2003.

[19] J. O. Holloszy, "Invited review: exercise-induced increase in muscle insulin sensitivity," *Journal of Applied Physiology*, vol. 99, no. 1, pp. 338–343, 2005.

[20] S. Lee, J. L. Kuk, L. E. Davidson et al., "Exercise without weight loss is an effective strategy for obesity reduction in obese individuals with and without Type 2 diabetes," *Journal of Applied Physiology*, vol. 99, no. 3, pp. 1220–1225, 2005.

[21] X. Pi-Sunyer, G. Blackburn, F. L. Brancati et al., "Reduction in weight and cardiovascular disease risk factors in individuals with Type 2 diabetes one-year results of the look AHEAD trial," *Diabetes Care*, vol. 30, no. 6, pp. 1374–1383, 2007.

[22] J. B. Redmon, A. G. Bertoni, S. Connelly et al., "Effect of the Look AHEAD study intervention on medication use and related cost to treat cardiovascular disease risk factors in individuals with type 2 diabetes," *Diabetes Care*, vol. 33, no. 6, pp. 1153–1158, 2010.

[23] W. C. Knowler, E. Barrett-Connor, S. E. Fowler et al., "Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin," *New England Journal of Medicine*, vol. 346, no. 6, pp. 393–403, 2002.

[24] W. Y. Fujimoto, K. A. Jablonski, G. A. Bray et al., "Body size and shape changes and the risk of diabetes in the diabetes prevention program," *Diabetes*, vol. 56, no. 6, pp. 1680–1685, 2007.

[25] W. C. Knowler, S. E. Fowler, R. F. Hamman et al., "10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study," *Lancet*, vol. 374, no. 9702, pp. 1677–1686, 2009.

[26] L. J. Appel, T. J. Moore, E. Obarzanek et al., "A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group," *New England Journal of Medicine*, vol. 336, no. 16, pp. 1117–1124, 1997.

[27] T. Uzu, G. Kimura, A. Yamauchi et al., "Enhanced sodium sensitivity and disturbed circadian rhythm of blood pressure in essential hypertension," *Journal of Hypertension*, vol. 24, no. 8, pp. 1627–1632, 2006.

[28] I. S. Hoffmann and L. X. Cubeddu, "Increased blood pressure reactivity to dietary salt in patients with the metabolic syndrome," *Journal of Human Hypertension*, vol. 21, no. 6, pp. 438–444, 2007.

[29] P. Strazzullo, G. Barba, F. P. Cappuccio et al., "Altered renal sodium handling in men with abdominal adiposity: a link to hypertension," *Journal of Hypertension*, vol. 19, no. 12, pp. 2157–2164, 2001.

[30] J. E. Hall, "Mechanisms of abnormal renal sodium handling in obesity hypertension," *American Journal of Hypertension*, vol. 10, no. 5, part 2, pp. 49S–55S, 1997.

[31] J. Chen, D. Gu, J. Huang et al., "Metabolic syndrome and salt sensitivity of blood pressure in non-diabetic people in China: a dietary intervention study," *Lancet*, vol. 373, no. 9666, pp. 829–835, 2009.

[32] J. A. Metz, J. S. Stern, P. Kris-Etherton et al., "A randomized trial of improved weight loss with a prepared meal plan in overweight and obese patients impact on cardiovascular risk reduction," *Archives of Internal Medicine*, vol. 160, no. 14, pp. 2150–2158, 2000.

[33] T. A. Mori, D. Q. Bao, V. Burke, I. B. Puddey, G. F. Watts, and L. J. Beilin, "Dietary fish as a major component of a weight-loss diet: effect on serum lipids, glucose, and insulin metabolism in overweight hypertensive subjects," *American Journal of Clinical Nutrition*, vol. 70, no. 5, pp. 817–825, 1999.

[34] K. Horvath, K. Jeitler, U. Siering et al., "Long-term effects of weight-reducing interventions in hypertensive patients: systematic review and meta-analysis," *Archives of Internal Medicine*, vol. 168, no. 6, pp. 571–580, 2008.

[35] J. McCaffree, "Position of the American Dietetic Association: integration of medical nutrition therapy and pharmacotherapy," *Journal of the American Dietetic Association*, vol. 103, no. 10, pp. 1363–1370, 2003.

[36] G. Mancia, G. de Backer, A. Dominiczak et al., "2007 guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)," *Journal of Hypertension*, vol. 25, no. 6, pp. 1105–1187, 2007.

[37] J. P. Bantle, J. Wylie-Rosett, A. L. Albright et al., "Nutrition recommendations and interventions for diabetes: a position statement of the American Diabetes Association," *Diabetes Care*, vol. 31, supplement 1, pp. S61–S78, 2008.

[38] K. J. Coppell, M. Kataoka, S. M. Williams, A. W. Chisholm, S. M. Vorgers, and J. I. Mann, "Nutritional intervention in patients with type 2 diabetes who are hyperglycaemic despite optimised drug treatment—lifestyle Over and Above Drugs in Diabetes (LOADD) study: randomised controlled trial," *British Medical Journal*, vol. 341, p. c3337, 2010.

[39] Institute of Medicine, *Dietary Reference Intakes: Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids*, National Academies Press, Washington, DC, USA, 2002.

[40] G. Rao, "Office-based strategies for the management of obesity," *American Family Physician*, vol. 81, no. 12, pp. 1429–1449, 2010.

[41] R. Caiazzo, C. Zerrweck, R. Verhaeghe, T. Hubert, L. Arnalsteen, and F. Pattou, "Gastric bypass and glucose metabolism," *Diabetes and Metabolism*, vol. 35, no. 6, part 2, pp. 528–531, 2009.

[42] H. Buchwald, R. Estok, K. Fahrbach et al., "Weight and Type 2 diabetes after bariatric surgery: systematic review and meta-analysis," *American Journal of Medicine*, vol. 122, no. 3, pp. 248.e5–256.e5, 2009.

[43] H. Buchwald, Y. Avidor, E. Braunwald et al., "Bariatric surgery: a systematic review and meta-analysis," *Journal of the American Medical Association*, vol. 292, no. 14, pp. 1724–1737, 2004.

[44] D. Hofsø, N. Nordstrand, L. K. Johnson et al., "Obesity-related cardiovascular risk factors after weight loss: a clinical trial comparing gastric bypass surgery and intensive lifestyle intervention," *European Journal of Endocrinology*, vol. 163, no. 5, pp. 735–745, 2010.

[45] D. R. Flum, S. H. Belle, W. C. King et al., "Perioperative safety in the longitudinal assessment of bariatric surgery," *New England Journal of Medicine*, vol. 361, no. 5, pp. 445–454, 2009.

[46] T. D. Adams, R. E. Gress, S. C. Smith et al., "Long-term mortality after gastric bypass surgery," *New England Journal of Medicine*, vol. 357, no. 8, pp. 753–761, 2007.

[47] L. Sjöström, K. Narbro, C. D. Sjöström et al., "Effects of bariatric surgery on mortality in Swedish obese subjects," *New England Journal of Medicine*, vol. 357, no. 8, pp. 741–752, 2007.

[48] J. Logue, L. Thompson, F. Romanes, D. C. Wilson, J. Thompson, and N. Sattar, "Management of obesity: summary of SIGN guideline.," *British Medical Journal*, vol. 340, p. c154, 2010.

[49] F. Rubino, L. M. Kaplan, P. R. Schauer, and D. E. Cummings, "The diabetes surgery summit consensus conference: recommendations for the evaluation and use of gastrointestinal surgery to treat type 2 diabetes mellitus," *Annals of Surgery*, vol. 251, no. 3, pp. 399–405, 2010.

SAGE-Hindawi Access to Research
International Journal of Hypertension
Volume 2011, Article ID 179124, 13 pages
doi:10.4061/2011/179124

Review Article

Moving Beyond the Stigma: Systematic Review of Video Games and Their Potential to Combat Obesity

Stacey Guy, Alexandria Ratzki-Leewing, and Femida Gwadry-Sridhar

I-THINK Research, Lawson Health Research Institute, Parkwood Hospital, 801 Commissioners Road East, Suite B3041, London, ON, Canada N6C 5J1

Correspondence should be addressed to Femida Gwadry-Sridhar, femida.gwadry-sridhar@lhsc.on.ca

Received 16 January 2011; Accepted 1 February 2011

Academic Editor: Kazuko Masuo

Increasing epidemic proportions of overweight children in the United States presents formidable challenges for education and healthcare. Given the popularity and pervasiveness of video gaming culture in North American children, the perfect opportunity arises to investigate the potential of video games to promote healthful behaviour. Our objective was to systematically review the literature for possible benefits of active and educational video games targeting diet and physical activity in children. A review of English-language journal articles from 1998 to 2011 using EMBASE and PubMed was conducted. Thirty-four studies concerned with children, video games, physical, and/or nutritional outcomes were included. Results of these studies that showed some benefit (increased physical activity and nutritional knowledge as a result of gaming) demonstrate the possibility of video games to combat childhood obesity—looking beyond the stigma attached to gaming.

1. Introduction

Overweight or obesity among American children has reached epidemic proportions [1]. Over the past 25 years, childhood overweight or obesity has nearly quadrupled in the United States, affecting almost 17% of children and adolescents aged 2–19 in 2007-2008 [2, 3]. Childhood overweight or obesity is defined as having a body mass index (BMI) greater or equal to the age- and sex-specific 95th percentile of the 2000 Centre for Disease Control growth charts [3]. Overweight-obese youth are increasingly suffering from comorbid conditions once considered limited to adults [4]. Despite considerable efforts to halt or reverse the growing rates of childhood overweight or obesity, the incidence continues to escalate.

Paediatric overweight or obesity has been implicated in a myriad of serious health concerns. Short-term consequences of overweight-obese status include chronic orthopedic and psychological disorders, nonalcoholic fatty liver diseases, metabolic syndrome, as well as a host of cardiovascular diseases such as hypertension and Type II diabetes mellitus [5, 6]. Long-term consequences have proven the persistence of childhood obesity into adulthood, with an estimated 50% of obese adolescents becoming obese adults [6]. This persistence into adulthood incites a cascade of cardiovascular risk factors and other chronic morbidities, dramatically increasing the risk for premature mortality [5]. The economic burden of overweight and obesity on the American healthcare system is expected to intensify with persevering rates of childhood overweight and obesity [7].

Physical activity and diet are important in the management of obesity. Increased rates of overweight and obesity among children have been attributed to an increase in sedentary pursuits and a decrease in physical activity [8]. Furthermore, children who participate in higher levels of physical activity are less likely to display risk factors for cardiovascular disease and more likely to have positive outcomes in weight regulation [9–13]. Motivating children to participate in physical activity may also preclude the persistence of childhood obesity into adulthood [14, 15]. Promoting optimal physical activity levels among children can reduce the overall incidence and prevalence of overweight and obesity [16, 17]. Further research is required to better explore and understand the relationship between physical activity and obesity prevention [18].

With growing rates of childhood overweight and obesity, it becomes increasingly more important to promote healthy eating as poor dietary behaviors are a known risk factor for the development of obesity [19, 20]. In addition, nutritional deficits and poor eating habits that develop in youth have been implicated with long-term health, growth, and developmental issues [21]. Obesity often results from an energy imbalance, with a greater energy intake to expenditure, with overweight or obese youth less likely to compensate for excess energy intake throughout the day than normal-weight children [22]. Research has identified physical activity and diet as factors implicated in childhood overweight. Exploring strategies that reduce overweight and obesity by targeting physical activity and healthy eating is a necessary endeavour.

The United States Department of Agriculture's dietary guidelines for Americans from the age of 2 years old focuses on balancing caloric intake with physical activity [23]. The message purported is to decrease the amount of calories consumed and increase calories expended through physical activity. To achieve this, the Surgeon General suggests the following for a healthy lifestyle: an increase in consumption of fruits, vegetables, whole grains, and lean proteins; reduction of sodas and juices with added sugars; increase amounts of water consumed; limit dairy products to low fat or nonfat; be more physically active, including limiting screen time to a maximum of 2 hours per day [24].

In addition, the Centers for Disease Control and Prevention recommends that children and adolescents partake in 60 minutes of physical activity a day. This should consist of aerobic activity (making up the bulk of the 60 minutes), muscle strengthening activities (a minimum of 3 days a week), and bone strengthening activities (a minimum of 3 days a week) [25].

Efforts to mitigate the formidable effects and prevalence of childhood overweight or obesity have been aimed at reducing sedentary behavior and poor nutrition [26]; indeed, compared to the rest of the world, early adolescents in the United States exhibit the worst rates of physical activity and the least healthy diets [27]. While several factors have been blamed for this disparity in healthy behavior, including preference for indoor pastimes, low energy levels, time constraints, unsafe neighborhoods, a lack of motivation, insufficient resources and poor social support [28], it is screen-based activities that seem to garner the most public criticism. While both watching television and playing video games have been accused of increased sedentariness among youth and growing rates of childhood overweight or obesity, video game playing has shown the strongest positive correlation, with the duration of screen time forecasting weight status [29, 30].

The United States houses the highest percentage of youth under 18 years of age using the internet, with approximately 93% of teens (aged 12–17 years old) going online [31]. While only 15% of households do not have a home computer [32]—83% of American youth have access to at least 1 video game console in their bedroom [28]. Thus, as a possible forward-thinking strategy, researchers can look at video gaming as a means of promoting physical activity and healthy nutrition among at-risk children, replacing passive screen time with active screen time [28]. Exergaming (video games that are a form of exercise) can be used to motivate direct physical activity in combating overweight and obesity among children. Similarly, interactive educational video gaming can aid in developing self-care abilities and healthy behavioral skill building.

The goal of this paper is to enlighten researchers to the possible benefits of active and educational video games targeting diet and physical activity in children. Our objective is to review the current literature on the role of video games (development and use) in the prevention of childhood overweight and obesity and provide a summary of findings that can be used to spur future research.

2. Methods

2.1. Data Sources. We conducted a systematic review of the literature utilizing the bibliographic databases EMBASE and PubMed in December 2010. The following search terms (MeSH headings for PubMed and keywords for EMBASE) were used: obesity, overweight, physical activity, fitness, exercise, energy expenditure, heart rate, energy metabolism, nutrition, BMI, diet, video gam*, exergam*, active video gam*, active computer gam*, new generation computer gam*, exertainment, active gam*, and computer gam*. Search terms were determined by examining the previous literature in the area.

The search was limited to articles written in the English-language and published between 1998 and 2011. Articles focusing on a 0- to 18-year-old population were included (Preschool child, School child, and Adolescent in EMBASE). All study design methodologies were considered. Two reviewers (S. Guy and A. R.-Leewing) hand searched references present in the included articles with a specific focus on journal articles discussing the use of video games to combat obesity.

2.2. Data Extraction and Synthesis. We retrieved 181 studies in total, 87 from EMBASE and 94 from PubMed. We ran a duplicate search which reduced the total to 128 articles. Further examination eliminated 4 references not classified as journal articles (2 were conference abstracts, 1 comment, and 1 forum document). Each article was reviewed by 2 reviewers (S. Guy and A. R.-Leewing). Articles were excluded if they only described the negative effects of screen time (watching television, playing video games, surfing the internet) on physical activity levels. Articles that only described obesity interventions in general without specific reference to video game interventions were also excluded. Of the 124 articles, 18 pertained to interventions utilizing video games and/or computer games. Upon hand searching references within retrieved articles, 18 journal articles were included (Figure 1). A previous literature review [33] was eliminated; however, it was examined for potentially useful references. Systematic reviews [26, 33–35] discovered during hand searching were used to inform study choice and discussion material.

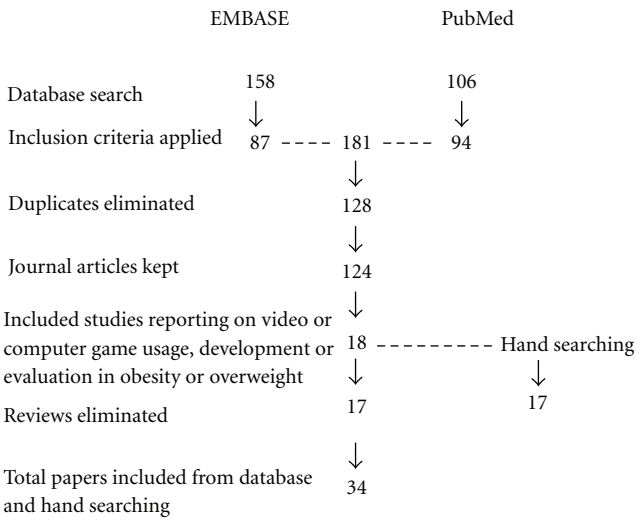


Figure 1: Identification of studies.

