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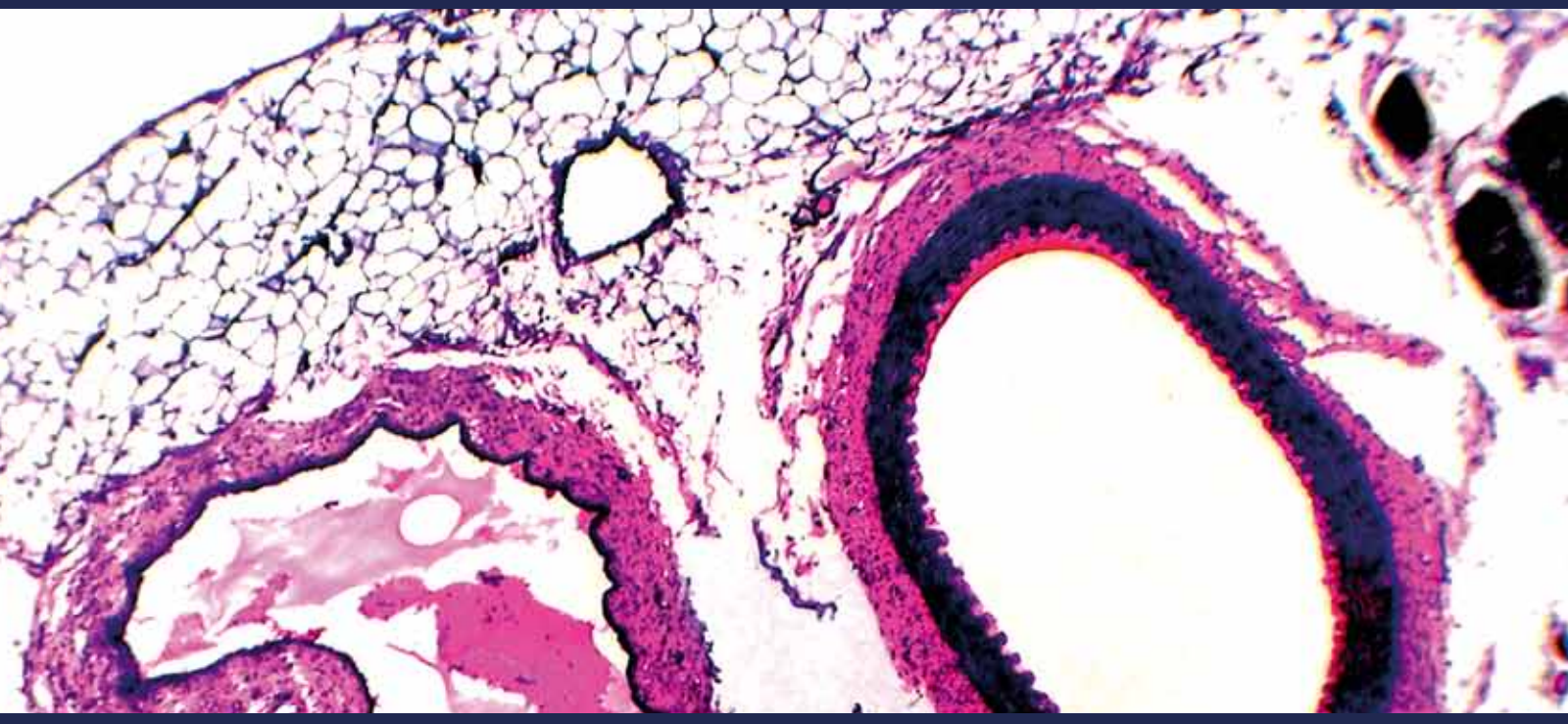
Hypertension: From Epidemiology to Therapeutics

Guest Editors: Manuel Velasco and Zafar Israili



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Editorial Board

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Editorial

Hypertension: From Epidemiology to Therapeutics

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P. Boli and R. Campbell discuss whether recommendations for the management (and control) of high blood pressure really result in improved cardiovascular (CV) outcomes. Adherence to the recommendations by the Canadian Hypertension Education Program did significantly improve all the aspects (awareness, treatment, and control) of hypertension, as well as mortality and hospitalization due to strokes, heart failure, and myocardial infarction. The authors suggest that application of similar recommendations for the management and control of hypertension in other regions of the world may be helpful. An interesting paper by C. Sierra reviewed that presence of cerebral white matter lesions (usually found in the aged population) were more severe and appeared early in patients with high blood pressure. There was an association between blood pressure parameters obtained by ambulatory blood pressure monitoring (ABPM) and presence of white matter lesions, suggesting that data obtained from ABPM may be helpful in identifying asymptomatic hypertensive patients with brain damage. R. Fagugli and C. Taglioni discuss that aldosteronism (hyperaldosteronism), which was thought to be rare (affecting 1% of the hypertensive population), occurs at a much higher incidence (5–20%) in patients with type 2 diabetics and resistant hypertension and is associated with a high incidence of cardiovascular (CV), cerebrovascular, and kidney complications. The variation in the estimates of prevalence may be due to methodology and definitions. M. Roy et al. determined that among African Americans with type 1 diabetes mellitus, without elevated blood pressure, 29% develop hypertension in the course of 6 years. The risk factors associated with the development of hypertension include age, duration of diabetes, family history of hypertension, higher baseline arterial pressure, overt proteinuria, presence of retinopathy or peripheral neuropathy, smoking, and psychological factors, such as perceived hostility. An interesting paper by M. Yamori et al. investigated the association of hypertension with periodontitis and/or tooth loss (apparently from periodontal disease) in a group of nonsmoking, nondrinking middle-aged African women. Their studies show that the severity of periodontal disease was significantly associated with increased systolic and diastolic blood pressure. In addition, low dietary intake of potassium and fiber was directly associated with higher blood pressure and periodontal inflammation. On the other hand, higher dietary intake of potassium, fruits, and vegetables decreased inflammation of the gums. The authors suggest that increased dietary intake of potassium, fruits, and vegetables may decrease the incidence of periodontitis. Q. Nguyen and coworkers analyzed cardiovascular risk factors in a large cross-sectional survey in Vietnam. The prevalence of the clustering of metabolic (such as in the metabolic syndrome) and behavioral risk factors was more prevalent in men than in women, and there was a 4-fold higher overall 10-year CV risk in men than in women. Targeting only a single risk factor would not decrease the overall risk. A pharmacological means of correcting endothelial dysfunction was proposed by M. Pokrovskiy et al., by the use of inhibitors of arginase (which catalyses the degradation of L-arginine and thereby reducing the production of nitric oxide), thus increasing the production of the vasodilating nitric oxide, thereby protecting the endothelium. In their studies in rats, R. Peroni and coworkers observed that phytoestrogens produced an estrogen receptor-dependent enhancement of anandamide-induced reduction of contractility (of mesenteric bed) caused by noradrenaline by modulation of calcitonin gene-related peptide. The in vivo suppression of adrenergic hyperactivity

(which precedes the onset of hypertension) by anandamide (such as by oral administration of genistein or daidzein) was observed in female but not in male rats or ovariectomized female rats.