3. Results

The results are organized into sections based on the type of game (Table 1).

3.1. Exergaming. All studies in this section focused on exploring physical activity and on determining the amount of physical activity expended during active video game play. Physical inactivity is a contributing factor in the prevention of overweight and obesity.

Chin A Paw et al. (2008) [36] conducted a randomized controlled trial with a 12-week home-based Dance Dance Revolution (DDR) (Konami Digital Entertainment, Redwood City, CA) intervention. The comparison group received DDR to use as often as they desired, while the multiplayer group played DDR with other children once a week in a 60-minute class at a sports center. A total of 29 children with a low fitness level aged 9–12 years from 4 primary schools were recruited. Of the 27 randomly assigned, 11 children dropped out of the study. Chin A Paw et al. (2008) measured aerobic fitness, physical and sedentary activity through self-report, anthropometry, body composition, playing time through self-report, and perceived competence in sport. Results showed that the multiplayer group played the game more (901 min) than the comparison group (376 min); however, this was nonsignificant. Children reported finding the game boring after a while.

Epstein et al. (2007) [37] examined the reinforcing value and activity levels of active dance and bicycle games in 18 overweight and 17 nonoverweight children aged 8–12 years. Children engaged in a behavioral choice task for dancing or bicycling. There were 3 conditions for the dance game (dancing with music, dancing with a video, and DDR) and 3 conditions for the bicycle game (bicycle alone, bicycle with video, and Freekstyle) (Electronic Arts, Redwood City, CA). Findings show DDR to be more reinforcing than dancing alone or dancing while watching the video; however, no difference was found across the 3 bicycle conditions. Nonoverweight children were more active playing the active dance game than overweight children.

Graf et al. (2009) [38] compared energy expenditure rates in children playing active video games in relation to treadmill walking. The sample comprised of 23 healthy children ranging in age from 10 to 13 years old. Participants were measured for energy expenditure, heart rate, step rate and perceived exertion watching television, playing DDR at 2 skill levels, playing Wii bowling and boxing (Nintendo, Redmond, WA), and walking at 2.6, 4.2, and 5.7 km/h. Energy expenditure while playing the active video games or walking increased 2- to 3-fold in comparison with watching television. Wii bowling and beginner level DDR elicited a 2-fold increase in energy expenditure compared to watching television.

A study conducted in the United Kingdom compared energy expenditure during sedentary and active gaming [39]. Eleven participants aged 13–15 years played 4 computer games for 15 minutes each: sedentary XBOX 360 (Microsoft, Redmond, WA), Wii Sports bowling, tennis, and boxing. Graves et al. (2007) found that energy expenditure was 51% greater during active gaming and highest during Wii Tennis. Male participants expended more energy during gaming than females. Graves et al. [40] further expanded on the energy expenditure in upper limb movement in comparison to total-body movement while engaged in sedentary and active video gaming. Youths between 11–17 years old played 3 active Wii games and one sedentary video game (XBOX 360). Energy expenditure, heart rate, and nondominant upper limb activity were significantly greater during boxing in comparison to tennis or bowling. Findings showed that hip activity best predicted energy expenditure.

Haddock et al. (2009) [41] measured oxygen consumption, energy expenditure, and perceived exertion during a comparison of stationary cycling with and without a video game. Children participating in this study ($N = 20$) were at risk for overweight and between the ages of 7–14 years old. Participants rode a stationary bicycle (CatEye Gamebike, USA) for 20 minutes. Testing session 1 consisted of riding the bicycle, while in session 2 the bicycle controlled the speed in the game Cars (Pixar Entertainment Inc.). Energy expenditure was significantly higher (4.4 ± 1.2 K cal min^{-1}) when cycling in conjunction with the video game than riding the bicycle on its own. There was no significant difference in perceived exertion between the 2 sessions.

A comparison of energy expenditure during sedentary video gaming and television viewing, active video game play, and treadmill walking was undertaken by Lanningham-Foster et al. (2006) [42]. Energy expenditure was calculated while participants watched television seated, played a traditional video game seated (Disney's Extreme Skate Adventure Activision, Los Angeles, CA), watched television while walking on a treadmill at 1.5 mile per hour, and played active video games (Nicktoons Movin', THQ, Calabasas Hills, CA; DDR Ultramix 2). Twenty-five children aged 8–12 participated. Active video games resulted in a larger increase in energy expenditure than playing the traditional video game seated. Energy expenditure increased by 382 ± 181 kJ/hour above levels of energy expended during rest.

Table 1: Summary of studies included in the systematic review.

Authors	Study description	Sample	Key findings
Exergames			
Chin A Paw et al., 2008 [36]	Comparison of home-based DDR and multiplayer DDR sessions with a 12-week RCT.	16 children with low fitness between 9 and 12 years old (mean 10.6 [0.8]) from 4 primary schools. 29 recruited, 27 randomly assigned, 11 dropped out.	Multiplayer group played more (901 min) than home-based (376 min). Children reported finding game boring after a while.
Epstein et al., 2007 [37]	Comparison study of activity levels and reinforcement value in active dance and bicycle games.	35 (18 M, 17 F) overweight (18) and nonoverweight (17) children aged 8 to 12 (10.8 [1.4]).	Active dance game is more reinforcing than dancing alone or while watching video. No difference found across 3 bicycle conditions.
Graf et al., 2009 [38]	Comparison EE rates playing AVG (DDR, Wii) in relation to treadmill walking (2.62, 4.2, and 5.7 km/h).	23 (14 M, 9 F) healthy children aged 10 to 13 (11.9 [1.2]) with a mean BMI of 19.1 [3.1].	EE increased 2- to 3-fold with AVG play and walking compared to watching TV. 2-fold increase in EE with bowing and DDR.
Graves et al., 2007 [39]	Determine EE with a cross section of 4 games.	11 (6 M, 5 F) children between 13 and 15 years (14.6 [0.5], BMI 21.2 [2.5])	EE was 51% greater during VG play. Highest EE with Wii Tennis. EE greater for M versus F.
Graves et al., 2008 [40]	Comparison of EE in upper limbs versus total body movement with sedentary and active gaming.	13 youths (6 F, 7 M) between 11 and 17 years (15.1 [1.4]) with a mean BMI of 22.0 [2.6]	Wii Boxing resulted in highest HR, EE, and nondominant upper limb activity.
Haddock et al., 2009 [41]	Determine EE when riding stationary bike with and without a video game.	20 children (13 M, 7F) at risk for or overweight between 7 and 14 years old.	EE higher cycling with video game than without. No sig. difference in average perceived exertion.
Lanningham-Foster et al., 2006 [42]	Comparison of EE during sedentary gaming, watching TV, AVG play, and treadmill walking.	25 children (12 M, 13 F) aged 8 to 12 years (9.7 [1.6]). 15 lean and 10 (5 M, 5 F) with mild obesity	EE increased by 108 ± 40% with EyeToy and by 172 ± 68% with DDR.
Maddison et al., 2007 [43]	Comparison of EE and physical activity during sedentary gaming and AVG play.	21 children (11 M, 10 F) between 10 and 14 years old (12.4 [1.1]) with a mean BMI of 20.3 [4.0]	Step counts increased 122 to 1288 during AVG play from sedentary play.
Maddison et al., 2009 [30]	Overview of the eGAME study. 2-arm parallel RCT to be carried. Determine effects of AVG on BMI, physical activity, cardiorespiratory fitness, waist circumference, and body composition.	330 overweight children between the ages of 10 and 14 years.	Phase 1: All children enjoyed AVGs. Phase 2: EE sig. greater in AVGs compared to rest and sedentary gaming conditions.
Madsen et al., 2007 [44]	Pre-/post-6-mth noncomparative trial. Determine if overweight would use DDR for exercise, reasons fuse, correlate use with BMI.	30 (18F, 12 M) obese (BMI 38.3 [9.0]) participants aged 9 to 18 (13.0 [2.6]).	Few used DDR regularly. Lack association between DDR use and change in BMI.
Maloney et al., 2008 [45, 46]	28-wk comparison of home-based DDR intervention focusing on physical activity and enjoyment.	60 children (30 M, 30 F) with a mean age of 7.5 [0.5]	DDR use highest in wk 1. Mean play duration 89 min/d. Use decreased to half prescribed level by study end. Sig. reduction in sedentary screen time in DDR group.
McDougall and Duncan, 2008 [47]	Mixed-methods, noncomparative design of 1 wk of lunchtime AVG play.	12 children (7 F, 5 M) aged 8–11 years	Mean play duration of 24 min/d. Game play resulted in 10% of recommended steps daily and 11 min sustained moderate-to-vigorous phys. activity.
Mellecker and McManus, 2008 [48]	Comparison study of EE and HR while seated and during AVG play.	18 children (11 M, 7 F) aged 6–12 years (9.6 [1.7])	EE above rest sig. higher for 2 AVGs compared with seated gaming. HR sig. higher during bowling and J-Mat compared to rest.

Table 1: Continued.

Authors	Study description	Sample	Key findings
Mellecker et al., 2009 [49]	Evaluation of newly developed walking media station for feasibility of ambulatory screen time.	29 (17M, 12 F) healthy children between 6 and 13 years old	Steady gait walking achieved in less than 1 min. No increase in EE when computer game added to walking.
Murphy et al., 2009 [50]	Determine whether DDR is effective in improving endothelial dysfunction in overweight. Randomly assigned to 12 wks of aerobic exercise using DDR or to a nonexercising delayed-treatment control group.	35 (17 F, 18 M) overweight children aged 7–12 years (10.21) with EDF.	Sig. improvements in FMD, exercise time, MAP, weight, and peak VO_2 compared with delayed-treatment group. 13 intervention participants achieved normal endothelial function.
Ni Mhurchu et al., 2008 [51]	Pilot 12-wk RCT to evaluate effect of AVG on phys. activity levels. Intervention received AVG upgrade package. Control received upgrade package at study end.	20 (8 F, 12 M) children aged 10–14 years (12 [1.5]). Had to own PlayStation 2 to be eligible	Phys. activity sig. higher in intervention group. Reduction in weight and waist circumference in intervention group at wk 12.
Penko and Barkley, 2010 [52]	Evaluation of physiologic cost, RRV, and liking. AVG play versus sedentary video game.	24 (12 M, 12 F) children (11 Lean, 13 obese) aged 8 to 12 years.	Mean HR, VO_2, and liking sig. greater for AVG play than all other conditions.
Ridley and Olds, 2001 [53]	Description of EE and child behavior while visiting game centres.	134 children from observed. 10 (5 M, 5 F) children aged 10–12 years (12.5 [0.5]) evaluated.	Gross energy cost ranged from 7.6 to 2.5 ml kg^{-1} min^{-1}.
Sit et al., 2010 [54]	Examining preferences and PA levels during interactive or online games.	70 (35 F, 35 M) overweight (20) and nonoverweight (50) children aged 9 to 12.	Split game time between interactive (52%) and online (48%). Sig. more moderate-to-vigorous PA with interactive than online. Boys and nonoverweight expended more energy during interactive games than girls and overweight.
Straker and Abbott, 2007 [55]	Comparison of cardiovascular response and EE during TV watching, sedentary gaming, and AVG play.	20 healthy children (12 M, 8 F) aged 9–12 years	AVG play increased EE by 224% and HR by 59% from rest. AVG play exertion levels were equivalent to activities of moderate intensity.
Unnithan et al., 2006 [56]	Comparison of energy costs of playing DDR between overweight and nonoverweight kids.	22 children (10 with mild obesity; 12 with normal weight) between 11 and 17 years old.	No sig. difference in HR or energy costs associated with DDR. Average VO_2 with DDR sig. higher in overweight than nonoverweight.
Educational Video Games			
Baranowski et al., 2011 [57–59]	2-group RCT evaluation of Diab and Nanoswarm play in intervention group versus control playing website games.	133 children (45% F, 58% M) between 10 and 12 years old (42.5% 10 years old). BMI percentile initially 50th–95th.	Playing Diab and Nanoswarm increased daily fruit consumption by 0.67 servings but not water intake, moderate-to-vigorous physical activity, or body composition.
Baranowski et al., 2003 [60]	2 group RCT (30 min/wk, 8 wks) to prevent obesity. The Fun, Food and Fitness! project.	35 African-American girls aged 8 years (8.3 [0.3] intervention; 8.4 [0.3] control) and their parents/guardians.	Intervention group consumed 232 less kcal; greater water, fruit, juice, and veg. consumption; fewer sweetened drinks consumed.
Baranowski et al., 2003 [61, 62]	5 wk 2 group RCT with pre/post test to increase fruit, juice and veg intake among healthy children via Squire's Quest!	26 elementary schools with 1578 (803 F) 4th-grade students (872 9 year olds).	1.0 fruit, juice, and veg. servings more in intervention group than control.

Table 1: Continued.

Authors	Study description	Sample	Key findings
Moore et al., 2009 [2]	Effectiveness of Color My Pyramid and Blast-Off Game on physical activity and nutrition knowledge over 3 month period (pre/post test).	126 4th-5th (9–11 years old) grade students (46 M, 80 F).	Increase in activity time from pretest to posttest and decrease in systolic BP for both groups. No sig. differences in BMI.
Munguba et al., 2008 [63]	Evaluation of an occupational therapy education nutrition education intvn using 2 interactive games (1 video game, 1 board game).	200 public school children between 8 and 10 years old (95 M, 105 F).	Both games promoted learning of nutritional concepts.
Pempek and Calvert, 2009 [64]	Examination of how advergames affect consumption of healthier and less healthy snacks.	30 (15 M, 15 F) low-income African-American school children between 9 and 10 years old from 5 elementary schools	Group playing healthier version of the game chose and ate more healthy snacks than less healthy game group.
D. R. Southard and B. H. Southard, 2006 [65]	Prelim. results of 4-wk RCT using MetaKenkoh to promote phys. activity and healthier food choice.	120 children (63% M) aged 9–11 years old. Of which 13.6% are at risk for overweight, 25.9% are overweight.	Underweight and normal weight in intervention group showed increase in activity.
Thompson et al., 2009 [66]	9 wk 2-group RCT evaluating Boy Scout 5-a-Day Badge on fruit, juice, and veg. consumption. With online knowledge games.	473 boy scouts (42 troops) aged 10–14 years.	Sig. increases in fruit juice consumption, fruit juice availability at home, and veg. consumption self-efficacy in the intervention group.
Turnin et al., 2001 [67]	2-group RCT evaluation of knowledge games nutritional knowledge and improving eating habits.	1876 7–12-year-old 3rd-5th graders (52.5% F) from 16 schools.	Intervention group sig. better nutritional knowledge and dietary intake compared with control.

AVG: Active Video Game; BMI: Body Mass Index; DDR: Dance Dance Revolution; EE: Energy expenditure; EDF: Endothelial dysfunction; FMD: Flow-mediated dilation; HR: Heart Rate; MAP: Mean arterial pressure; Min: Minutes; N: Sample size; P/w: Per week; RCT: Randomized Controlled Trial; RRV: Relative reinforcing value.

Obese children had significantly greater increases in energy expenditure in response to active video games.

Maddison et al. (2007) [43] examined energy expenditure and physical activity associated with playing active and sedentary video games using PlayStation 2 (Sony Corporation, Tokyo, Japan) EyeToy games. Each participant ($N = 21$) completed the study protocol. This involved resting while seated, playing a sedentary video game, and playing active video games (EyeToy Knockout, Homerun, Groove, AntiGrav, and Dance UK). Significant increases in energy expenditure and heart rate were found during active game playing. Step counts increased from 122 to 1288 steps during active video games in comparison to sedentary game play. The energy expended during active video game play was comparable to light or moderate exercise. A recent publication by Maddison et al. (2009) [30] provides an overview of their eGAME study (a 2-arm parallel randomized controlled trial) and includes the plan for Phase 3 which is their future direction. The Phase 3 objective is to determine the effects of an active video game intervention (Sony EyeToy) over 6 months on BMI, body composition, waist circumference, cardiorespiratory fitness, and physical activity levels in 330 overweight children. All Australian participants ranging in age from 10 to 14 years will be randomized to either an active video game upgrade package or to a control group (no intervention). Phase 1 contained focus groups with children, and Phase 2 was a laboratory study (described above).

A 6-month pretest, posttest trial with a noncomparative design was conducted by Madsen et al. (2007) [44]. Obese children ($N = 30$) aged 9–18 years old were provided with DDR and motivated biweekly with a semistructured telephone interview for 24 weeks. The goal was for children to play 30 minutes a day for 5 days a week. Findings show that few children used DDR regularly with a lack of association between DDR use and change in BMI. Children reported that group play, competition, and greater variety would increase their motivation to play.

Maloney et al. (2008) [45, 46] examined physical activity and enjoyment with a controlled group comparison design of an intervention—home-based DDR play—and control group. A total of 60 children between the ages of 7-8 years old participated in a 28-week study. The authors collected self-reported screen time, DDR use, accelerometry, pedometry, body composition, blood pressure and pulse, anthropometry, game satisfaction, and assessment of participation support. Participants played DDR for 89 min per day (mean) and used the game the most in week 1. Absence of other video games and parent participation was associated with this high level of usage in week 1. By

the end of the study, usage had decreased to half of the prescribed level. No significant changes in physical activity across both groups were found. The intervention group saw a reduction in sedentary screen time. In week 10, sibling and friend participation was associated with usage of DDR.

McDougall and Duncan (2008) [47] reported a mixed-methods, noncomparative study, where British children ($N = 12$) aged 8–11 years old engaged in school lunch-time active video game play for 1 week. Children played on average for 24 minutes per day with game play resulting in 10% to 11% of the recommended steps allocated daily and 11 minutes of sustained moderate-to-vigorous physical activity per day. Children reported preferring active video games to more traditional forms of activity.

Mellecker and McManus (2008) [48] examined energy expenditure and cardiovascular responses in children during seated (10-pin bowling computer game) and active gaming (XaviX bowling and J-Mat) (Shiseido, Tokyo, Japan). A total of 18 children aged 6 to 12 years participated in a 25-minute gaming protocol: 5 minutes of seated, 5 minutes of seated bowling, 5 minutes of XaviX bowling, 5 minutes of seated rest, and 5 minutes of XaviX J-Mat. In each game format, energy expenditure was significantly higher than resting (39% for seated bowling, 98% for XaviX bowling, 451% for XaviX J-Mat). Heart rate was significantly higher during gaming than rest. In another study, Mellecker et al. (2009) [49] tested the feasibility of a newly developed walking media station they had created. This station was a treadmill with a screen attached. Twenty-nine healthy children between the ages of 6 and 13 years old tested the media station in a laboratory and home setting. Each participant completed the following protocol: rest, playing a computer bowling game seated, walking, and walking while playing a computer bowling game. No increase in energy cost was found when adding the game to walking. Participants reported that they would use the media station.

Murphy et al. (2009) [50] randomized 35 (17 female, 18 male) overweight children with endothelial dysfunction, between the ages of 7 and 12, to 12 weeks of exercise using DDR or to a nonexercising delayed treatment control group. The exercising intervention group saw significant improvements in flow-mediated dilation, exercise time on a graded test, mean arterial pressure, weight, and peak VO_2 compared to the control group. During the study 13 intervention participants achieved normal endothelial function.

A randomized controlled trial conducted by Ni Mhurchu et al. (2008) [51] evaluated the effect of home-based active video game play on the physical activity levels of 20 children aged 10 to 14 years in New Zealand. The intervention group ($N = 10$) received an upgrade package for their Sony PlayStation 2 console, including a Sony EyeToy camera, EyeToy active games, and dance mat. The participants and families were instructed to substitute usual video game play with active video games. The control group received the same upgrade package at the end of the study without an intervention. The authors used the following measurements to evaluate physical activity: accelerometry, self-reported activity, physical activity questionnaire, established activity compendium, anthropometry, and body composition. Results showed that physical activity was significantly higher in the intervention group than the control at both followups. Children in the intervention group spent less total time playing all video games. No significant group differences were found between time spent in moderate or vigorous physical activities. The intervention group showed weight loss (mean = 0.13 kg) and a reduction in waist circumference (mean = 1.4 cm) at the end of 12 weeks.

The physiological cost, relative reinforcing value, and satisfaction of playing Wii Sports bowling compared with Wii PunchOut! (a traditional sedentary video game) was the subject of investigation for Penko and Barkley (2010) [52]. A sample of 11 lean and 13 overweight or obese 8 to 12 year olds participated in 4, 10-minute activity sessions: resting, treadmill walking, sedentary video game play (Wii PunchOut!), and active video game play (Wii Sports Boxing). Participants performed a computer task designed to assess relative reinforcing value. Results showed that average heart rate, oxygen consumption, and liking were significantly greater for Wii than all other conditions.

Ridley and Olds (2001) [53] examined energy cost and observed the behavior of children playing video games and games in an Australian game centre. The authors measured the energy cost of 10 elementary school children (5 females and 5 males aged 10–12, with a mean of 12.5 years) under 5 experimental conditions which were each 5 minutes in duration: seated in front of a sedentary video game and playing 4 games—Daytona (a simulated driving game), Final Furlong (a simulated horse-racing game), Air Hockey (table hockey), and Mini Dunxx (a minibasketball shooting game). Gross energy cost ranged from 7.6 to 2.5 ml kg^{-1} min^{-1}.

Sit et al. (2010) [54] conducted a study in Hong Kong examining preferences and physical activity levels during interactive electronic games. Seventy overweight and nonoverweight children aged 9 to 12 participated in 2, 60-minute recreation sessions. Session 1 involved playing either an active (XaviX bowling) or an online bowling game. Session 2 was a choice of an active (Aerostep, Shiseido Co. of Japan) or an online electronic running game. Participants chose to play the games during 94% of their session time with time split between active (52%) and online (48%) gaming. Significant moderate-to-vigorous physical activity was observed during active game play. Participants who were male ($N = 35$) and nonoverweight ($N = 50$) expended relatively more energy during active games than females and overweight children.

A within-subjects design of a comparison between cardiovascular response and energy expended among television watching, sedentary gaming, and active video game play was carried out by Straker and Abbott (2007) [55]. Measures of interest include heart rate, energy expenditure, oxygen uptake, and ventilation. Twenty healthy 9−12-year-old children, who had previous experience with playing electronic games, were recruited. Heart rate and energy expenditure were comparable for television watching and sedentary gaming. Energy expenditure and heart rate increased from resting during active video gaming (Sony EyeToy) by 224%

and 59%, respectively. The exertion levels observed during active video game play were equivalent to moderate intensity activity.

Unnithan et al. (2006) [56] determined the difference between the submaximal energy cost of movement and cardiorespiratory measures for overweight and nonoverweight children playing DDR. Each group of children ($N = 22$) completed 12 minutes of DDR and a maximal treadmill walking test. There was no difference in heart rate and energy costs associated with DDR between overweight and nonoverweight groups. Heart rate intensity levels, but not oxygen consumption reserve, were sufficient for developing and maintaining cardiorespiratory fitness.

3.2. Video Games. These games are either stand-alone or embedded within a larger intervention study containing elements such as face-to-face group education sessions. The games referred to in this section are developed by the respective researchers.

Two interactive video games developed by Baranowski et al. (2011) [57–59] targeting healthier food choices (fruit and vegetable consumption), body composition, and physical activity were evaluated in a 2-group randomized controlled trial. Participants ($N = 133$) aged 10 to 12 years participated in either the intervention group, which played "Escape from Diab" and "Nanoswarm: Attack from Inner Space" in sequence, or the control group, which played diet and physical activity knowledge-based games on popular websites. The authors found that playing the video games in the intervention increased fruit consumption by 0.67 servings per day but did not increase water intake, moderate-to-vigorous physical activity, or body composition.

The Fun, Food, and Fitness Project [60] is a randomized 2-arm parallel randomized controlled trial designed to prevent obesity. This 12-week intervention, taking place at a summer day camp and at home, was designed to motivate the participants ($N = 35$, 8 years old, African-American females) to eat 5 servings of fruit and vegetables, drink 5 glasses of water, and engage in 30 minutes of physical activity per day. Participants in the intervention group attended a special 4-week summer day camp and received an 8-week home internet intervention featuring a computer game with comic strip characters who overcome barriers to goals with regard to physical activity. The control group attended a summer camp with usual activities followed by a monthly home internet intervention without the game. Results showed significant difference in BMI between both groups.

"Squire's Quest" [61, 62] is a multimedia game that aims to increase preferences for fruit, juice, and vegetable consumption among children. In a 2-group randomized controlled trial, Baranowski et al. (2003) evaluated the effectiveness of this game. A population of 1578 4th grade students were recruited to participate in the study. The intervention group received 10 sessions twice a week with a duration of 25 minutes of "Squire's Quest." The control group did not receive the intervention. Findings indicate an increase of fruit and vegetables servings per day (1.0) in the intervention group.

The "MyPyramid Blast-Off Game" educates children about the food pyramid and physical activity [2]. In a pretest, posttest study Moore et al. (2009) examined the effect of a nutrition education program "Color My Pyramid" (United States Department of Agriculture, 2007). A total of 126, 4th and 5th grade Washington, DC students took part in an intervention of 6 classes taught over 3 months aimed at increasing knowledge about nutrition and physical activity. Both schools received the educations and activity content. While 1 school received a more didactic presentation on playing the "Blast-Off Game," the other school required students to use individual computers to evaluate their diets in small groups. This program included the interactive computer game described above. Results of this study show an increase in nutrition knowledge of the control group. In both groups activity time was increased and systolic blood pressure decreased. No significant differences in BMI were seen.

Munguba et al. (2008) [63] evaluated the use of 2 interactive games—a video game and a board game that were interconnected in relation to theme, character, and foods—in a nutrition education program for obese children in Brazil. Two hundred children aged 8–10 years took part in this study with each taking part in weekly 30-minute game sessions over a 4-month period. Both games were based on the food pyramid and promoted the learning of nutritional concepts. Participants preferred the video game (27% compared to 6%).

Pempek and Calvert (2009) [64] reported a cross-sectional study examining how marketing games (advergames) affect the consumption of snack type. Participants (30 low-income 3rd- and 4th-grade African-American children) were randomly assigned to 1 of 3 conditions of which they would play 2 levels of each game: a healthier advergame, a less healthy advergame, or the control group. The classic arcade game Pac-Man (Namco, Tokyo, Japan) was used as a prototype for 2 versions created. In the healthier game option, 10 points were awarded for each nutritious snack eaten and penalized the same amount of points for every less nutritious snack. While in the less healthy option children were rewarded 10 points for every less nutritious snack and penalized for every healthier snack eaten. In the intervention groups children were asked to choose a snack after they played the game. In the control group snack selection took place before the game. The children playing the healthier version of the game selected and ate significantly more healthy snacks.

"MetaKenkoh" is an internet-based adventure game that targets physical activity promotion and healthier food choices [65]. D. R. Southard and B. H. Southard (2006) present preliminary results of a 4-week randomized controlled trial of 63 children aged 9–11 years. Intervention group participants played a game and wore a pedometer (with the pedometer controlling game performance). In contrast the control group was monitored without video game playing. Within 1 week, underweight and normal weight children in the intervention group showed an increase in activity. In comparison, a decrease in physical activity

was observed in the control group. The overweight and at-risk participants in both groups showed a slight increase in activity levels.

In the Boy Scout 5-a-Day Badge study, 473 boy scouts aged 10 to 14 years old participated in a 2-group randomized controlled trial for 9 weeks [66]. This program was aimed at increasing fruit and vegetable consumption that included knowledge games focusing on diet and contained interactive comic characters that underwent challenges to eating more fruits and vegetables. While the game cannot be evaluated by its own, the study saw an increase of 0.83 servings per day of fruit and vegetable and a 1.24 increase in fruit and vegetable items available at home in the intervention group.

Turnin et al. (2001) [67] conducted a 2-group randomized controlled trial in 1876, 3rd to 5th graders (16 schools) evaluating 4 nutritional teaching computer games aimed at increasing nutritional knowledge and improving eating habits. The schools taking part (16) were randomized into 2 groups: an intervention group, which received nutritional learning games; and a control group, where a teacher provided the nutritional information. Participants played "Store" (categorization of food), "Guess who" (food contents), "Granny Smith" (food choices), and "The Restaurant" (nutritional balance) for 1 hour twice a week for 5 weeks. A significant improvement in nutritional knowledge and dietary intake was noted amongst intervention participants.

4. Discussion and Conclusions

Researchers have utilized a number of commercial active video games or new-generation video games in an effort to quantify their impact on children's physical activity levels. The games included in the reviewed papers are Aerostep; Dance Dance Revolution; Wii Sports; Freekstyle; Nicktoons Movin'; EyeToy games such as Knockout, XaviX bowling; XaviX J-Mat.

Educational video games, either as a stand-alone or part of a larger intervention, are predominantly focused on dietary and nutrition issues. Games included in this paper include Escape from Diab, Guess who, Granny Smith, Nanoswarm, Squire's Quest, MyPyramid Blast-off Game, The Restaurant, an altered version of Pac-Man, MetaKenkoh, and Store.

Assumptions are often made about the value of video games and their potential to improve lifestyle and dietary habits. Although video games may have benefit, it is equally important to have an evidence-based approach to developing and evaluating these games—as they are in fact an intervention. Appropriate strategies to evaluate the games and deliver them in ways that are reproducible are important from a knowledge translation perspective. We found a lot of heterogeneity in terms of the outcomes also, both the metrics that were used and the methods of measurement. It may be time to consider some guidance for those who design and use these games in research to have common metrics that can be compared across different games. This will, in the future, allow us to provide more relevant and interpretable comparisons.

Evidence is indisputable about the need for an ecological, multilevel approach in childhood obesity interventions. Educating both the parent and child, given the complex interactions between social determinants in a family setting, is essential to the success of an intervention. It is unreasonable to expect a total and significant behaviour change or outcome based on modifying nutrition knowledge alone. While education is undoubtedly important for motivating behaviour change, other factors such as home environment, parent income, and parental education level have been implicated in obesity. Although a parent's knowledge of healthful eating and their socioeconomic status may play a role in obesity, it is necessary to note these 2 factors may not be the main driving forces. A recent report of National Health and Nutrition Examination Survey data showed that (a) childhood obesity prevalence decreased as the education level of the head of the household increased; however, this trend was not consistent across race and ethnicity and (b) the majority of children and adolescents who are obese are not from low-income households [3]. This suggests that a lack of financial resources may not be a main barrier to healthful eating. Further research is needed looking at the role an "educated" child can play in transforming the outlook of the family as parents. While additional research is needed to understand and determine the most effective avenues to promote healthy eating, it is well supported that educating children in healthy eating not only provides immediate benefit but fosters long-term health habits as well. Thus, while active and serious gaming poses an excellent opportunity for increased physical activity and nutritional knowledge, it is not a sole solution to the obesity epidemic among children. Looking at integrating AVG and educational gaming in classroom settings or in collaboration with community or national level programs such as the Expanded Food and Nutrition Education Program (EFNEP) [68] is a potential step forward to using gaming as a tool for combating obesity.

Research has proven that AVG use can elicit light to moderate physical activity among youth. While we are not advocating that a child only plays video games to get their recommended daily physical activity, we are proposing that physical activity as a result of AVG engagement can contribute toward daily recommendations of physical activity.

Gaming companies invest significant resources into determining the multifactors that influence choice and duration of game use. So the question becomes, how can we sustain use of health promoting games in children? One avenue of exploration is the involvement of the family unit—parents and siblings. Emphasizing the social aspects of gaming, including competition and feelings of camaraderie, may be an effective means of promoting game use. A review conducted by Biddiss and Irwin (2010) [28] found "fun" to be the primary reason for participation in physical activity. Conducting needs assessments to determine what game factors constitute "fun" may not only encourage physical activity while gaming but additionally promote user sustainability.

Given the fact that a child's attention is already captured by video gaming, why not develop games targeted at obesity

reduction that use active "new generation" style games to increase children's knowledge and self-care ability? The time that children already spend playing video games can be simultaneously used to promote physical activity and health behavior education. The climate in North America lends itself to periodic episodes of limited outdoor play thus making safe, indoor play an easier option. Capitalizing on the novelty of active video gaming can encourage physical activity and simultaneous learning, a strategy which again may promote sustained use of the game.

Engaging participants in game development is a strategy employed by many corporations. By examining product development and marketing strategies, health games could further ensure audience acceptability and investment. Using these strategies in a pure research setting may prove advantages when developing an appropriate and effective AVG for overweight and obese children.

Self-initiation and choice are key factors in motivating physical activity among children [28]. Intrinsic motivators such as enjoyment, mastery, and achievement drive initiation and long-term continuation with behaviors [35]. Biddiss and Erwin (2010) suggest five strategies on how to sustain video game play in children. First, AVGs must provide positive feedback and be accessible through low cost and ease of use. Second, early exposure to active gaming, as opposed to passive or sedentary gaming, may encourage greater acceptance of AVGs; this strategy may allude to a future need for games that appeal to a wide range of ages and interests. Third, acceptance and motivation to play AVGs may increase when game play is perceived as a personal choice rather than a prescribed treatment therapy. And finally, short- and long-term reinforcement (i.e., enjoyment, goal-achievement, and skills development, resp.) are needed to ensure long-term adherence to game play.