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Research Article

Cardiovascular Disease Risk Factor Patterns and Their Implications for Intervention Strategies in Vietnam

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Background. Data on cardiovascular disease risk factors (CVDRFs) in Vietnam are limited. This study explores the prevalence of each CVDRF and how they cluster to evaluate CVDRF burdens and potential prevention strategies. *Methods*. A cross-sectional survey in 2009 (2,130 adults) was done to collect data on behavioural CVDRF, anthropometry and blood pressure, lipidaemia profiles, and oral glucose tolerance tests. Four metabolic CVDRFs (hypertension, dyslipidaemia, diabetes, and obesity) and five behavioural CVDRFs (smoking, excessive alcohol intake, unhealthy diet, physical inactivity, and stress) were analysed to identify their prevalence, cluster patterns, and social predictors. Framingham scores were applied to estimate the global 10-year CVD risks and potential benefits of CVD prevention strategies. *Results*. The age-standardised prevalence of having at least 2/4 metabolic, 2/5 behavioural, or 4/9 major CVDRF was 28%, 27%, 13% in women and 32%, 62%, 34% in men. Within-individual clustering of metabolic factors was more common among older women and in urban areas. High overall CVD risk (≥20% over 10 years) identified 20% of men and 5% of women—especially at higher ages—who had coexisting CVDRF. *Conclusion*. Multiple CVDRFs were common in Vietnamese adults with different clustering patterns across sex/age groups. Tackling any single risk factor would not be efficient.

1. Introduction

Myocardial infarction (MI) and stroke are the leading causes of cardiovascular (CVD) morbidity and mortality worldwide, especially in low- and middle-income countries (LMICs) where 80% of the total CVD burden occurs. CVD death rates, already higher in poorer populations, are also rising, as the death rates in many wealthy countries are waning [1–3]. In Vietnam, stroke is the leading cause of death followed by heart disease [4], although mortality from coronary heart disease has recently risen [5].

Findings from INTERHEART [6] and INTERSTROKE [7] studies suggest that a few traditional modifiable risk factors could explain over 90% of the population attributable risk of both MI and stroke. These include hypertension, abnormal lipids, tobacco use, obesity, diabetes mellitus, diets with low intakes of fruits and vegetables, physical inactivity, excessive alcohol intake, and psychosocial factors. Modification of currently known risk factors has the potential to prevent most premature cases of both MI and stroke worldwide, providing that there are differences in the relative importance of each risk factor for stroke or MI between men and women and across different geographic regions or ethnic groups [6–10], due to variations in risk factor profile, CVD burden, and socioeconomic cultural circumstances. In offering an evidence-based context for policy planners and health education programmes in a low-resource setting like Vietnam, it is important to quantify the proportion of the population at high overall risk of CVD in order to match this with availability of resources. In reality,

a substantial proportion of the population carry individual clusters of several risk factors [11], which demonstrates the need for comprehensive population-wide strategies and approaches. When treatment decisions are to be made concerning individual clinical interventions, it is clear that a smaller proportion of people are at highest risk due to individual clustering of risk factors, including age and sex, and need to be identified for rational resource and health system planning.

This study aims to describe the prevalence of each important CVD risk factor as well as providing a profile of the individual clustering of major CVD risk factors in a representative sample of the adult population of Vietnam, highlighting the differences between men and women. The study also aims to estimate the prevalence of people having high overall 10-year CVD risks using the Framingham general cardiovascular risk score [12]. These findings will be important for optimizing the selection of risk-factor targets for population-based or individual-based programmes to prevent and reduce the burden of cardiovascular diseases in the studied communities as well as in extrapolations to the population of Vietnam.

2. Materials and Methods

2.1. Study Population and Study Design. A cross-sectional survey was conducted in March and August 2009, using a multistage sampling strategy to identify the prevalence of major cardiovascular risk factors including lipidaemia profile in Thai Binh (a rural province) and Hanoi (a urban province) of Vietnam. This survey followed the framework of the national survey on hypertension, in which Hanoi represented city areas and Thai Binh represented lowland areas, but the blood tests were only taken from a 1-in-5 sample of participants in the city area for fasting glucosaemia and lipidaemia profile due to limited financial resources [13]. Similarly to the previous national survey, a representative sample of the adult population (≥25 years old) from both Hanoi and Thai Binh provinces was randomly selected from 24 primary sampling units (communes: 110 person sample per commune), following 3 communes per district and 4 districts per province [13].

Data were collected at local health stations in the selected communes by trained and qualified surveyors using a questionnaire which included personal medical history of any relevant chronic diseases, demographic background (age, sex, residential area, occupation, and education level) and self-reported behavioural risk factors (smoking history, alcohol consumption, dietary salt habit, daily fruit and vegetable consumption, level of physical activities, level of stress). In addition, all participants were requested to fast overnight in order to have an oral glucose tolerance (OGT) test and a blood sample for lipid profiles (including total cholesterol, triglyceride, low-density lipoprotein cholesterol LDL-C and high-density lipoprotein HDL-C). Blood samples were collected, stored, and analysed by specialists from the Department of Biochemistry, Bach Mai Hospital Hanoi, Vietnam. People with no history of diabetes were asked to perform OGT test loaded with 75 g anhydrous glucose. Portable glucometer devices from Terumo with corresponding strips were used to measure glucosaemia pretest and 2 h after OGT test.

Among 2,640 invited subjects, 2,306 participated in the survey, giving an overall response rate of 87.3% (99.8% in Thai Binh province and 75.0% in Hanoi province). A further 176 (7.6%) participants were excluded from analysis due to pregnancy status or missing important information or blood test results.

2.2. Social and Cardiovascular Risk Factors: Assessments and Classification. Occupational status was classified into three groups: government staff, manual workers (farmers, building workers), and other occupations (housewives, handicraft makers, jobless, disabled). Educational level, which was determined by years of schooling and level at graduation, was classified into 2 groups: incomplete secondary schooling (≤9 years of education) and higher (>9 years of education including graduation from high school or higher). Residential area, which was divided into urban and rural, was identified on an administrative basis for each commune within each province.