Additional research on video gaming and motivation is required to explore goal setting and achievement as well as factors that initiate game play among children. Also, intensities and durations of physical activity over extended periods (>12 months) must be analyzed [35]. A propensity toward short-term home-based studies has curtailed research in long-term adherence and efficacy of AVG use among children (>7 months) [45]. Additional long-term research is required to determine the role of game diversification, the importance of story or plot development in AVGs, and the potential benefits of group play. While these strategies have been successful for short-term game play, their role in long-term adherence and efficacy is yet to be determined [44].

Given the prevalence of past studies and media attention towards the negative effects of video gaming (e.g., increased screen time), it is important to consider the potential barriers that may impede AVG use. Research into overcoming potential barriers would be advantageous to the future of health gaming.

An interesting avenue for future research is the potential of AVG play as an entry way into organized sports. Psychological factors accompanying AVG play may include increases to self-efficacy, self-competency, and self-empowerment. These qualities may be translated to an increase in confidence and attitudes towards organized sports, ultimately leading to a greater likelihood of the child participating in organized sports activities. As children learn and become more familiar with the rules and play of sports activities, they may become more inclined to participate in physical activity.

An additional area to question and possibly incorporate into the research is what value do people put on their health? The premise is that people will want to play games that improved their self-health and quality of life. However, we do not really know whether people play games, because it is a game. Knowing this will help us design games that clearly state that their value has more subtle or "hidden" benefits so the patient is blinded to the intent. If people value their health, they may be more likely to engage in healthful behaviours in a sustainable way rather than sporadically. Would knowing that the game is aimed at promoting healthy behaviour encourage or impede the use of the intervention by children?

Clearly with the environmental constraints in both emerging economies and developed economies, where access to green space and exercise facilities is limited, consideration has to be given to other avenues for exercise, which makes a good case for healthful games.

Interdisciplinary research teams would prove invaluable to the development of health video games; individuals with specialized knowledge in one field may collaborate with an expert in another to ensure a tailored intervention.

The stigmatization of video gaming, with implications of increased sedentary screen time and decrease in physical activity, is slowly being eroded by the advancement of active video games. The potential of active video gaming or exergaming in the fight against childhood obesity is evidenced through the studies referenced in this paper. However it is also important to consider interactive educational video games that aid in self-management and skill building as an equally valuable tool to combat childhood obesity. In a society so dependent on technology, using that dependency to create a more healthful existence becomes an easy choice.

The popularity of games such as Farmville (Zynga Inc.) and the realms of Second Life (Linden Research Inc.) suggest a new avenue of games in obesity prevention and self-care: social gaming. Rather than fight the enormous role (given how many hours children spend playing them) gaming has in children and adolescent's lives, we should embrace the opportunity to influence health behaviour through this avenue and use an evidence-based approach to do this in a thoughtful way. Otherwise we risk sporadic outcomes, where commercial interests dominate use.

References

[1] A. P. Rocchini, "Childhood obesity and a diabetes epidemic," *The New England Journal of Medicine*, vol. 346, no. 11, pp. 854–855, 2002.

[2] J. B. Moore, L. R. Pawloski, P. Goldberg, K. M. Oh, A. Stoehr, and H. Baghi, "Childhood obesity study: a pilot study of the effect of the nutrition education program Color My Pyramid," *Journal of School Nursing*, vol. 25, no. 3, pp. 230–239, 2009.

[3] C. L. Ogden, M. M. Lamb, M. D. Carroll, and K. M. Flegal, "Obesity and socioeconomic status in children and adolescents: United States, 2005–2008," 2010.

[4] Y. M. Kim and S. J. Lee, "Physical activity and abdominal obesity in youth," *Applied Physiology, Nutrition and Metabolism*, vol. 34, no. 4, pp. 571–581, 2009.

[5] J. J. Reilly, E. Methven, Z. C. McDowell et al., "Health consequences of obesity," *Archives of Disease in Childhood*, vol. 88, no. 9, pp. 748–752, 2003.

[6] L. R. Hardy, J. S. Harrell, and R. A. Bell, "Overweight in children: definitions, measurements, confounding factors, and health consequences," *Journal of Pediatric Nursing*, vol. 19, no. 6, pp. 376–384, 2004.

[7] L. DeMattia and S. L. Denney, "Childhood obesity prevention: successful community-based efforts," *Annals of the American Academy of Political and Social Science*, vol. 615, no. 1, pp. 83–99, 2008.

[8] A. J. Atkin, T. Gorely, S. J. H. Biddle, S. J. Marshall, and N. Cameron, "Critical hours: physical activity and sedentary behavior of adolescents after school," *Pediatric Exercise Science*, vol. 20, no. 4, pp. 446–456, 2008.

[9] C. Boreham and C. Riddoch, "The physical activity, fitness and health of children," *Journal of Sports Sciences*, vol. 19, no. 12, pp. 915–929, 2001.

[10] W. B. Strong, R. M. Malina, C. J. R. Blimkie et al., "Evidence based physical activity for school-age youth," *The Journal of Pediatrics*, vol. 146, no. 6, pp. 732–737, 2005.

[11] B. Gutin, P. Barbeau, S. Owens et al., "Effects of exercise intensity on cardiovascular fitness, total body composition, and visceral adiposity of obese adolescents," *The American Journal of Clinical Nutrition*, vol. 75, no. 5, pp. 818–826, 2002.

[12] S. Y. S. Kimm, N. W. Glynn, E. Obarzanek et al., "Relation between the changes in physical activity and body-mass index during adolescence: a multicentre longitudinal study," *The Lancet*, vol. 366, no. 9482, pp. 301–307, 2005.

[13] L. M. LeMura and M. T. Maziekas, "Factors that alter body fat, body mass, and fat-free mass in pediatric obesity," *Medicine and Science in Sports and Exercise*, vol. 34, no. 3, pp. 487–496, 2002.

[14] R. Telama, X. Yang, J. Viikari, I. Välimäki, O. Wanne, and O. Raitakari, "Physical activity from childhood to adulthood: a 21-year tracking study," *American Journal of Preventive Medicine*, vol. 28, no. 3, pp. 267–273, 2005.

[15] J. W. R. Twisk, H. C. G. Kemper, and W. Van Mechelen, "Tracking of activity and fitness and the relationship with cardiovascular disease risk factors," *Medicine and Science in Sports and Exercise*, vol. 32, no. 8, pp. 1455–1461, 2000.

[16] T. Lobstein, L. Baur, and R. Uauy, "Obesity in children and young people: a crisis in public health," *Obesity Reviews, Supplement*, vol. 5, supplement 1, pp. 4–104, 2004.

[17] K. S. Steinbeck, "The importance of physical activity in the prevention of overweight and obesity in childhood: a review and an opinion," *Obesity Reviews*, vol. 2, no. 2, pp. 117–130, 2001.

[18] Active Healthy Kids Canada, "Healthy Habits Start Earlier Than You Think. The Active Healthy Kids Canada Report Card on Physical Activity for Children and Youth," 2010, http://www.activehealthykids.ca/ecms.ashx/2010ActiveHealthyKidsCanadaReportCard-shortform.pdf.

[19] J. D. Wright, C. Y. Wang, J. Kennedy-Stephenson, and R. B. Ervin, "Dietary intake of ten key nutrients for public health, United States: 1999–2000," *Advance Data*, no. 334, pp. 1–4, 2003.

[20] K. Patrick, K. J. Calfas, G. J. Norman et al., "Randomized controlled trial of a primary care and home-based intervention for physical activity and nutrition behaviors: PACE+ for adolescents," *Archives of Pediatrics & Adolescent Medicine*, vol. 160, no. 2, pp. 128–136, 2006.

[21] R. Wahl, "Nutrition in the adolescent," *Pediatric Annals*, vol. 28, no. 2, pp. 107–111, 1999.

[22] N. F. Krebs, J. H. Himes, D. Jacobson, T. A. Nicklas, P. Guilday, and D. Styne, "Assessment of child and adolescent overweight and obesity," *Pediatrics*, vol. 120, supplement 4, pp. S193–228, 2007.

[23] United States Department of Agriculture, "Dietary Guidelines for Americans 2011," 2011, http://www.cnpp.usda.gov/dietaryguidelines.htm.

[24] U.S. Department of Health & Human Services, "The Surgeon General's Vision for a Healthy and Fit Nation Fact Sheet 2010," 2011, http://www.surgeongeneral.gov/library/obesityvision/obesityvision2010.pdf.

[25] Centers for Disease Control and Prevention, "How much physical activity do children need? 2010," 2011, http://www.cdc.gov/physicalactivity/everyone/guidelines/children.html.

[26] E. M.F. Van Sluijs, A. M. McMinn, and S. J. Griffin, "Effectiveness of interventions to promote physical activity in children and adolescents: systematic review of controlled trials," *British Medical Journal*, vol. 335, no. 7622, pp. 703–707, 2007.

[27] M. Frenn, S. Malin, R. L. Brown et al., "Changing the tide: an internet/video exercise and low-fat diet intervention with middle-school students," *Applied Nursing Research*, vol. 18, no. 1, pp. 13–21, 2005.

[28] E. Biddiss and J. Irwin, "Active video games to promote physical activity in children and youth: a systematic review," *Archives of Pediatrics & Adolescent Medicine*, vol. 164, no. 7, pp. 664–672, 2010.

[29] E. A. Vandewater, M. S. Shim, and A. G. Caplovitz, "Linking obesity and activity level with children's television and video game use," *Journal of Adolescence*, vol. 27, no. 1, pp. 71–85, 2004.

[30] R. Maddison, L. Foley, C. Ni Mhurchu et al., "Feasibility, design and conduct of a pragmatic randomized controlled trial to reduce overweight and obesity in children: the electronic games to aid motivation to exercise (eGAME) study," *BMC Public Health*, vol. 9, article 146, 2009.

[31] Z. Wilson, "Pew survey: teens love facebook, hate blogging, are always online, and don't use twitter," 2010, http://www.fastcompany.com/blog/zachary-wilson/and-how/pew-survey-finds-increase-social-media-internet-time-decrese-blogging-te.

[32] Center for the Digital Future, "Annual internet survey by the center for the digital future finds large increases in use of online newspapers 2009: 1–9," USC Annenberg School for Communication, http://www.digitalcenter.org/pdf/2009_Digital_Future_Project_Release_Highlights.pdf.

[33] A. J. Daley, "Can exergaming contribute to improving physical activity levels and health outcomes in children?" *Pediatrics*, vol. 124, no. 2, pp. 763–771, 2009.

[34] JO. Salmon, M. L. Booth, P. Phongsavan, N. Murphy, and A. Timperio, "Promoting physical activity participation among children and adolescents," *Epidemiologic Reviews*, vol. 29, no. 1, pp. 144–159, 2007.

[35] T. Baranowski, R. Buday, D. I. Thompson, and J. Baranowski, "Playing for real: video games and stories for health-related behavior change," *American Journal of Preventive Medicine*, vol. 34, no. 1, pp. 74–82, 2008.

[36] M. J.M. Chin A Paw, W. M. Jacobs, E. P.G. Vaessen, S. Titze, and W. van Mechelen, "The motivation of children to play an active video game," *Journal of Science and Medicine in Sport*, vol. 11, no. 2, pp. 163–166, 2008.

[37] L. H. Epstein, M. D. Beecher, J. L. Graf, and J. N. Roemmich, "Choice of interactive dance and bicycle games in overweight and nonoverweight youth," *Annals of Behavioral Medicine*, vol. 33, no. 2, pp. 124–131, 2007.

[38] D. L. Graf, L. V. Pratt, C. N. Hester, and K. R. Short, "Playing active video games increases energy expenditure in children," *Pediatrics*, vol. 124, no. 2, pp. 534–540, 2009.

[39] L. Graves, G. Stratton, N. D. Ridgers, and N. T. Cable, "Energy expenditure in adolescents playing new generation computer games," *British Medical Journal*, vol. 335, no. 7633, pp. 1282–1284, 2007.

[40] L. E. F. Graves, N. D. Ridgers, and G. Stratton, "The contribution of upper limb and total body movement to adolescents' energy expenditure whilst playing Nintendo Wii," *European Journal of Applied Physiology*, vol. 104, no. 4, pp. 617–623, 2008.

[41] B. L. Haddock, S. R. Siegel, and L. D. Wikin, "The addition of a video game to stationary cycling: the impact on energy expenditure in overweight children," *The Open Sports Sciences Journal*, vol. 2, pp. 42–46, 2009.

[42] L. Lanningham-Foster, T. B. Jensen, R. C. Foster et al., "Energy expenditure of sedentary screen time compared with active screen time for children," *Pediatrics*, vol. 118, no. 6, pp. e1831–e1835, 2006.

[43] R. Maddison, C. Ni Mhurchu, A. Jull, Y. Jiang, H. Prapavessis, and A. Rodgers, "Energy expended playing video console games: an opportunity to increase children's physical activity?" *Pediatric Exercise Science*, vol. 19, no. 3, pp. 334–343, 2007.

[44] K. A. Madsen, S. Yen, L. Wlasiuk, T. B. Newman, and R. Lustig, "Feasibility of a dance videogame to promote weight loss among overweight children and adolescents," *Archives of Pediatrics & Adolescent Medicine*, vol. 161, no. 1, pp. 105–107, 2007.

[45] A. E. Maloney, T. C. Bethea, K. S. Kelsey et al., "A pilot of a video game (DDR) to promote physical activity and decrease sedentary screen time," *Obesity*, vol. 16, no. 9, pp. 2074–2080, 2008.

[46] S. Paez, A. Maloney, K. Kelsey, C. Wiesen, and A. Rosenberg, "Parental and environmental factors associated with physical activity among children participating in an active video game," *Pediatric Physical Therapy*, vol. 21, no. 3, pp. 245–253, 2009.

[47] J. McDougall and M. J. Duncan, "Children, video games and physical activity: an exploratory study," *International Journal on Disability and Human Development*, vol. 7, no. 1, pp. 89–94, 2008.

[48] R. R. Mellecker and A. M. McManus, "Energy expenditure and cardiovascular responses to seated and active gaming in children," *Archives of Pediatrics & Adolescent Medicine*, vol. 162, no. 9, pp. 886–891, 2008.

[49] R. R. Mellecker, A. M. McManus, L. M. Lanningham-Foster, and J. A. Levine, "The feasibility of ambulatory screen time in children," *International Journal of Pediatric Obesity*, vol. 4, no. 2, pp. 106–111, 2009.

[50] E. C. S. Murphy, L. Carson, W. Neal, C. Baylis, D. Donley, and R. Yeater, "Effects of an exercise intervention using Dance Dance Revolution on endothelial function and other risk factors in overweight children," *International Journal of Pediatric Obesity*, vol. 4, no. 4, pp. 205–214, 2009.

[51] C. Ni Mhurchu, R. Maddison, Y. Jiang, A. Jull, H. Prapavessis, and A. Rodgers, "Couch potatoes to jumping beans: a pilot study of the effect of active video games on physical activity in children," *International Journal of Behavioral Nutrition and Physical Activity*, vol. 5, article 8, 2008.

[52] A. L. Penko and J. E. Barkley, "Motivation and physiologic responses of playing a physically interactive video game relative to a sedentary alternative in children," *Annals of Behavioral Medicine*, pp. 1–8, 2010.

[53] K. Ridley and T. Olds, "Video center games: energy cost and children's behaviors," *Pediatric Exercise Science*, vol. 13, no. 4, pp. 413–421, 2001.

[54] C. H. Sit, J. W. Lam, and T. L. McKenzie, "Direct observation of children's preferences and activity levels during interactive and online electronic games," *Journal of Physical Activity & Health*, vol. 7, no. 4, pp. 484–489, 2010.

[55] L. Straker and R. Abbott, "Effect of screen-based media on energy expenditure and heart rate in 9- to 12-year-old children," *Pediatric Exercise Science*, vol. 19, no. 4, pp. 459–471, 2007.

[56] V. B. Unnithan, W. Houser, and B. Fernhall, "Evaluation of the energy cost of playing a dance simulation video game in overweight and non-overweight children and adolescents," *International Journal of Sports Medicine*, vol. 27, no. 10, pp. 804–809, 2006.

[57] T. Baranowski, J. Baranowski, D. Thompson et al., "Video game play, child diet, and physical activity behavior change: a randomized clinical trial," *American Journal of Preventive Medicine*, vol. 40, no. 1, pp. 33–38, 2011.

[58] D. Thompson, T. Baranowski, R. Buday et al., "Serious video games for health: how behavioral science guided the development of a serious video game," *Simulation and Gaming*, vol. 41, no. 4, pp. 587–606, 2010.

[59] D. Thompson, T. Baranowski, R. Buday et al., "In pursuit of change: youth response to intensive goal setting embedded in a serious video game," *Journal of Diabetes Science and Technology*, vol. 1, pp. 907–917, 2007.

[60] T. Baranowski, J. C. Baranowski, K. W. Cullen et al., "The fun, food, and fitness project (FFFP): the baylor GEMS pilot study," *Ethnicity & Disease*, vol. 13, no. 1, pp. S1–S1, 2003.

[61] T. Baranowski, J. Baranowski, K. W. Cullen et al., "Squire's Quest!: dietary outcome evaluation of a multimedia game," *American Journal of Preventive Medicine*, vol. 24, no. 1, pp. 52–61, 2003.

[62] K. W. Cullen, K. Watson, T. Baranowski, J. H. Baranowski, and I. Zakeri, "Squire's quest: intervention changes occurred at lunch and snack meals," *Appetite*, vol. 45, no. 2, pp. 148–151, 2005.

[63] M. C. Munguba, M. T. M. Valdés, and C. A. B. da Silva, "The application of an occupational therapy nutrition education programme for children who are obese," *Occupational Therapy International*, vol. 15, no. 1, pp. 56–70, 2008.

[64] T. A. Pempek and S. L. Calvert, "Tipping the balance: use of advergames to promote consumption of nutritious foods and beverages by low-income African American children," *Archives of Pediatrics & Adolescent Medicine*, vol. 163, no. 7, pp. 633–637, 2009.

[65] D. R. Southard and B. H. Southard, "Promoting physical activity in children with MetaKenkoh," *Clinical and Investigative Medicine*, vol. 29, no. 5, pp. 293–297, 2006.

[66] D. Thompson, T. Baranowski, J. Baranowski et al., "Boy Scout 5-a-Day Badge: outcome results of a troop and Internet intervention," *Preventive Medicine*, vol. 49, no. 6, pp. 518–526, 2009.

[67] M. C. Turnin, M. T. Tauber, O. Couvaras et al., "Evaluation of microcomputer nutritional teaching games in 1,876 children at school," *Diabetes and Metabolism*, vol. 27, no. 4, pp. 459–464, 2001.

[68] United States Department of Agriculture, "Expanded Food and Nutrition Education Program (EFNEP) 2010," 2011, http://www.csrees.usda.gov/nea/food/efnep/efnep.html .

SAGE-Hindawi Access to Research
International Journal of Hypertension
Volume 2011, Article ID 904742, 12 pages
doi:10.4061/2011/904742

Review Article

Statins: Cardiovascular Risk Reduction in Percutaneous Coronary Intervention—Basic and Clinical Evidence of Hyperacute Use of Statins

Enrique C. Morales-Villegas,[1] Germano Di Sciascio,[2,3] and Carlo Briguori[4]

[1] *Centro de Investigación Cardiometabólica, Quinta Avenida 702-210, Frac. Agricultura, Aguascalientes, 20234 México, AGS, Mexico*
[2] *Università Campus Bio-Medico di Roma, 00128 Rome, Italy*
[3] *Università di Roma "La Sapienza", 00185 Rome, Italy*
[4] *Clinica Mediterranea, Laboratorio di Emodinamica e Cardiologia Interventistica, 80122 Naples, Italy*

Correspondence should be addressed to Enrique C. Morales-Villegas, drmorvi@prodigy.net.mx

Received 26 November 2010; Revised 12 January 2011; Accepted 17 January 2011

Academic Editor: Kazuko Masuo

Reduction of LDL-cholesterol concentration in serum, blocking the isoprenylation of GTPases and the activation of myocyte-protective enzyme systems are three mechanisms that currently explain the lipid and non-lipid effects of statins. However, the decrease of LDL-cholesterol, the reduction of inflammation biomarkers and even the atheroregresion, as surrogate effects to the mechanisms of action of statins would be irrelevant if not accompanied by a significant decrease in the incidence of cardiovascular events. Statins like no other pharmacological group have proven to reduce the incidence of cardiovascular events and prolong life in any clinical scenario. This article review the basic and clinical evidence that support a new indication for HMG-CoA reductase inhibitors "pharmacological myocardial preconditioning before anticipated ischemia" or hyperacute use of statins in subjects with any coronary syndrome eligible for elective, semi-urgent or primary percutaneous coronary intervention: ARMYDA-Original, NAPLES I-II, ARMYDA-ACS, ARMYDA-RECAPTURE, Non-STEMI-Korean, Korean-STEMI trials.

1. Introduction

The inhibitors of Hydroxy Methyl Glutaryl-Coenzyme A Reductase (I-HMG-CoA-R) or statins have become the cornerstone of drug therapy that aimed at reducing cardiovascular risk. Statins are the pharmacological group with the highest reduction power of the serum LDL cholesterol concentration, apart from other lipid and pleiotropic actions. Therefore, their therapeutic efficacy can be explained if we remember that LDL cholesterol modified by oxidation becomes an epitope, which provokes along with other endothelial-vascular lesion factors, a pathological sequence with atherosis, endothelial activation-dysfunction lesion, atherosclerosis, and atherothrombosis. Thus, statins have become the most important pharmacological weapon for cardiovascular risk reduction when associated to atherosclerosis.

This paper reviews the most important pharmacological properties of statins, starting with new information on the mechanisms of action and effects that explain the reduction of LDL cholesterol concentration in serum, as well as nonlipid or pleiotropic effects. These basic concepts will be the foundations that will lead us to a better understanding of the impact of statins in new clinical applications, specially focusing on the role they play as reducers of Percutaneous Coronary Intervention (PCI) complications in individuals with stable and unstable coronary syndromes with and without ST segment elevation.

2. Statins: Mechanism of Action

The first statin extracted from *Penicillium citrinum* was discovered by Dr. Akira Endo in the 70s. Based on the knowledge of cholesterol synthesis from acyl and acetyl-CoA, Endo showed that compactin when competing with the HMG-CoA was an inhibitor of the enzyme that regulates cholesterol synthesis. Statins specifically compete with

HMG-CoA for the catalytic site of its reductase (HMG-CoA-R). This competition inhibits the metabolic pathway of HMG-CoA into mevalonate, a precursor molecule for the synthesis of cholesterol and other molecules such as the isoprenoids, Farnesyl and Geranyl Pyrophosphates [1, 2]. Endo's discovery was complemented and made clinically relevant by the studies of Joseph Goldstein and Michael Brown. Both researchers discovered the cellular receptor for LDL cholesterol (LDL-R) and described three concepts that would revolutionize medicine. Such concepts gave them a Nobel Prize in 1985 [3]. These "classical" concepts of and new data on the mobilization of intracellular cholesterol are presented as follows (see Figure 1).

(a) Receptor-Mediated Endocytosis. Each LDL macromolecule contains an average of 1500 molecules of cholesteryl ester; it gets into cells through the existence of LDL-R. These receptors are glycoproteins with 5 domains, embedded in convex structures of the cell membrane, formed by clathrin protein, and called "clathrin-coated pits." These structures serve as gathering places for cell surface receptors aimed at endocytosis. Once the LDL cholesterol is taken up by the LDL-R, an endocytic vesicle called endosome or receptosome is formed. Within the cell the LDL-R leaves the endosome and returns to the cell membrane; this dissociation is favored by a decrease in pH within the endosome. The LDL is transferred from the endosomes to the lysosomes and within them; both lipids and apoproteins are hydrolyzed, the first one into nonesterified cholesterol and the second into amino acids [3–5].

(b) Self-Regulation of the Receptor. Nonesterified cholesterol due to its being hydrophobic cannot move freely within the cell cytoplasm. The transport means of nonesterified cholesterol from the lysosome to the cell membranes was recently described by Brown and Goldstein and has been called "hydrophobic handoff mechanism." In this process proteins Niemann Pick 2 and 1 form a "hydrophobic core" that contains and carries the nonesterified cholesterol. The concentration of cholesterol in cell membranes, including the membrane of the Sarcoplasmic Reticulum/Golgi Apparatus system, is the signal to regulate the connection between the transcription factor, Sterol Regulatory Element Binding Protein (SREBP), and its anchor protein SREBP-Cleavage Activating Protein (SCAP). Cytoplasmic sequestration of SREBP by SCAP prevents the synthesis of LDL-R and other enzymes involved in cholesterol synthesis, especially HMG-CoA-R. The higher the concentration of cholesterol in cell membranes, the greater the inhibition of the synthesis of LDL-R. Free nonesterified cholesterol in the cytoplasm is reesterified by Acyl-CoA Cholesterol Acyl Transferase 1 (ACAT1) and then it can be integrated to the cellular metabolism [3–6].

(c) Recycling of the Receptor. The LDL-R plays an inside-out cell cycle every 10 minutes, so each LDL-R makes more than hundred cycles during its average 20-hour life. The cell cycle of the LDL-R can be interrupted by the action of the recently discovered Proprotein Convertase Subtilisin Kexin type 9 (PCSK9) [7].

Thus, by inhibiting the HMG-CoA-R, the mechanisms that allow statins to reduce concentrations of cholesterol in serum are the following: (a) reduction of cholesterol hepatic synthesis and therefore a reduction in the synthesis of VLDL, an IDL and LDL precursor; (b) reduction in the concentration of cholesterol in the membranes of the hepatocyte and increased transcription, synthesis and expression of LDL-R with an affinity for IDL (in apo-E) and LDL (in apo-B100); (c) increase in hepatic uptake of IDL and LDL and cholesterol hepatobiliary elimination [8, 9]. The cholesterol-lowering power of statins is directly related to the number of links they establish with the catalytic site of HMG-CoA-R; atorvastatin establishes 8 links while rosuvastatin 9, and therefore the inhibition coefficients of 50% (IC-50) of the enzymatic action of HMG-CoA-R are of 5.4 and 8.2 nanomoles, respectively [8–12].

3. Statins—Effects on Cholesterol, Biomarkers of Inflammation, and Myocyte Protection: Cholesterol Reduction

The average reduction of cholesterol in serum is a function of the statin and its dosage; 10 mg of atorvastatin or rosuvastatin 5 mg achieve an average reduction of 35% in the baseline value of LDL cholesterol, while the maximum therapeutic doses 80 mg and 40 mg, respectively, produce an average reduction of 50% and 55%. This effect is independent of the hydrophilicity (facilitated diffusion by Organic Anion Transporters of Polypeptides or OATP) or lipophilicity (direct diffusion) of the statin. These data allows us to calculate the optimal therapeutic dose of a statin according to baseline LDL cholesterol, the goal regarding the cardiovascular risk level and the treatment gap [13–15].

Reduction in Inflammation Biomarkers. Statins not only reduce the concentration of LDL cholesterol in serum, as mentioned above, inhibition of the synthesis of mevalonate by statins also blocks the synthesis of isoprenoids (Farnesyl and Geranyl Pyrophosphates). In the phenomenon of endothelial activation, isoprenoids play a very important role [16, 17]; in endothelial cells, binding of oxidized LDL cholesterol to its LOX Receptor activates the expression of its inflammatory phenotype; during such process, the intracellular switch is the isoprenylation of small G type proteins (smgs). These proteins are called G for their guanosine content, when nonactive, smgs are "floating" in the cellular cytoplasm linked to Guanosine Diphosphate (GDP), and its activation depends on the presence of isoprenoids and the Guanosine Exchange Factor (GEF). With the participation of both molecules, the GDP acquires a phosphate group and becomes Guanosine Triphosphate (GTP); thus, the inactive smgs acquire the characteristic of GTPases, migrate, anchor themselves to the cell membrane, and exert their phosphorylating action on various substrates for activation of multiple enzymatic cascades. GTPases are divided into several enzyme families, the most important are

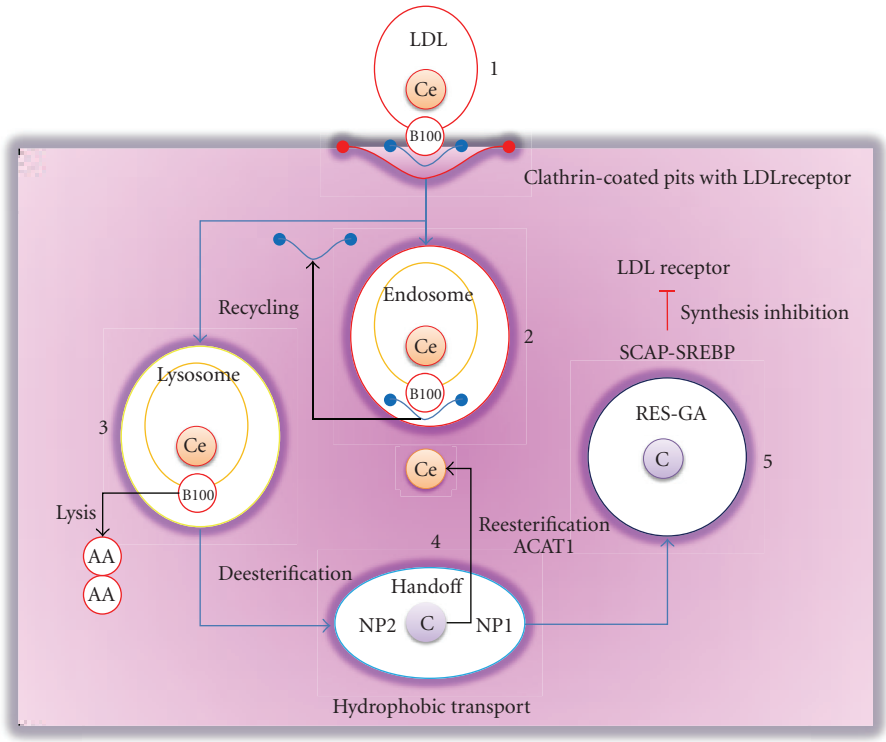


Figure 1: *Regulation of LDL-R in 5 steps. Step 1.* The LDL is recognized in apo-B100 by the LDL-R located in the membrane structures "clathrin-coated pits." *Step 2.* It forms an endocytic vesicle or endosome containing LDL and LDL-R, the LDL-R is dissociated through lowering of the pH within the endosome, and the LDL is transferred to the lysosomes. *Step 3.* In lysosomes, apo-B100 is hydrolyzed into amino acids and cholesteryl ester is deesterified by enzymatic hydrolysis. *Step 4.* Nonesterified cholesterol (hydrophobic) is transported to the cell membranes by the "hydrophobic handoff mechanism"; in this mechanism Niemann Pick 2 and 1 proteins form a hydrophobic core containing nonesterified cholesterol. *Step 5.* Nonesterified cholesterol is transferred by the binomial NP2-NP1 to cell membranes, its concentration in the Sarcoplasmic Reticulum/Golgi Apparatus membranes is the signal that inhibits the dissociation of SCAP-SREBP and thus blocks the synthesis of LDL-R.

the so-called Ras, Rho, and Rab, each stimulating different cellular processes involved in the inflammatory process (e.g., the smg Ras modulate cell division and growth, the smg Rho proteins activate the cell cytoskeleton, and the smg Rab regulate intracellular vesicular movement) (see Figure 2) [18, 19].

Thus, inhibition of isoprenoid synthesis by statins reduces isoprenylation of smgs proteins and blocks in different degrees the inflammatory response initiated by oxidized LDL cholesterol binding to LOX-R. Inflammatory endothelial activation initiated by the binding of other ligands to their receptors (e.g., angiotensin II to AT1-R or AGEs to RAGEs) is also generated from a process of smgs and G proteins isoprenylation; this explains why the anti-inflammatory effect of statins is not proportional to the reduction of LDL cholesterol; its anti-inflammatory capacity goes beyond this fact due to its potential to inhibit the switch of inflammatory endothelial activation, regardless of the stimulus [20, 21].