People who smoked tobacco products such as cigarettes, cigars, or pipes over the previous month were classified as current smokers. People who took more than 2 standard units of drink per day (women) or more than 3 per day (men) were defined as having an excessive alcohol intake. People who ate less than five servings of fruit and/or vegetables on average per day were defined as having a diet with low fruit and vegetable consumption [14]. People who preferred daily foods that contained more salt than the similar foods ordered by other adult members in the family or people around them were classified as having salty diets. Energy requirement in metabolic equivalents (METs) for each individual was estimated based on details of duration and type of all self-reported physical activities in a typical week. People with total physical activity less than 3000 METs minutes per week were classified as physically inactive [15]. Similarly to the INTERHEART study [16], psychosocial stress was assessed and semiquantitated by several simple questions to evaluate whether the participants had any stress at work or at home, any financial stress, any major life events (such as marital separation or divorce, loss of crop or job, major intrafamily conflict, death, illness of a close family member/spouse, etc.) or any other major stress in the past year at different levels (none, mild, moderate, and severe). People who had more than 2 moderate stressors were classified as having psychosocial stress.

Blood pressure (BP) was measured at least twice, at least two minutes apart in a resting and sitting position using an automatic digital sphygmomanometer (OMRON Healthcare Inc., Bannockburn, Illinois, USA), with an appropriate sized cuff, following a similar standardized protocol as undertaken in the national survey. A third measurement was performed if the difference between the first two measurements was more than 10 mmHg. Hypertension was defined as an average systolic BP (SBP) ≥ 140 mmHg, and/or average diastolic

BP (DBP) ≥ 90 mmHg, and/or self-reported current treatment with antihypertensive medications [17–20].

Body weight, height, waist and hip circumference were measured by trained and qualified surveyors twice strictly following the standardised protocol previously described elsewhere [13]. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Overweight was defined as BMI ≥ 23 and obesity was defined as BMI ≥ 25 or having central obesity (BMI ≥ 23 with waist circumference either ≥90 cm in men or ≥80 cm in women), both mentioned criteria having been specified for South-Asian populations by WHO Regional Office for Western Pacific (WPRO) [21].

Dyslipidaemia was defined as self-reported current treatment with cholesterol-lowering medications and/or having one or more of the following, based on blood test results: total cholesterol ≥5.17 mmol/L; HDL-C <1.03 mmol/L; LDL-C ≥3.36 mmol/L; triglyceride ≥1.7 mmol/L, as recommended by National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) guidelines [22].

Diabetes was defined as fasting glucose ≥7.0 mmol/L and/or 2 h after OGTT glucose ≥11.1 mmol/L and/or self-reported as currently taking any diabetes medication, as recommended by American Diabetes Association (ADA) guidelines [23–26].

2.3. Data Analysis. The prevalence of each risk factor and their clustering within individuals were calculated for men and women, stratified by age group to identify the differences in CVD risk factor patterns between women and men. Details of age distribution by sex in urban and rural areas of selected districts in Hanoi and Thai Binh provinces from Vietnam Population and Housing Census in 2009 [27] were used to weight and age-standardise the above prevalences for the studied population as well as for extrapolation to the whole population.

These CVD risk factors were divided into two groups: metabolic factors (including hypertension, abnormal lipids, obesity, diabetes mellitus) and behavioural factors (including tobacco use, excessive alcohol intake, unhealthy diet, physical inactivity, and psychosocial factors). Unhealthy diet was determined from both self-reported diet-related risk factors (either high salt or low fruit and vegetable consumption). People who had ≥2/4 metabolic factors, ≥2/5 behavioural factors, or ≥4/9 of all mentioned risk factors were considered to have individual clusters of respective risk factors.

Framingham general cardiovascular risk scores [12], which apply to individuals from 30 to 74 years old without baseline CVD, were used to estimate the overall 10-year risk of developing coronary heart disease (myocardial infarction, coronary death) and other important potential adverse cardiac events (stroke, heart failure) in the community. The score incorporated the following variables: age, sex, tobacco use, treated and untreated systolic blood pressure, diabetes, and lipid profile (total cholesterol, HDL-cholesterol) or BMI (replacing lipids in a simpler model). People who had overall 10-year cardiovascular risk ≥20% were classified as having a high overall CVD risk.

Both descriptive and analytical statistical analyses were carried out using STATA 11 software (Stata Corporation, Texas, USA). Means with standard errors and proportions with 95% confidence intervals (CIs) for variables of interest were calculated. Multivariable logistic regression analyses were performed to examine the association between social characteristics and clustering of risk factors and their associated odds ratios (ORs) and 95% CIs were presented, separately for women and men. A P value < 0.05 (two tailed) was considered to represent statistical significance.

2.4. Ethical Issues. This study protocol was approved by both Scientific Ethical Committees in Biomedical Research at Bach Mai Hospital, Hanoi, Vietnam and at the International Medical Centre of Japan (IMCJ) Hospital, Tokyo, Japan. All human subjects in the study were asked for their consent before collection of data and venous blood, and all had complete rights to withdraw from the study at any time without any threat or disadvantage. Any participants with high blood pressure or other disorders were referred to appropriate facilities for further investigation and treatment.

3. Results

After excluding 176 records with missing data, a total of 2,130 subjects were analysed, of which 1,345 (63.2%) were women and 830 (36.5%) were men. The average age for women was 52.0 years and for men 53.7 years; there was no difference in age group structure. The sex ratio in our study population was quite similar to the results from the previous national survey on hypertension [13], in which the study sample was also randomly selected from to the entire list of current inhabitants at the study regions in multistage sampling. Both our study and the previous national survey probably reflected the contemporary sex ratio of the local remaining adult population, which obviously excluded a substantial number of people (mostly male) who temporarily out-migrated to earn money for their families. Table 1 shows the characteristics of the studied population, including social factors, biological and self-reported behavioural factors. Compared to biological characteristics among women, men had significantly higher weight, waist circumference, waist hip ratio, blood pressure (both systolic and diastolic), LDL-cholesterol, triglyceride, and fasting glucosaemia but lower HDL-cholesterol. There was no difference in BMI and total cholesterol between the sexes. In terms of behavioural risk factors, significantly higher proportions of men were currently smoking ($P < 0.01$), having excessive alcohol intake ($P < 0.01$), unhealthy diet with low consumption of fruit/vegetable or high salt diets ($P < 0.05$), but there were no differences in the proportions of physical inactivity or experience of stress in men compared to women (Table 1). The prevalence of unhealthy diets was lower in women (53%) than in men (60%).

Table 2 shows the prevalence of each CVD risk factor and prevalence for having clusters of CVD risk factors, stratified

Table 1: General characteristics of the study population.

Characteristics	Women ($n = 1,345$)	Men ($n = 785$)
Biological factors	Mean ± SD	Mean ± SD
Age (year)	52.0 ± 14.3	53.7 ± 14.7
Weight (kg)	49.6 ± 8.1	56.2 ± 9.4
Body mass index BMI (kg/m^2)	21.5 ± 3.1	21.5 ± 3.0
Waist circumference (cm)	73.5 ± 7.5	75.9 ± 7.9
Waist-hip ratio	0.85 ± 0.06	0.88 ± 0.06
Systolic blood pressure (mmHg)	129.1 ± 23.0	135.0 ± 22.0
Diastolic blood pressure (mmHg)	77.3 ± 12.0	80.4 ± 12.4
Total cholesterol (mmol/L)	4.69 ± 0.99	4.65 ± 1.06
HDL cholesterol (mmol/L)	1.32 ± 0.33	1.26 ± 0.34
LDL cholesterol (mmol/L)	2.71 ± 0.73	2.59 ± 0.75
Triglyceride (mmol/L)	1.80 ± 1.29	2.19 ± 1.82
Fasting glucosaemia (mmol/L)	4.7 ± 1.2	5.0 ± 1.3
OGTT-2 h glucosaemia (mmol/L)	6.8 ± 2.2	6.8 ± 3.0
Self-reported behavioural factors	%	%
Current daily smoking	4.3	54.1
Excessive alcohol intake	1.1	24.1
Low fruit and vegetable diet	38.1	44.3
High salt diet	27.1	32.2
Physical inactivity	11.5	13.7
Having stress	25.3	22.2
Social factors	%	%
Residence		
In rural area	51.9	45.7
In urban area	48.1	54.3
Education level		
Secondary school and below	69.3	67.5
High school and above	30.7	32.5
Occupation		
Government staff	18.7	24.0
Manual workers	60.5	64.7
Other	20.8	11.3

by age group and sex, after weighting with the national age distribution in 2009 [27] in order to reflect the current profile of CVD risk factors in the studied population of Vietnam. Overall, the prevalence of all CVD risk factors, except for physical inactivity and experiencing stress, was considerably higher in men than in women. Figures 1(a) and 1(b) show the different trends of clustered CVD risk factors between men and women: the average number of CVD metabolic risk factors in women tended to increase more steeply with age and exceed the trend in men over 55 years of age, while the average number of CVD behavioural risk factors in men tended to decrease with age.

Both versions of Framingham general CVD risk score, one using lipid profiles and the other using BMI, were applied to calculate the overall risk of cardiovascular events within 10 years. Within the studied population, the risks estimated using BMI were higher, around 10% in women and 20% in men, than the estimates using lipid profiles. The prevalence for having an overall risk greater than 15% and 20%, respectively, is shown in Table 3. The prevalence of having high overall CVD risk sharply increased with age, exceeding 10% after the age of 45 years in men and after 55 years in women.

Multivariable logistic regression models were constructed to analyse the associations between having clusters of CVD risk factor and age, residence, occupation, and educational level (Table 4). The models showed that having clusters of metabolic risk factors was less common at younger ages, among people living in rural areas or doing manual work for both sexes, while having cluster of behavioural risks was more common in women with higher educational levels and in men with manual jobs. This could be explained by the higher proportion of excessive alcohol intake and physical inactivity in women having higher education or

Table 2: Prevalence of cardiovascular diseases risk factors in a studied population of Vietnamese adults stratified by sex and age group.

Major cardiovascular disease (CVD) risk factors	Prevalence in women by age group (%)						Prevalence in men by age group (%)						Prevalence by sex (%)	
	25–34	35–44	45–54	55–64	65–74	≥75	25–34	35–44	45–54	55–64	65–74	≥75	Women	Men
Metabolic CVD risk factors														
Hypertension	4.4	7.2	25.4	50.4	63.1	63.5	12.4	22.2	31.4	43.9	61.7	66.2	25.0[a]	31.2
Diabetes	0.0	4.5	5.4	13.2	12.5	13.7	3.2	4.8	9.8	9.6	12.4	21.4	6.2[a]	8.0
Obesity	8.0	11.1	18.6	29.3	27.6	19.1	19.8	11.6	11.6	18.2	16.5	10.8	17.4[b]	14.5
Dyslipidaemia	33.4	38.0	56.0	74.7	72.0	66.5	54.8	65.5	63.5	66.9	61.8	63.9	52.4[b]	62.8
Behavioural risk factors														
Current smoking	2.5	6.0	2.2	4.5	6.4	3.5	56.1	65.4	61.7	58.7	44.5	25.3	3.8[a]	58.8
Excessive alcohol intake	1.2	0.6	0.6	1.6	1.7	0.0	27.9	31.6	30.8	22.8	17.8	8.1	0.9[a]	27.6
Unhealthy diet	52.8	52.2	52.7	49.3	47.8	62.2	70.3	53.2	57.2	62.0	52.7	66.3	52.0[a]	59.4
Physical inactivity	20.4	16.5	19.9	18.2	24.4	27.1	26.1	19.1	19.2	15.6	20.7	32.4	19.3	20.3
Having stress	24.5	26.4	31.5	24.1	24.2	15.2	25.8	28.3	22.0	24.6	11.8	16.0	27.1	23.5
Individual clustering of CVD risk factors														
≥2/4 metabolic risk factors	9.8	14.4	26.1	54.5	60.7	51.1	24.9	24.9	30.6	41.7	48.8	57.1	28.1	32.1
≥2/5 behavioural risk factors	26.7	22.5	31.0	24.7	24.9	32.4	64.4	64.5	63.1	60.4	49.9	51.9	27.0[a]	62.0
≥4/9 major CVD risk factors	4.8	4.3	15.3	21.6	28.3	23.2	30.4	33.5	35.7	35.1	36.2	42.5	13.0[a]	34.4

[a] $P < 0.01$; [b] $P < 0.05$ when compared between men and women.

Table 3: Average estimated overall CVD 10-year risk using Framingham general risk score (either using lipid profile or BMI) and prevalence of high overall risk in a studied population of Vietnamese adults, stratified by sex and age group.

	Average overall risk (%)		Difference (%) between (1) and (2)	Prevalence of overall (%)		
	Using lipid profile (1)	Using BMI (2)		Risk ≥10%	Risk ≥20%	Risk ≥30%
Women						
30–34	1.0	1.1	7.3	0.0	0.0	0.0
35–44	1.9	2.0	11.9	0.0	0.0	0.0
45–54	5.1	5.3	10.9	5.9	1.3	0.1
55–64	12.0	12.3	7.0	41.2	13.6	4.2
65–74	17.1	18.0	11.0	68.4	27.5	9.3
Men						
30–34	3.3	3.6	23.2	0.0	0.0	0.0
35–44	7.1	7.3	19.5	14.3	0.8	0.0
45–54	13.7	15.5	21.1	63.7	12.9	1.6
55–64	22.7	25.0	19.7	86.9	46.9	20.4
65–74	37.0	39.6	12.9	98.4	81.4	57.2
Total						
Women	5.8	6.1	10.1	13.9	4.6	1.4
Male	14.6	16.0	20.0	52.5	20.4	9.0
Both sexes	8.8	9.4	13.4	27.0	10.0	3.9

higher proportions of smoking, self-reported unhealthy diet and physical activity in men having manual jobs, while there was no difference among the remaining behavioural factors.