Multiple in vitro evidence has been published, in vivo in experimental animals and in vivo in individuals with atherosclerosis such evidence has shown that statins attenuate vascular endothelial inflammatory process of atherosclerosis itself. This endothelium-vascular inflammatory attenuation is independent but synergistic with LDL cholesterol reduction. The following are among the most important pieces of evidence. Dr. Jain's team at Harvard proved in vitro that statins promote on endothelial cells the expression of Kruppel-Like Factor 2 (KLF2), transcription factor for the synthesis of eNOS and thrombomodulin [22]. Thus, statins stimulate the synthesis of eNOS, an enzyme responsible for the production of nitric oxide, which among its many actions promotes on the endothelial cell the intracytoplasmic sequestration of the transcription factor NFκB (group of "master" transcription factors of the inflammatory response). The translation in vivo, in the experimental animal, of the anti-inflammatory effect of statins has been published by several researchers. For example, in the animal model of aortocoronary atherosclerosis in mice, when blindly compared with placebo, statins decrease "acutely" the monocyte infiltration into atherosclerotic aortocoronary areas [23]. This phenomenon is equivalent to the in vivo demonstration in humans of "acute" reduction of the inflammatory activity in aortas with atherosclerosis in subjects treated with statins. By using 18FDG-PET, it has been shown that the administration of atorvastatin

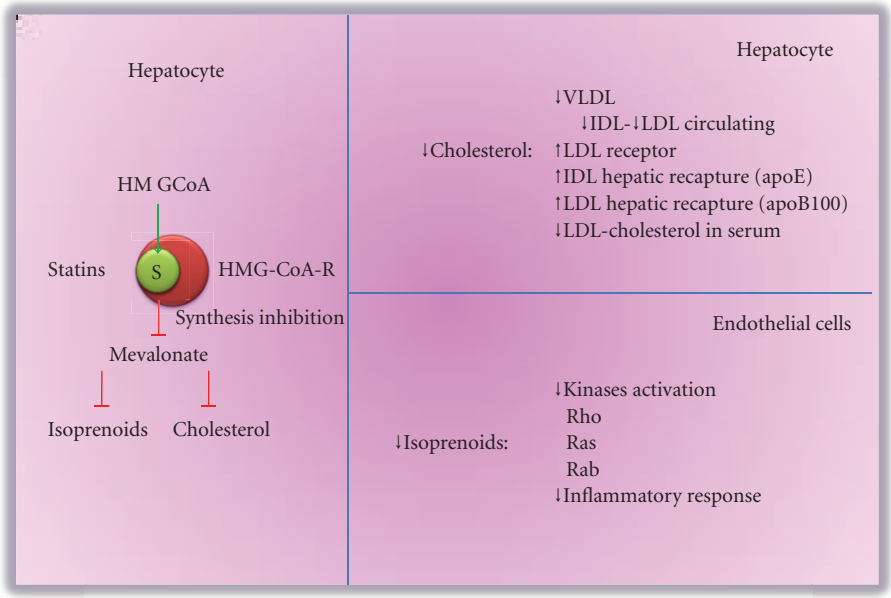


Figure 2: *Statins reduce cholesterol, and isoprenoids synthesis.* The statins inhibit HMG-CoA-R and block the synthesis of mevalonate, cholesterol, and isoprenoids. In the hepatocyte, the reduction in cholesterol synthesis determines a reduction in VLDL synthesis and increase in the synthesis of LDL-R; thus, the reduced production of VLDL, IDL, and LDL and increased elimination of circulating IDL, and LDL, explain the reduction in LDL concentration. In the endothelial cells the reduction in the synthesis of isoprenoids determines a reduction of the inflammatory response mediated by inactivation of smgs from different families (Rho, Ras, Rab).

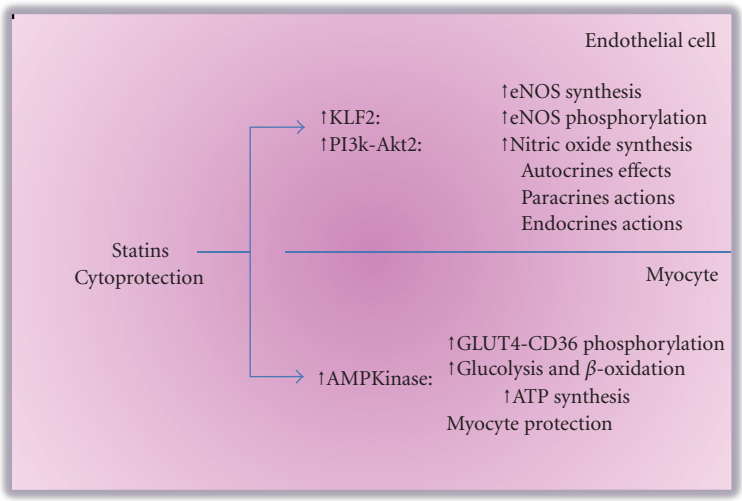


Figure 3: *Statins, mechanisms, and myocyte-protective effects.* Statins increase the expression of KLF2 and eNOS synthesis and also increase the activation of eNOS and nitric oxide production. In the myocyte the activation of AMPK increases the income and energy substrate utilization, as well as the production of ATP.

significantly reduced inflammatory activity in human aortas with atherosclerosis; this change in inflammatory activity occurs within days and was not associated with significant changes in the concentration of LDL cholesterol in serum [24].

Myocyte Protection. Statins in experimenting animals have shown a myocyte-protective effect, this effect is independent of LDL-cholesterol reduction and anti-inflammatory effect and have been associated with the activation of two cellular protective enzyme systems, the Reperfusion Ischemic Salvage Kinases pathway (RISK pathway) and the AMP-activated Kinase (see Figure 3) (AMPK) [25–30].

RISK Pathway. Nitric oxide production by activation of enzymatic cascade PI3Kinase-Akt2-eNOS is a physiological

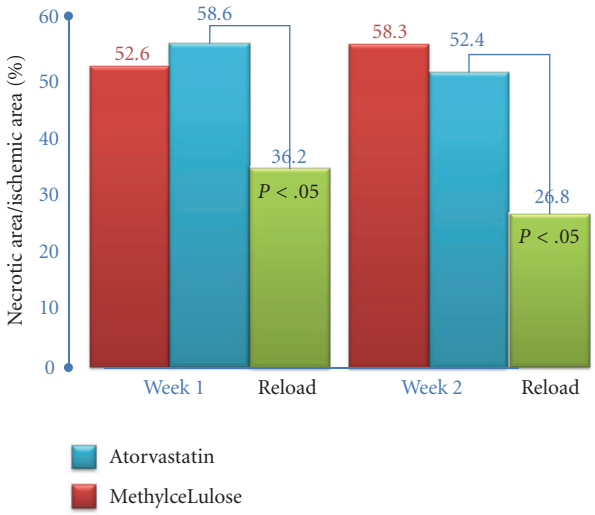


FIGURE 4: *Statins and recapture of the RISK pathway.* This modified graphic of Mensah's work, shows how the quotient (necrosis/ischemia) is similar in rats treated for 1 or 2 weeks with methylcellulose (red bars) or atorvastatin (blue bars). This loss of myocyte-protective effect is "recaptured" significantly with the reload of atorvastatin (green bars).

process of cell protection against ischemia and statins have been proven to potentiate this process. However, Yellon and his colleagues have shown in experimental animals that "chronic" experimental administration of statins prevents the production of nitric oxide through RISK pathway. This inhibition is due to the overexpression of the Phosphatase Tensin (PTEN) with an antagonistic action towards PI3Kinase. This blockade of the RISK pathway can be recaptured with the administration of a statin reload [31]. Mensah demonstrated in experimental rats subjected to myocardial ischemia and postischemia reperfusion that the quotient (myocardial necrosis/ischemia) after reperfusion was significantly reduced by administration prior to the ischemia of an acute dose (day 1 and day 3) of atorvastatin. This myocyte-protective effect was canceled when the statin was administered for longer periods (1 and 2 weeks) before induction of myocardial ischemia. The cancellation of the myocyte-protective effect was associated with a significant increase in the concentration of PTEN. The most important finding of this series of experiments was the evidence that, in animals treated for 1 or 2 weeks with atorvastatin, the reload of atorvastatin in day 1 significantly reduced the quotient (myocardial necrosis/ischemia), which, means that it "recaptured the RISK pathway." (see Figure 4) The hypothesis is that statins reload manages to inhibit the expression of PTEN and enhances the expression of PI3Kinase-Akt2-eNOS with increased production of nitric oxide [31]. This evidences provided the rationale and name of the study ARMYDA-RECAPTURE analyzed as follow.

AMPKinase. This enzyme is considered the energetic switch of the ischemic, cell. In the ischemic cell there is an inversion of the quotient ATP/AMP by increased cytoplasmic concentration of AMP (ADP + ADP = 1 ATP + 1 AMP). The AMP increase is the signal that activates the gamma subunit of the AMPK and initiates multiple phosphorylation substrates (AMPK-kinases). Among the substrates activated by AMPK are the glucose transporters (GLUT4), fatty acid transporters (CD36) and key enzymes of the pathways of glycolysis and beta-oxidation. Thus activation of AMPK increases cellular entry, the use of glucose and free fatty acids, as well as the production of ATP. There is much evidence that molecules such as adiponectin, metformin, and statins are indirect AMPK activators, thereby exercising a myocyte-protective effect, especially in scenarios of myocardial ischemia [28]. To summarize, the RISK pathway and the AMPK are activated by statins in an LDL-independent manner. The RISK pathway increases nitric oxide production and AMPK increases cellular income and utilization of glucose and fatty acids which optimizes the energy efficiency of the ischemic cell [25–31].

4. Statins: Clinical Effects in Percutaneous Coronary Intervention (Hyperacute Use)

Based on observational studies, most notably Chang's [32] randomized studies were designed and provided solid evidence resulting in new options for therapeutic use of statins in subjects undergoing elective, semiurgent (12–48 hours of "interventional window"), and primary Percutaneous Coronary Intervention (PCI). The reduction in the risk of Myocardial Infarction-PCI associated (MI-PCI associated) with a statin load prior to PCI is undoubtedly an important therapeutic benefit that is changing the therapeutic approach on the hemodynamics prelude, which will probably give statins a new indication (*pharmacologic preconditioning against anticipated myocardial ischemia*) [33–42]. The Italian group led by Germano Di Sciascio began, with its publication in 2004, the series of formal clinical studies supporting the concept of myocardial preconditioning by statin against anticipated myocardial ischemia. This series of studies include the following: ARMYDA-Original [34], ARMYDA-CAMs [35], NAPLES I-II [36, 37], ARMYDA-ACS [38], ARMYDA-RECAPTURE [39], ARMYDA-AMI [40], still under recruitment stage, and the recently published Koreans studies on Non-STEMI [41] and Statin-STEMI [42] (see Table 1).

Before addressing the analysis of these studies, it is important to review the definition of MI-PCI associated, its frequency, and prognosis implications. Since 2007, the diagnosis criteria for MI-PCI associated is 3 times greater than the normal maximum value of CPK-MB and/or troponins (before 2007 the criteria was 2 times more) [43]. The MI-PCI associated is common, its incidence has been reported as high as 70%, and its pathogenesis involves several factors: some of the most important are the endothelial-vascular size and condition of the compromised territory, the spontaneous microembolization, as well as the microembolization induced by the triad catheter-balloon-Stent with distally compromised microcirculation, collateral circulation, and myocardial ability to respond to trans

Table 1: Randomized trials with statins in percutaneous coronary intervention. This table is a summary of the 8 randomized trials (versus placebo or versus control groups) published with statins in individuals under PCI. All studies except Vaselka's have shown positive results for the use of statins prior to PCI. The results in individuals with elevated *CRP* before PCI (NAPLES II) and in individuals with ACS (ARMYDA-ACS y ARMYDA-RECAPTURE, ACS soubgroup), are particularly favorable. MI-PCI-A: Myocardial Infarction-PCI associated. MACE: Mayor Adverse Cardiovascular Events. MRI: Myocardial Reperfusion Indicators.

Trial	Interventional scenario		Treatment	Primary end point
ARMYDA-Original N 153 naive (76/77)		Non-ACS	Atorvastatin versus placebo 40 mg/7 days pre-PCI	↓ MI-PCI-A. CPK-MB > 2x ULN 05.0% versus 18.0% ($P = .025$)
NAPLES I N 451 naive (226/225)		Non-ACS	Various statins versus control Different doses >72 hr pre-PCI	↓ MI-PCI-A. CPK-MB > 3x ULN 08.0% versus 15.6% ($P = .012$)
NAPLES II N 668 naive (338/330)		Non-ACS	Atorvastatin versus control 80 mg/24 hr pre-PCI	↓ MI-PCI-A. CPK-MB > 3x ULN 09.5% versus 15.8% ($P = .014$) ↓ MI-PCI-A. CPK-MB > 3x ULN 04.6% versus 16.5% ($P = .016$) (subgroup CRP > 6 mg/lt)
ARMYDA-ACS N 171 naive (85/86)	Non-STEMI ACS		Atorvastatin versus placebo 120 mg/12 hr pre-PCI	↓ MACE day 30. 05.0% versus 17.0% ($P = .01$) ↓ MI-PCI-A. CPK-MB > 2x ULN 0.5% versus 15.0% ($P = .04$)
ARMYDA-REC N 383 preTx (192/191)	Non-STEMI ACS 47%	Non-ACS 53%	Atorvastatin versus placebo 120 mg/12 hr pre-PCI	↓ MACE day 30. 03.7% versus 09.4% ($P = .037$). ↓ MACEs day 30. 03.3% versus 14.8% ($P = .015$) (subgroup ACS)
Non-STEMI Korean N 445 naive (220/225)	Non-STEMI ACS		Rosuvastatin versus control 40 mg/16 hr pre-PCI	↓ MI-PCI-A. CPK-MB > 2x ULN. 05.8% versus 11.4% ($P = .035$).
STEMI Korean N 171 naive (86/85)	STEMI ACS		Atorvastatin high versus low dose 80 mg versus 10 mg in primary PCI	↓ MACE day 30. 05.8% versus 10.6% ($P = .26$) ↑ MRIs min 90 after PCI. All indicators $P < .05$
Vaselka N 200 naive (100/100)		Non-ACS	Atorvastatin versus Control 80 mg/48 hr pre-PCI	↓ MI-PCI-A. CPK-MB > 3x ULN 10.0% versus 12.0% ($P = .065$)

and postreperfusion ischemia (myocardial preconditioning) [44]. The MI-PCI associated, even if it is only enzymatic, is associated with deterioration in the prognosis; even when the importance of MI-PCI associated has been minimized, the morbidity and mortality in the medium and long term are directly proportional to the magnitude of PCI-related enzyme increase [45].

5. Clinical Studies in Percutaneous Coronary Intervention

5.1. ARMYDA-Original. Aware of observational evidence, Germano Di Sciascio leading the group Romano ARMYDA designed the Original ARMYDA study. This pivotal study showed that individuals with stable coronary syndromes, statin-naive, and with indication of elective coronary angioplasty, who received 40 mg of atorvastatin a day, seven days before PCI, underwent a significant reduction of the relative risk of MI-PCI associated (CPK-MB > 2x ULN, 2004 criteria) as compared to those treated with placebo; 18% in the placebo group versus 5% in the atorvastatin with $P = .025$ (see Figure 5).

5.2. ARMYDA-CAMs. The substudy ARMYDA-CAMs (Cell Adhesion Molecules) provided a mechanistic explanation for the overall study results of the ARMYDA-Original study. Patty showed that in the arm treated with 40 mg of atorvastatin a day for seven days before PCI, the increase in adhesion molecules (E-selectin and ICAM-1) 24 hours after intervention, was limited significantly ($P = .0001$) [35]. This finding reflects a facet of the anti-inflammatory effect of statins, which while inhibiting the expression of the transcription factors like NFκB, decrease endothelial cells synthesis of these adhesion molecules [16–19] (see Figure 6).

5.3. NAPLES I-II. Carlo Briguori, inspired by the results of the pilot study (NAPLES I) [36] and the already mentioned ARMYDA-Original, developed and published in 2009 the results of NAPLES II trial. This relevant study showed that individuals with stable coronary syndromes, statin-naïve, and with indication of elective coronary angioplasty, who received 80 mg of atorvastatin a day, 24 hours before PCI, underwent a significant reduction of the relative risk of MI-PCI associated (CPK-MB > 3x ULN, 2007 criterion) as compared to those treated with placebo, 15.8% in the placebo group versus 9.5% in the atorvastatin group with $P = .014$. With this study, the Naples-Milan group suggested that it is possible to shorten the therapeutic window of the statin load from 7 days to 24 hours. The therapeutic result of the statins load was outstanding in the subgroup with positive

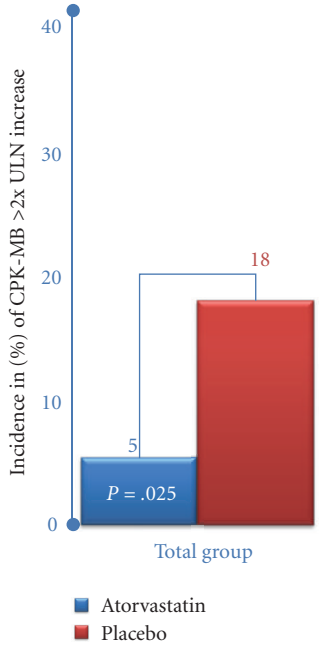


Figure 5: *ARMYDA-Original study.* This modified graphic of the ARMYDA-Original study (Vincenso Pasceri as first author) demonstrated for the first time as a randomized study the favorable effect of statins before PCI. In individuals with stable coronary syndromes, statin-naïve, undergoing elective PCI, the administration of atorvastatin 40 mg/7 days before PCI significantly reduces the incidence of MI-PCI associated (CPK-MB > 2x ULN, 2004 criteria). The MI-PCI associated was 18% in the placebo group versus 5% in the atorvastatin group with $P = .025$.