4. Discussion

Findings from our study showed that major modifiable CVD risk factors were common and often individually clustered in the studied adult population of Vietnam, increasing with age and having different patterns between sexes. We acknowledge that the cross-sectional design might introduce some misclassification due to self-reported information and the data might not truly reflect the time and context-bound aspects of CVD risk factor patterns. In addition, some factors such as experiencing stress were challenging to measure and there was no clear evidence on how to address stress in

Table 4: Adjusted odds ratios (OR) with 95% confidence interval (CI) for having individually clustered CVD risk factors in a studied population of Vietnamese adults.

Social factors	Having cluster (≥2/4) of metabolic CVD risk factor		Having cluster (≥2/5) of behavioural CVD risk factor		Having cluster (≥4/9) of all major CVD risk factor	
	Women OR (95% CI)	Men OR (95% CI)	Women OR (95% CI)	Men OR (95% CI)	Women OR (95% CI)	Men OR (95% CI)
Age group						
25–34	1	1	1	1	1	1
35–44	1.9 (0.9–3.8)	1.3 (0.7–2.6)	1.0 (0.6–1.5)	0.8 (0.4–1.4)	1.2 (0.4–3.7)	1.2 (0.7–2.2)
45–54	3.4 (1.8–6.6)[a]	1.9 (1.0–3.6)[b]	1.5 (1.0–2.3)	0.7 (0.4–1.2)	4.5 (1.8–11.7)[a]	1.2 (0.7–2.0)
55 – 64	12.8 (6.7–24.5)[a]	3.0 (1.6–5.6)[a]	1.0 (0.6–1.6)	0.7 (0.4–1.1)	6.8 (2.6–17.5)[a]	1.2 (0.7–2.1)
65 – 74	16.5 (8.3–32.9)[a]	3.2 (1.7–6.2)[a]	1.0 (0.6–1.6)	0.5 (0.3–0.8)[b]	9.8 (3.7–26.9)[a]	1.3 (0.7–2.2)
75 ++	14.0 (6.8–29.1)[a]	4.4 (2.2–9.2)[a]	1.3 (0.8–2.4)	0.5 (0.2–0.9)[b]	9.8 (3.5–27.0)[a]	1.4 (0.7–2.7)
Residence area						
Rural	1	1	1	1	1	1
Urban	2.6 (1.9–3.5)[a]	1.9 (1.4–2.7)[a]	0.8 (0.6–1.1)	0.9 (0.7–1.3)	2.9 (1.9–4.3)[a]	1.8 (1.3–2.5)[a]
Educational status						
High school and higher	1	1	1	1	1	1
Less than high school	0.9 (0.7–1.2)	0.9 (0.6–1.3)	0.7 (0.6–1.0)[b]	1.0 (0.7–1.4)	0.8 (0.6–1.1)	0.9 (0.6–1.3)
Occupational status						
Manual workers	1	1	1	1	1	1
Government staff	1.0 (0.7–1.5)	2.0 (1.3–2.9)[a]	0.8 (0.5–1.1)	0.7 (0.5–1.0)[b]	1.0 (0.6–1.5)	0.9 (0.6–1.4)
Others	1.4 (1.0–2.0)[b]	1.3 (0.8–2.1)	0.8 (0.6–1.2)	0.9 (0.5–1.4)	1.1 (0.7–1.6)	0.9 (0.6–1.5)

[a] $P < 0.01$; [b] $P < 0.05$.

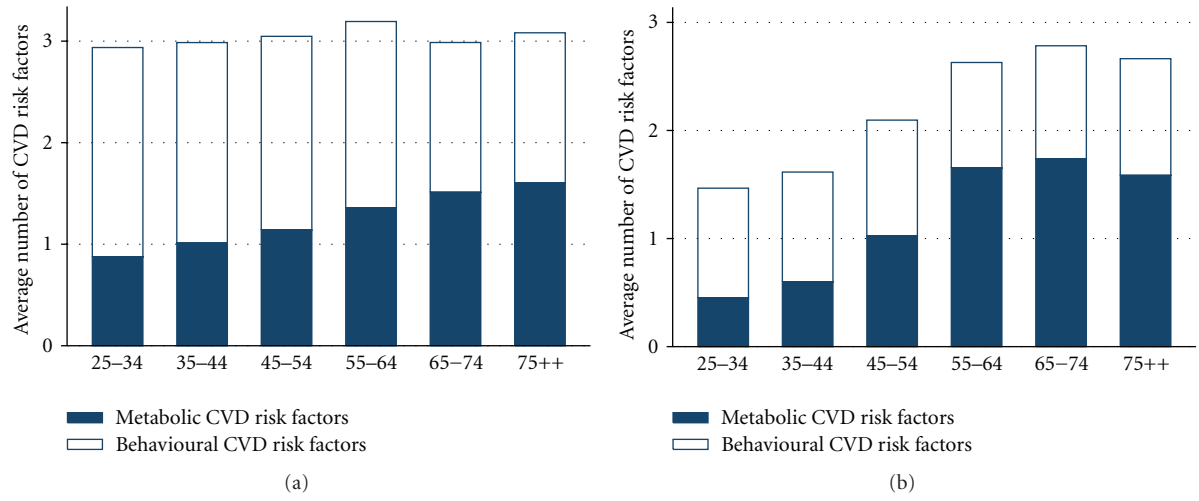

Figure 1: Average number of cardiovascular disease risk factors among men (a) and women (b), stratified by age group.

primary prevention [28]. Using the same frameworks as the previous national survey and implementing in two similar provinces (Hanoi and Thai Binh) [13], both glucosaemia and lipidaemia disorders were extensively investigated in this study in order to fill gaps in our understanding of major metabolic CVD risk factors in the Vietnamese population, although the data were only available from two provinces rather than the eight provinces in the national surveys, due to limited financial resources. Bearing in mind these limitations, the study tried to obtain a snapshot across a panorama of nine changeable risk factors, which accounted for over 90% risk of cardiovascular events [6, 7], then

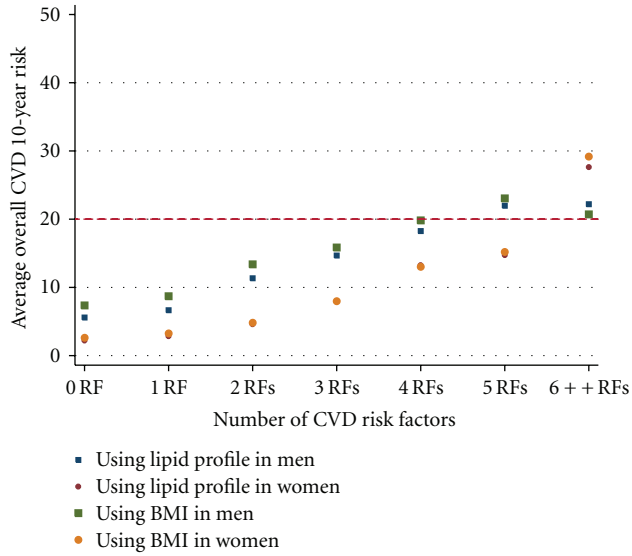

Figure 2: Trends of average overall cardiovascular disease risk by the number of risk factors.

extrapolating and proceeding to image the contemporary population burden of CVD risk factors both as single factors and within-individual clusters.

Hypertension, smoking, and excessive alcohol intake are considered as the most prominent risk factors for chronic and cardiovascular diseases [13, 29]. Estimates from our study that 26.4% of adults (≥25 years old) suffered from hypertension would extrapolate to 12.5 million people nationally, while only 26.7% (equivalent to 3.3 million) of these hypertensives were treated. However our results showed that lipid abnormalities (60% in the sample, extrapolating to 28.5 million people) and unhealthy diet (54.6%, 25.9 million) were the most common in both sexes, while smoking and excessive alcohol intake were prominent only in men. Future intervention programmes to cover newly emerging CVD risk factors such as unhealthy diets or dyslipidaemia measured by changes in cholesterol levels may be important in countries such as Vietnam where changes in food consumption patterns are occurring at a rapid pace.

Although our data from one cross-sectional survey could not differentiate the sequence in which metabolic risk factors developed, the increasing trend with age for each risk factor was consistent with suggestions that high adiposity and cholesterol often preceded the development of hypertension and diabetes from young adulthood to middle age in 20-year followup of CARDIA study [30, 31], and consistent with causal web of lifestyle risk factors for chronic disease prevention [32].

Quite a few studies showed the substantial proportion of CVD risk factors clustered among individuals in the population although the variations could be influenced by various differences in geographical, socioeconomic characteristics, age structure, time of study (seasonal variations), cut-off points for high risk classification, exclusion or inclusion criteria for CVD risk factors [10, 33–35]. Projected from our study, 20.4% adults aged 25 years and above in the population had clusters (≥4/9) of all major CVD risk factors. CVD incidence and mortality increase as quality of life decreases progressively with the number of CVD risk factors [36–39]. In our study, both systolic and diastolic BP increased with the number of risk factors in both sexes. The overall CVD 10-year risk also increased with the number of CVD risk factors in both sexes (Figure 2). In reality, blood pressure control worsened as the number of CVD risk factors increased [40] even with multiple drug therapies [41–43]; therefore, decisions about hypertension management should always consider the presence of other CVD risk factors rather than BP level alone [44].

CVD risk was influenced in a cumulative fashion by socioeconomic, behavioural, and biological factors acting throughout the life course, in which people with lower social economic status would be more susceptible and likely to have CVD risk factors, leading to cardiovascular events later in life [45–50]. Influences on metabolic disorders from lifestyle and culture habits are even stronger than those from genetic factors [51]. Our results suggested the importance of urban living conditions where people had higher prevalence of metabolic disorders after adjusting for age and other social factors, in accordance with results from other studies [8, 33, 52].

A number of multivariate risk models [12, 22, 53–57] have been developed to integrate individual factors in apparently healthy, asymptomatic individuals for estimating the risk of specific cardiovascular events such as coronary heart disease (fatal or nonfatal) and stroke over a certain period of time. Theoretically, the estimated risk of important cardiovascular events would be very useful both for patient education (e.g., motivating patients to adhere to risk-reduction therapies) and for clinical practice (identification of high-risk patients who deserved immediate care and modification of the intensity of management strategies). However, the complexity of the equation, time and context-bound results, confused assessment of outcome or risk factors, lack of some variables in low-resource settings, regular need for validation [58, 59], regulatory constraints, and the nature of the physician-patient relationship [60] all are hidden barriers to the routine use of CVD risk scores in daily practice, especially in primary care where blood tests were not available in low-resource settings. In addition, the overall risk stratification approach is likely to counter the established clinical practice in most LMICs that tend to focus on risk-factor thresholds, even though risk-based care is more effective and cost-effective [61].

In this study, the Framingham general cardiovascular 10-year risk scores [12] were applied to estimate potential adverse cardiovascular events individually and then totally in the studied population, including both stroke and coronary heart disease outcomes, bearing in mind that these scores could be overestimates or underestimates of the event risks in the population of Vietnam, where there has been no validation or calibration studies so far. We acknowledge that the equation only covered a few CVD risk factors, and their impacts on predicted outcomes were assumed to be linear for all variables and similar to the original