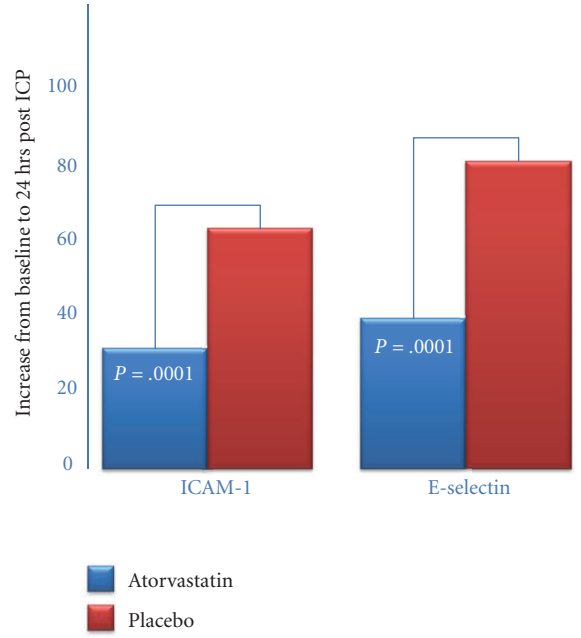


Figure 6: *ARMYDA-CAMs study.* This modified graphic of the ARMYDA-CAMs study showed that, in a preselected subgroup or the ARMYDA-Original study, in individuals with stable coronary syndromes, statin-naïve, and undergoing elective PCI, the administration of atorvastatin 40 mg/7 days before PCI significantly reduced the percentage of elevation 24 hours after PCI of ICAM and E-selectin. This reduction was not observed with VCAM (not shown in the graphic).

CRP by latex (CRP > 6 mg/L) before PCI; in this subgroup, the incidence of MI-PCI associated (CPK-MB > 3x ULN, 2007 criterion) was 16.5% in the control group compared with 4.6% in the atorvastatin group with $P = .016$ [37] (see Figure 7).

The results of previous studies in individuals with stable coronary syndromes, motivated the design of ARMYDA-ACS and later ARMYDA-RECAPTURE, the first in statin-naive individuals and the second in people with chronic statin treatment. These are the two recent studies published by the ARMYDA group, pending the publication of ARMYDA-AMI (Acute Myocardial Infarction).

5.4. ARMYDA-ACS. ARMYDA-ACS study showed that, in individuals with Acute Coronary Syndromes, without ST-segment elevation, statin-naïve, and with semiurgent indication of percutaneous coronary angioplasty, who were administrated 120 mg of atorvastatin divided into two doses, a dose of 80 mg twelve hours before and another 40 mg two hours before PCI, there was a significant reduction in the incidence of MACEs or Major Adverse Cardiovascular Events (myocardial infarction, re intervention or cardiovascular death), as compared to those treated with placebo. The relative risk reduction of MACEs reached 88%; 17% in the placebo group versus 5% in the atorvastatin group with $P = 0.01$. This reduction in MACEs was dominated by a decrease in MI-PCI associated (CPK-MB > 2x ULN, 2004 criterion), 15% in the placebo group versus 5% in the atorvastatin group with $P = .04$ [38].

5.5. ARMYDA-RECAPTURE. The ARMYDA-RECAPTURE or RELOAD raised the hypothesis that the recapture of RISK pathway observed in experimental animals could be reproduced in the hospital. This study included individuals with an indication of PCI, who evolved into a stable or unstable coronary syndrome without ST-segment elevation, when chronically treated with statins and LDL < 100 mg/dl. In a design similar to ARMYDA-ACS, this study demonstrated that administration of atorvastatin 120 mg, divided into two doses, a dose of 80 mg twelve hours before and another of 40 mg two hours before PCI, significantly reduced the incidence of MACEs (myocardial infarction, reintervention, or cardiovascular death) as compared with those treated with placebo; 9.4% in the placebo group versus 3.7% in the atorvastatin group with $P = .037$. This reduction in MACEs was dominated by a decrease in MI-PCI associated (CPK-MB > 3x ULN, 2007 criterion), 8.9% in the placebo group versus 3.7% in the atorvastatin group. The therapeutic benefit reached its maximum in the subgroup with unstable coronary syndromes, with an incidence of MACEs greater than 14.8% in the placebo group versus 3.3% in the atorvastatin group with $P = .015$, and a Number Needed to

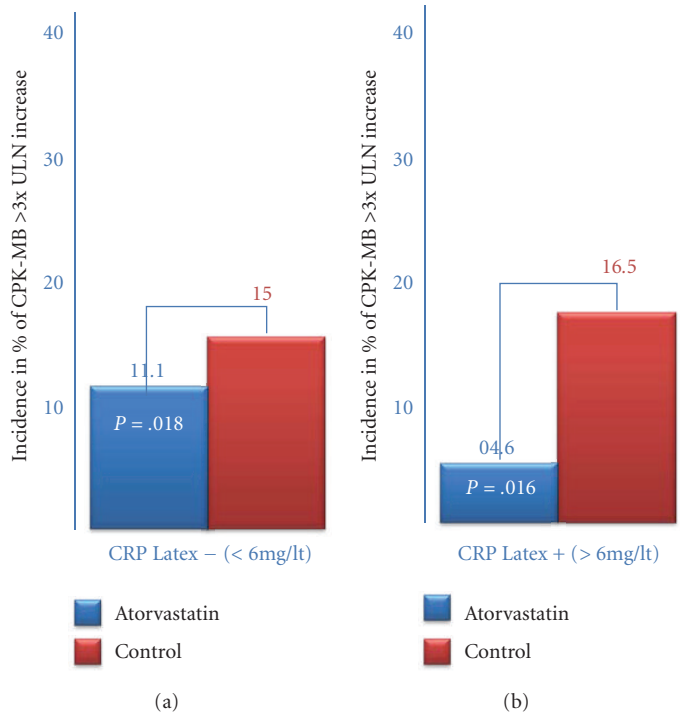


Figure 7: *NAPLES II Study.* This modified graphic of the NAPLES II study, confirmed with a randomized study, as compared to a control group, the favorable effect of statins before PCI. In individuals with stable coronary syndromes, statin-naive undergoing elective PCI, the administration of atorvastatin 80 mg/24 hours before PCI significantly reduces the incidence of MI-PCI associated (CPK-MB > 3x ULN, 2007 criteria). As can be seen, the benefit was especially significant in the subgroup of individuals with CRP > 6 mg/L before PCI, in this subgroup the incidence of MI-PCI associated was 16.5% in the control group versus 4.6% in the atorvastatin group with $P = .016$.

Treat (NNT) of 9 individuals to avoid an MACE, an excellent cost-benefit relation [39] (see Figure 8).

5.6. Non-STEMI and Statin-STEMI Korean Studies. The Korean group led by Ho Yun Kyeong reproduced the results of ARMYDA-ACS. The author used 40 mg of rosuvastatin a day administered an average of 16 hours before PCI, compared with a control group, in individuals with Non-STEMI acute coronary syndromes, and reported a significant reduction in the incidence of MI-PCI associated (CPK-MB > 2x ULN, 2004 criterion), 11.4% in placebo group versus 5.8% in the rosuvastatin group with $P = .035$ [41].

In early 2010 they were also published by a Korean group (the first author was Kim Jung-Sum), the results of Statin-STEMI study which explored the effect of an 80 mg dose versus 10 mg dose of atorvastatin in subjects with STEMI undergoing primary coronary angioplasty. In this study, the primary objective (MACEs at day 30 after PCI) was not positive, but still it did show a trend towards the benefit with the high dose of atorvastatin; MACEs at day 30 after PCI 5.8% in the 80 mg atorvastatin group versus 10.6% in the 10 mg atorvastatin group with $P = .026$. This result is probably explained by the size of the sample (171 individuals), the low dose of atorvastatin after PCI (10 mg/day) and/or the short followup time. However, in the secondary objective (Myocardial Reperfusion Indicators or MRI), there actually was a significant difference favoring the high dose of atorvastatin; corrected TIMI Frame Count (cTFC) 29.6 versus 34.1 with $P = .01$; completed STResolution (cSTR) 61.8 versus 50.6 with $P = .01$; and Myocardial Blush Grade (MBG) 2.2 versus 1.9 with $P = .02$ [42] (see Figure 9).

As a whole, the results of the studies mentioned, all performed in a quintessential endothelial-vascular inflammatory environment, strengthen the presence and importance of nonlipid effects of statins. These results not only support the anti-inflammatory potential of statins due to the effect of "endothelial passivation" but also highlight the myocyte-protective actions of these drugs. From a clinical-therapeutic perspective, the evidence presented here represents a new indication for statins, which although not yet reflected in the guidelines, is changing the therapeutic behavior of Clinical and Interventional Cardiologists at the hemodynamics prelude, because as Stephen Ellis wrote in his editorial for the ARMYDA-RECAPTURE study, "*the benefit of statins in PCI, is virtually indisputable and is associated with pleiotropic actions*" [29].

6. Statins and PCI: Abstract

After compactin, discovered by Akira Endo in the 70s, statins have shown that, when competing with the HMG-CoA by the catalytic site of its reductase, they very effectively inhibit the synthesis of mevalonate, cholesterol, and isoprenoids [1]. This metabolic block favors the reduction in the

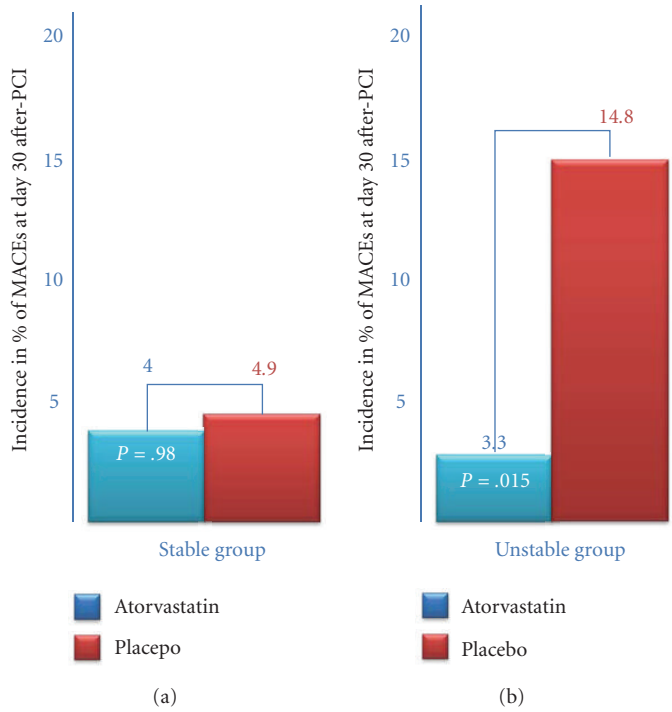


Figure 8: *ARMYDA-RECAPTURE study.* This modified graphic of the ARMYDA-RELOAD (RECAPTURE) study, showed with a randomized design, as compared to patients treated with placebo, the recapture effect of statins. In individuals with stable and unstable coronary syndromes, chronically treated with statins and LDL <100 mg/dl, who underwent elective or semiurgent PCI, the administration of 120 mg of atorvastatin before PCI significantly reduces the incidence of MACEs on day 30 after PCI. This benefit was very significant in the subgroup of individuals with unstable coronary syndromes, with an MACEs incidence of 14.8% in the placebo group versus 3.3% in the atorvastatin group with $P = .015$.

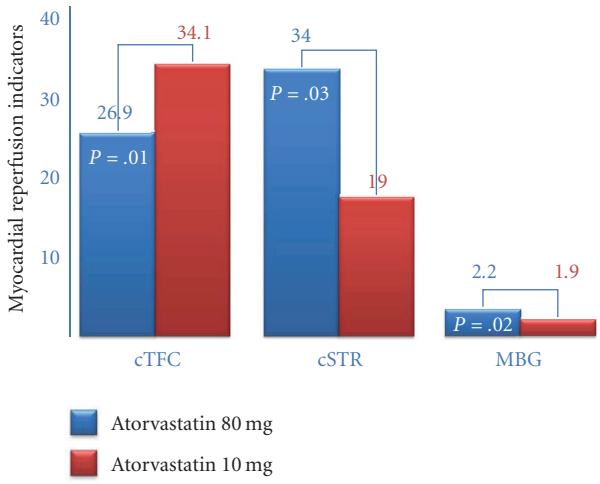


Figure 9: *Statin-STEMI study.* This modified graphic of the Statin-STEMI study, demonstrated the favorable effect of high doses of atorvastatin before primary PCI on the Myocardial Reperfusion Indicators (cTFC, CSTR, and MBG) after procedure in individuals with STEMI.

cellular synthesis and concentration of cholesterol in the membranes of hepatocytes, this condition being the signal that upregulates the synthesis, expression, and activity of LDL-R discovered by Brown and Goldstein. The activity of the LDL-R increases the uptake and hepatobiliary elimination of circulating cholesterol this along with the reduction in VLDL synthesis; the mechanisms that explains the effective (35% to 50%) reduction in LDL-cholesterol in serum [2–15]. The block of Farnesyl and Geranyl Pyrophosphates synthesis attenuates isoprenylation and activation of GTPases (Ras, Rho and Rab), inhibiting at various degrees, disregarding the external stimulus, the activity of endothelium-vascular inflammatory enzyme cascades [16–24]. Direct activation of PI3K-Akt2-eNOS and indirect activation of AMPK optimizes the supply, uptake and metabolism of energy substrates in the ischemic myocardial cell [25–31]. Thus, the reduction of LDL-cholesterol concentration in serum, blocking the isoprenylation of GTPases and the activation of myocyte-protective enzyme systems are three mechanisms that currently explain the lipid and nonlipid effects of statins [1–31].

As commented in the body of this paper, the decrease of LDL cholesterol, the reduction of inflammation biomarkers and even the atheroregression [46–49], as surrogate effects to the mechanisms of action of statins would be irrelevant if not accompanied by a significant decrease in the incidence of cardiovascular events. Statins like no other pharmacological group have proven to reduce the incidence of cardiovascular events and prolong life in any clinical scenario: in individuals

of medium or high risk, with no clinical evidence of cardiovascular disease (CTT meta-analysis and ASCOT-LLA, CARDS, JUPITER trials) [50–54]; in individuals with clinical cardiovascular disease, regardless of its manifestation, be it stable coronary syndrome (TNT trial) [55–57], unstable coronary syndrome (MIRACL, PROVE-IT trial) [58–63], carotid vertebral (SPARCL trial) [64]; in subjects with any coronary syndrome eligible for elective, semiurgent, or primary PCI (ARMYDA-Original, NAPLES I-II, ARMYDA-ACS-RECAPTURE ARMYDA, Non-STEMI-Korean, STEMI Korean trials) [34–42].

Furthermore, the benefit of statins is being studied in other scenarios dominated by inflammation with positive results in rheumatic mitral valve disease [65]. In addition to this, new lines of research are being explored on the effect of statins on endothelial regeneration [66–68]. Finally, inhibition at pre- and posttranslational levels of the PCSK9 is an option that poses an interesting future in the treatment of high LDL cholesterol [69]. Obviously the treatment of other atherogenic lipid fractions (non-HDL cholesterol) and anti-atherogenic (HDL cholesterol), as well as other modifiable factors of vascular-endothelial injury (visceral adiposity, arterial hypertension, dysglycemia, etc.), complement the wonderful pharmacological effect of statins [70].

References

[1] A. Endo, "The discovery and development of HMG-CoA reductase inhibitors," *Journal of Lipid Research*, vol. 33, no. 11, pp. 1569–1582, 1992.

[2] M. S. Brown and J. L. Goldstein, "A tribute to Akira Endo, discoverer of a "Penicillin" for the cholesterol," *Atherosclerosis Supplements*, no. 5, pp. 13–16, 2004.

[3] M. S. Brown and J. L. Goldstein, "A receptor-mediated pathway for cholesterol homeostasis," *Science*, vol. 232, no. 4746, pp. 34–47, 1986.