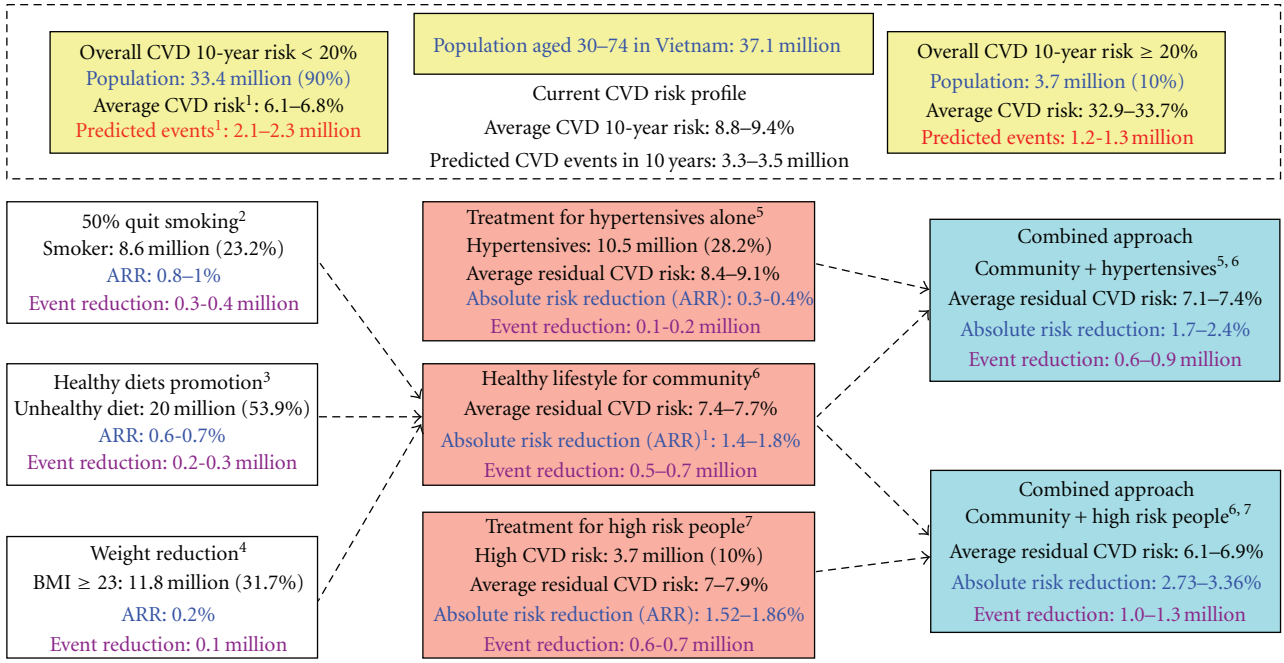

Figure 3: Estimation of cardiovascular burden and potential benefits of intervention strategies for the adult population of Vietnam, extrapolated from the average of individual overall CVD 10-year risks in a studied population. [1] Overall cardiovascular (CVD) risk, residual risk, absolute risk reduction (ARR), and predicted CVD events or predicted event reduction were estimated by both versions of Framingham general risk score, one used lipid profile and the other used BMI, and weighted by national age structure of the Vietnamese population in 2009. [2] In assumption that the prevalence of current smoking will reduce by 50%. [3] In assumption that the effect of healthy diet (especially salt reduction) will reduce 5 mmHg of systolic blood pressure (SBP). [4] In assumption that the obesity (BMI ≥ 23) will reduce 10% of weight, the risk was only estimated by BMI version of Framingham general risk score. [5]Approach for hypertensive alone included drug therapy to control BP (targeted SPB ≤ 140 for any hypertensives and ≤130 for diabetes). [6]Approach for community included healthy lifestyle promotion campaigns: quitting smoking (in assumption of 50% reduction of current prevalence), healthy diet (salt reducuon, low-fat and high-fiber diet, in assumption of 5 mmHg reduction of SBP), and encouraging physical activity and 10% weight reduction for obesity (BMI ≥ 23). [7] Approach for high-risk people (overall CVD 10-year risk ≥20%) included quitting smoking (100%), drug therapy to control BP (targeted SBP ≤ 140 for any hypertensives and ≤130 for diabetes), statin for dyslipidaemia (in assumption of 20% reduction of total cholesterol, 10% increase HLD-C), and 10% weight reduction for obesity (BMI ≥ 23).

Framingham population, which might not be true in the context of transition and development in contemporary Vietnam. Bearing in mind these limitations, an estimate of 10% in the studied population (extrapolated to 3.7 million people in the Vietnamese population) aged from 30 to 74 (4.6% in women and 20.4% in men) had an overall CVD 10-year risk ≥20%; the more risk factors, the higher the overall CVD risk [33]. The results also showed the homogeneity between two versions of the Framingham score using either BMI or lipid profiles (Table 3) and suggested that the simplified score version using BMI has potential advantage for wider application in low-resource settings, obviating the need for blood tests for lipid profiles in prioritising available strategies or approaches to intervention against CVD risk factors in primary care. Absolute risk charts using similar predictors (age, sex, smoking status, SBP, BMI, and/or diabetes) were a feasible and replaceable solution [61] for individuals in daily practice but were not sensitive enough to capture small changes in overall risk resulting from interventions and for summarising the benefits for heterogeneous populations with diverse CVD risk patterns. However, further cohort studies should be used to calibrate these equations in order to improve the local predictability of future cardiac events.

Based on individual calculated overall risk profiles, we estimated the average overall risk at the population level and predicted potential adverse cardiovascular events over 10 years. Our extrapolations revealed that the average overall risk for any cardiovascular event over 10 years for whole population aged from 30 to 74 years was 8.8–9.4%, in other words, 3.3–3.5 million CVD events could happen over 10 years (Figure 3). It has been estimated that just three cost-effective interventions, tobacco control, salt reduction, and a multidrug clinical service to treat individuals at high overall risk of cardiovascular disease would avert deaths in Vietnam [61, 62]. Recently, other interventions, though less cost-effective and feasible, have been implemented to tackle unhealthy diets, physical inactivity, obesity [63], focusing more on BMI-mediated distal risk factors [32] as well as policy-level solutions to create favourable environments for implementing effective strategies in primary care [64]. Based on some assumptions about the effectiveness of healthy

lifestyle interventions [65–69] or drug therapy to manage blood pressure [19] or dyslipidaemia [22], we tried to calculate the absolute risk reduction (ARR) of average overall CVD risk in the population and predict the reduction of potential adverse cardiovascular events, which could arise as benefits from various scenarios of risk factor intervention (Figure 3).

Previous studies showed that hypertension is a major public health problem in Vietnam [13, 29], requiring a lot of effort to detect and deliver appropriate management, constituting a high priority in the existing system of primary care. However, our extrapolated estimation suggested that treatment of a CVD risk factor alone (such as hypertension) without taking into consideration other modifiable CVD risk factors (such as smoking, unhealthy diet) would not be an efficient approach for achieving a high general health impact. A population strategy to reduce tobacco consumption in men and halt the rise in women should be the first priority. The high level of unhealthy diet and potential benefit from interventions suggests a population-wide strategy though the mass media aimed at reducing salt content in food is the next strategy. The high-risk individual approach would benefit the entire population more than only approaching hypertensives. If there were not enough resources to assess overall CVD risk on a wide scale, especially where expensive blood tests are required, simplified equations using age, sex, tobacco use, blood pressure levels, and BMI could be used to estimate the overall risk [61]. In addition, where resources allow, a combined community approach (mostly by healthy lifestyle promotion) and individual approaches using simpler and more feasible measurements to identify people at high risk could be employed.

5. Conclusions

In conclusion, nine major CVD risk factors, often clustered within individuals, were common in the adult population of Vietnam with differences noted between sex and age groups, testifying to the need for inclusion of age and sex in any risk prediction models. Tackling any single risk factor alone without considering other modifiable CVD risk factors is not an efficient or sustainable approach. Combination of population and individual approaches are required to reduce the burden of CVD risk factors and maximise the protective effects for the whole community. Modification and calibration of an existing score for the Vietnamese population, for identifying individuals at high risk of CVD, is a priority.