[4] J. L. Goldstein and M. S. Brown, "Regulation of the mevalonate pathway," *Nature*, vol. 343, no. 6257, pp. 425–430, 1990.

[5] J. L. Goldstein and M. S. Brown, "The LDL receptor. History of discovery," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 29, no. 4, pp. 431–438, 2009.

[6] J. L. Goldstein and M. S. Brown, *Hidrophobic Handoff Mechanism*, Nobel Laureate Lecture, American Heart Association Meeting, Chicago, Ill, USA, 2010.

[7] B. Cariou, K. Ouguerram, Y. Zaïr et al., "PCSK9 dominant negative mutant results in increased LDL catabolic rate and familial hypobetalipoproteinemia," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 29, no. 12, pp. 2191–2197, 2009.

[8] H. N. Ginsberg, N. A. Le, M. P. Short, R. Ramakrishnan, and R. J. Desnick, "Suppression of apolipoprotein B production during treatment of cholesteryl ester storage disease with lovastatin. Implications for regulation of apolipoprotein B synthesis," *Journal of Clinical Investigation*, vol. 80, no. 6, pp. 1692–1697, 1987.

[9] Y. Arad, R. Ramakrishnan, and H. N. Ginsberg, "Lovastatin therapy reduces low density lipoprotein apoB levels in subjects with combined hyperlipidemia by reducing the production of apoB-containing lipoproteins: implications for the pathophysiology of apoB production," *Journal of Lipid Research*, vol. 31, no. 4, pp. 567–582, 1990.

[10] E. S. Istvan and J. Deisenhofer, "Structural mechanism for statin inhibition of HMG-CoA reductase," *Science*, vol. 292, no. 5519, pp. 1160–1164, 2001.

[11] F. McTaggart, L. Buckett, R. Davidson et al., "Preclinical and clinical pharmacology of rosuvastatin, a new 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor," *American Journal of Cardiology*, vol. 87, supplement, pp. 28B–32B, 2001.

[12] G. A. Holdgate, W. H. J. Ward, and F. McTaggart, "Molecular mechanism for inhibition of 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase by rosuvastatin," *Biochemical Society Transactions*, vol. 31, no. 3, pp. 528–531, 2003.

[13] P. H. Jones, M. H. Davidson, E. A. Stein et al., "Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* trial)," *American Journal of Cardiology*, vol. 92, no. 2, pp. 152–160, 2003.

[14] J. M. McKenney, P. H. Jones, M. A. Adamczyk, V. A. Cain, B. S. Bryzinski, and J. W. Blasetto, "Comparison of the efficacy of rosuvastatin versus atorvastatin, simvastatin, and pravastatin in achieving lipid goals: results from the STELLAR trial," *Current Medical Research and Opinion*, vol. 19, no. 8, pp. 689–698, 2003.

[15] S. J. Nicholls, G. Brandrup-Wognsen, M. Palmer, and P. J. Barter, "Meta-analysis of comparative efficacy of increasing dose of atorvastatin versus rosuvastatina versus simvastatin on lowering levels of atherogenic lipids (from VOYAGER)," *American Journal of Cardiology*, vol. 105, no. 1, pp. 69–76, 2010.

[16] P. J. Casey, "Protein lipidation in cell signaling," *Science*, vol. 268, no. 5208, pp. 221–225, 1995.

[17] F. L. Zhang and P. J. Casey, "Protein prenylation: molecular mechanisms and functional consequences," *Annual Review of Biochemistry*, vol. 65, pp. 241–269, 1996.

[18] J. K. Liao, "Isoprenoids as mediators of the biological effects of statins," *Journal of Clinical Investigation*, vol. 110, no. 3, pp. 285–288, 2002.

[19] W. Dichtl, J. Dulak, M. Frick et al., "HMG-CoA reductase inhibitors regulate inflammatory transcription factors in human endothelial and vascular smooth muscle cells," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 23, no. 1, pp. 58–63, 2003.

[20] S. I. McFarlane, R. Muniyappa, R. Francisco, and J. R. Sowers, "Clinical review 145: pleiotropic effects of statins: lipid reduction and beyond," *Journal of Clinical Endocrinology and Metabolism*, vol. 87, no. 4, pp. 1451–1458, 2002.

[21] J. K. Liao and U. Laufs, "Pleiotropic effects of statins," *Annual Review of Pharmacology and Toxicology*, vol. 45, pp. 89–118, 2005.

[22] S. Sen-Banerjee, S. Mir, Z. Lin et al., "Kruppel-like factor 2 as a novel mediator of statin effects in endothelial cells," *Circulation*, vol. 112, no. 5, pp. 720–726, 2005.

[23] M. F. Kircher, J. Grimm, F. K. Swirski et al., "Noninvasive in vivo imaging of monocyte trafficking to atherosclerotic lesions," *Circulation*, vol. 117, no. 3, pp. 388–395, 2008.

[24] J. H. F. Rudd, F. Hyafil, and Z. A. Fayad, "Inflammation imaging in atherosclerosis," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 29, no. 7, pp. 1009–1016, 2009.

[25] R. M. Bell and D. M. Yellon, "Atorvastatin, administered at the onset of reperfusion, and independent of lipid lowering, protects the myocardium by up-regulating a pro-survival

pathway," *Journal of the American College of Cardiology*, vol. 41, no. 3, pp. 508–515, 2003.

[26] A. Prasad, G. W. Stone, D. R. Holmes, and B. Gersh, "Reperfusion injury, microvascular dysfunction, and cardioprotection: the "dark side" of reperfusion," *Circulation*, vol. 120, no. 21, pp. 2105–2112, 2009.

[27] A. Ludman, V. Venugopal, D. M. Yellon, and D. J. Hausenloy, "Statins and cardioprotection—more than just lipid lowering?" *Pharmacology and Therapeutics*, vol. 122, no. 1, pp. 30–43, 2009.

[28] L. H. Young, "AMP-activated protein kinase conducts the ischemic stress response orchestra," *Circulation*, vol. 117, no. 6, pp. 832–840, 2008.

[29] S. G. Ellis and S. Anwaruddin, "Recapturing the magic. Revisiting the pleiotropic effects of statins in percutaneous coronary revascularization," *Journal of the American College of Cardiology*, vol. 54, no. 6, pp. 566–568, 2009.

[30] D. J. Hausenloy and D. M. Yellon, "Cell membrane repair as a mechanism for ischemic preconditioning?" *Circulation*, vol. 121, no. 23, pp. 2547–2549, 2010.

[31] K. Mensah, M. M. Mocanu, and D. M. Yellon, "Failure to protect the myocardium against ischemia/reperfusion injury after chronic atorvastatin treatment is recaptured by acute atorvastatin treatment: a potential role for phosphatase and tensin homolog deleted on chromosome ten?" *Journal of the American College of Cardiology*, vol. 45, no. 8, pp. 1287–1291, 2005.

[32] S. M. Chang, N. Yazbek, and N. M. Lakkis, "Use of statins prior to percutaneous coronary intervention reduces myonecrosis and improves clinical outcome," *Catheterization and Cardiovascular Interventions*, vol. 62, no. 2, pp. 193–197, 2004.

[33] A. Nusca, R. Melfi, G. Patti, and G. Di Sciascio, "Statin loading for acute coronary syndromes," *Current Opinion in Cardiology*, vol. 25, no. 4, pp. 373–378, 2010.

[34] V. Pasceri, G. Patti, A. Nusca, C. Pristipino, G. Richichi, and G. Di Sciascio, "Randomized trial of atorvastatin for reduction of myocardial damage during coronary intervention: results from the ARMYDA (Atorvastatin for Reduction of MYocardial Damage during Angioplasty) study," *Circulation*, vol. 110, no. 6, pp. 674–678, 2004.

[35] G. Patti, M. Chello, V. Pasceri et al., "Protection from procedural Myocardial injury by atorvastatin is associated with lower levels of adhesion molecules after percutaneous coronary intervention. Results from the ARMYDA-CAMs (Atorvastatin for Reduction of Myocardial Damage during Angioplasty-Cell Adhesion Molecules)," *Journal of the American College of Cardiology*, vol. 48, no. 8, pp. 1560–1566, 2006.

[36] C. Briguori, A. Colombo, F. Airoldi et al., "Statin administration before percutaneous coronary intervention: impact on periprocedural myocardial infarction," *European Heart Journal*, vol. 25, no. 20, pp. 1822–1828, 2004.

[37] C. Briguori, G. Visconti, A. Focaccio et al., "Novel Aproaches for Preventing or Limiting Events (Naples) II trial. Impact of a single high loading dose of atorvastatin on periprocedural myocardial infarction," *Journal of the American College of Cardiology*, vol. 54, no. 23, pp. 2157–2163, 2009.

[38] G. Patti, V. Pasceri, G. Colonna et al., "Efficacy of atorvastatin reload in patients on chronic statin therapy undergoing percutaneous coronary intervention. Results of the ARMYDA-RECAPTURE randomized trial," *Journal of the American College of Cardiology*, vol. 49, no. 12, pp. 1272–1278, 2007.

[39] G. Di Sciascio, G. Patti, V. Pasceri, A. Gaspardone, G. Colonna, and A. Montinaro, "Efficacy of Atorvastatin Reload in Patients on Chronic Statin Therapy Undergoing Percutaneous Coronary Intervention. Results of the ARMYDA-RECAPTURE (Atorvastatin for Reduction of Myocardial Damage During Angioplasty) Randomized Trial," *Journal of the American College of Cardiology*, vol. 54, no. 6, pp. 558–565, 2009.

[40] G. Di Sciascio, "Personal communication".

[41] K. H. Yun, M. H. Jeong, S. K. Oh et al., "The beneficial effect of high loading dose of rosuvastatin before percutaneous coronary intervention in patients with acute coronary syndrome," *International Journal of Cardiology*, vol. 137, no. 3, pp. 246–251, 2009.

[42] J. S. Kim, J. Kim, D. Choi et al., "Efficacy of high-dose atorvastatin loading before primary percutaneous coronary intervention in ST-segment elevation myocardial infarction," *American College of Cardiology Interview*, vol. 3, no. 3, pp. 332–339, 2010.

[43] K. Thygesen, J. S. Alpert, and H. D. White, "On behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Redifinition of Myocardial Infarction. Universal definition of myocardial infarction," *European Heart Journal*, vol. 28, pp. 2535–2538, 2001.

[44] G. Heusch, P. Kleinbongard, D. Böse et al., "Coronary microembolization: from bedside to bench and back to bedside," *Circulation*, vol. 120, no. 18, pp. 1822–1836, 2009.

[45] A. Prasad, M. Singh, A. Lerman, R. J. Lennon, D. R. Holmes, and C. S. Rihal, "Isolated elevation in troponin T after percutaneous coronary intervention is associated with higher long-term mortality," *Journal of the American College of Cardiology*, vol. 48, no. 9, pp. 1765–1770, 2006.

[46] S. E. Nissen, E. M. Tuzcu, P. Schoenhagen et al., "Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis," *Journal of the American Medical Association*, vol. 291, no. 9, pp. 1071–1080, 2004.

[47] S. E. Nissen, E. M. Tuzcu, P. Schoenhagen et al., "Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease," *The New England Journal of Medicine*, vol. 352, no. 1, pp. 29–38, 2005.

[48] S. E. Nissen, S. J. Nicholls, I. Sipahi et al., "Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial," *Journal of the American Medical Association*, vol. 295, no. 13, pp. 1556–1565, 2006.

[49] J. Rodés-Cabau, J. C. Tardif, M. Cossette et al., "Acute effects of statin therapy on coronary atherosclerosis following acute coronary syndromes," *American Journal of Cardiology*, vol. 104, no. 6, pp. 750–757, 2009.

[50] Cholesterol Treatment Trialist (CTT) Collaborators, "Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomized trials of statins," *The Lancet*, vol. 366, pp. 1267–1278, 2005.

[51] P. S. Sever, B. Dahlöf, N. R. Poulter et al., "Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial," *The Lancet*, vol. 361, no. 9364, pp. 1149–1158, 2003.

[52] H. M. Colhoun, D. J. Betteridge, P. N. Durrington et al., "Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial," *The Lancet*, vol. 364, no. 9435, pp. 685–696, 2004.

[53] P. M. Ridker, E. Danielson, F. A.H. Fonseca et al., "Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein," *The New England Journal of Medicine*, vol. 359, no. 21, pp. 2195–2207, 2008.

[54] P. M. Ridker, E. Danielson, F. A. Fonseca et al., "Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial," *The Lancet*, vol. 373, no. 9670, pp. 1175–1182, 2009.

[55] J. C. LaRosa, S. M. Grundy, D. D. Waters et al., "Intensive lipid lowering with atorvastatin in patients with stable coronary disease," *The New England Journal of Medicine*, vol. 352, no. 14, pp. 1425–1435, 2005.

[56] J. C. La Rosa, S. M. Grundy, J. J. Kastelein, J. B. Kostis, and H. Greten, "Treating to New Targets (TNT) Steering Committee and Investigators. Safety and efficacy of atorvastatin induced very low density lipoprotein cholesterol levels in patients with coronary heart disease (a post hoc analysis of the Treating to New Targets (TNT) Study," *American Journal of Cardiology*, vol. 100, pp. 747–752, 2007.

[57] J. C. LaRosa, P. C. Deedwania, J. Shepherd et al., "Comparison of 80 mg versus 10 mg of atorvastatin on occurrence of cardiovascular events after the first event (from the TNT trial)," *American Journal of Cardiology*, vol. 105, no. 3, pp. 283–287, 2010.

[58] G. G. Schwartz, A. G. Olsson, M. D. Ezekowitz et al., "Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes the MIRACL study: a randomized controlled trial," *Journal of the American Medical Association*, vol. 285, no. 13, pp. 1711–1718, 2001.

[59] C. P. Cannon, E. Braunwald, C. H. McCabe et al., "Intensive versus moderate lipid lowering with statins after acute coronary syndrome," *The New England Journal of Medicine*, vol. 350, no. 15, pp. 1495–1504, 2004.

[60] P. M. Ridker, C. P. Cannon, D. Morrow et al., "C-reactive protein levels and outcomes after statin therapy," *The New England Journal of Medicine*, vol. 352, no. 1, pp. 20–28, 2005.

[61] K. K. Ray, D. A. Morrow, M. S. Sabatine et al., "Long-term prognostic value of neopterin: a novel marker of monocyte activation in patients with acute coronary syndrome," *Circulation*, vol. 115, no. 24, pp. 3071–3078, 2007.

[62] V. Fuster, Ed., *In the AHA Guidelines and Scientific Statements Handbook*, chapter 2, 2009.

[63] S. A. Murphy, C. P. Cannon, S. D. Wiviott, C. H. McCabe, and E. Braunwald, "Reduction in recurrent cardiovascular events wit intensive-lowering statin therapy compared with moderate-lipid lowering statin therapy after acute coronary syndromes from the PROVE-IT. TIMI 22 trial," *Journal of the American College of Cardiology*, vol. 54, no. 25, pp. 2358–2362, 2009.

[64] P. Amarenco, J. Bogousslavsky, A. Callahan III et al., "High-dose atorvastatin after stroke or transient ischemic attack," *The New England Journal of Medicine*, vol. 355, no. 6, pp. 549–559, 2006.

[65] F. Antonini-Canterin, L. M. Moura, R. Enache et al., "Effect of hydroxymethylglutaryl coenzyme-a reductase inhibitors on the long-term progression of rheumatic mitral valve disease," *Circulation*, vol. 121, no. 19, pp. 2130–2136, 2010.

[66] M. Vasa, S. Fichtlscherer, K. Adler et al., "Increase in circulating endothelial progenitor cells by statin therapy in patients with stable coronary artery disease," *Circulation*, vol. 103, no. 24, pp. 2885–2890, 2001.

[67] U. Landmesser, N. Engberding, F. H. Bahlmann et al., "Statin-induced improvement of endothelial progenitor cell mobilization, myocardial neovascularization, left ventricular function, and survival after experimental myocardial infarction requires endothelial nitric oxide synthase," *Circulation*, vol. 110, no. 14, pp. 1933–1939, 2004.

[68] S. Dimmeler, "Regulation of bone marrow-derived vascular progenitor cell mobilization and maintenance," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 30, no. 6, pp. 1088–1093, 2010.

[69] O. N. Akram, A. Bernier, F. Petrides, G. Wong, and G. Lambert, "Beyond LDL cholesterol, a new role for pcsk9," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 30, no. 7, pp. 1279–1281, 2010.

[70] E. Morales-Villegas, Ed., *Atlas de Riesgo Cardio Metabólico Total*, Atheros, Aguascalientes, Mexico, 1st edition, 2009.