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Research Article

Phytoestrogens Enhance the Vascular Actions of the Endocannabinoid Anandamide in Mesenteric Beds of Female Rats

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In rat isolated mesenteric beds that were contracted with NA as an in vitro model of the vascular adrenergic hyperactivity that usually precedes the onset of primary hypertension, the oral administration (3 daily doses) of either 10 mg/kg genistein or 20 mg/kg daidzein potentiated the anandamide-induced reduction of contractility to NA in female but not in male rats. Oral treatment with phytoestrogens also restored the vascular effects of anandamide as well as the mesenteric content of calcitonin gene-related peptide (CGRP) that were reduced after ovariectomy. The enhancement of anandamide effects caused by phytoestrogens was prevented by the concomitant administration of the estrogen receptor antagonist fulvestrant (2.5 mg/kg, s.c., 3 daily doses). It is concluded that, in the vasculature of female rats, phytoestrogens produced an estrogen-receptor-dependent enhancement of the anandamide-vascular actions that involves the modulation of CGRP levels and appears to be relevant whenever an adrenergic hyperactivity occurs.

1. Introduction

Endocannabinoids contribute to reduce vascular contractility under pathological conditions where vascular responsiveness is altered. Hence, compounds that selectively modulate the action as well as the levels of endocannabinoids represent templates for potential new therapeutic strategies [1]. In this sense, the exogenous administration of the endocannabinoid anandamide is known to induce the decrease of blood pressure in spontaneously hypertensive rats [2] as well as in Wistar rats fed with a high-salt diet [3]. Inhibition of the fatty acid amide hydrolase, enzyme involved in intracellular anandamide degradation, normalizes the cardiovascular function in hypertensive rats without producing adverse metabolic effects [4]. Estrogens are also positive modulators of the anandamide effects at the vascular wall since they stimulate the release of anandamide from human endothelial cells [5] as well as potentiate the anandamide-induced vasorelaxations by increasing the bioavailability of the calcitonin-related peptide (CGRP) in the rat mesenteric vasculature [6]. This potent vasodilator peptide is released, at least in part, as a consequence of the activation of the transient receptor potential vanilloid type 1 (TRPV1) by anandamide [7].

Phytoestrogens, such as genistein and daidzein, are able to activate estrogen receptors which confer to them weak estrogen-like activity [8]. They are associated with a favorable cardiovascular risk profile [9] and therefore constitute an interesting food-based alternative to the hormone replacement therapy during the menopausal transition in women [10]. Since in a variety of rat cell lines phytoestrogens inhibit anandamide uptake by blocking the fatty acid amide hydrolase [11], it is possible that phytoestrogens also regulate the vascular effects of anandamide. Hence, the aim of the

present study was to elucidate whether oral administration of the soy-derived phytoestrogens genistein and daidzein modulates the anandamide-induced reductions of the contractions to NA in the rat isolated mesenteric bed that was used as an in vitro model of the adrenergic hyperactivity that usually precedes the onset of primary hypertension [12].

The hypothesis is that the endocannabinoid system could be another target, in addition to nitric oxide, prostanoids, and antioxidant defense genes, for the beneficial cardiovascular actions proposed for phytoestrogens [13, 14].

2. Materials and Methods

2.1. Animals. Male and female Sprague-Dawley rats were housed under a 12 : 12 h light: dark cycle, at controlled room temperature with food and water *ad libitum*. Experiments were conducted in accordance to the Guide for the Care and Use of Laboratory Animals of the National Research Council (USA, 1996). Adult female rats (8–10 weeks, 165–200 g body weight) were either bilaterally ovariectomized (OVX) or sham-operated through dorsal incision, under anaesthesia (40–60 mg/kg ketamine hydrochloride + 10 mg/kg xylazine hydrochloride). After 21 days of endogenous hormonal decline, the animals were randomly allocated to either drug-treated or vehicle-treated groups.

2.2. Animal Treatments. Dose and duration of treatment with phytoestrogens were selected on the basis that they reverted partially, but significantly the uterine atrophy caused by ovariectomy that is considered a parameter of estrogenic activity [15]. According to this, genistein (10 mg/kg) or daidzein (10–20 mg/kg) was administered by oral gavage (p.o.) once daily during three days. Drugs were dissolved in dimethylsulfoxide (residual concentration <1%) and were diluted in corn oil. Some intact as well as OVX female rats treated with phytoestrogen received concomitant subcutaneous administrations of the estrogen receptor antagonist 2.5 mg/kg fulvestrant (ICI 182,780) dissolved in ethanol and diluted in corn oil. All groups were analyzed by comparison with the corresponding vehicle-treated animals.

2.3. Mesenteric Vascular Bed Preparation. Adult male (250–350 g) and female (230–350 g) Sprague-Dawley rats were anaesthetized with urethane (1.2 g kg^{-1} body weight), the abdomen was opened, and the mesenteric vascular bed was cannulated and removed according to [16]. The isolated mesenteric bed was transferred to a perspex chamber and perfused with the Krebs solution at 37°C bubbled with 95% O_2 plus 5% CO_2 at a constant flow rate of 2 mL/min, maintained by a peristaltic pump. Changes in vascular resistance were measured as changes in perfusion pressure and recorded through a Statham pressure transducer connected to a Grass polygraph. Up to nine consecutive, 20 min apart bolus injections of noradrenaline (NA) were performed in one preparation because the short contractile responses induced by this drug are highly reproducible. On the contrary, the sustained contractions that are obtained whenever the agonists are added to the perfusate are difficult to reproduce in the same preparation [17].

Table 1: Noradrenaline-induced contractions.

Group	*n*	NA-induced contraction (mm Hg)
Male rats		
Control	6	51.39 ± 8.46
Vehicle for phytoestrogens	7	52.50 ± 4.72
10 mg/kg genistein	4	43.75 ± 6.38
10 mg/kg daidzein	5	62.5 ± 9.68
Intact female rats		
Control	6	53.54 ± 8.08
Vehicle for phytoestrogens	5	47.68 ± 6.67
10 mg/kg genistein	4	51.88 ± 4.72
10 mg/kg daidzein	6	55.42 ± 5.02
20 mg/kg daidzein	5	53.80 ± 1.70
Ovariectomized female rats		
Control	8	52.81 ± 3.61
Vehicle for phytoestrogens	4	41.25 ± 6.49
Vehicle for 17β-oestradiol	6	43.76 ± 4.55
10 mg/kg genistein	4	56.25 ± 11.48
10 mg/kg daidzein	4	55.00 ± 8.42
20 mg/kg daidzein	4	47.50 ± 4.50
450 μg/kg 17β-oestradiol	6	52.50 ± 9.64

Table 1 shows that the contractile responses to NA in the mesenteric bed had similar magnitudes between the groups (e.g., males and intact and ovariectomized females). Moreover, phytoestrogen treatment did not modify per se either the basal tone or the reactivity to NA; respect to the vehicle-treated groups.

To evaluate anandamide-induced effect, after the first NA bolus injection considered as control, cumulative anandamide concentrations were perfused during 20 min, and the responsiveness to NA (a submaximal pressor effect, i.e., 40 to 60 mm Hg) was challenged on every one concentration. Anandamide was dissolved in ethanol (<0.1%), and further dilutions were made in the Krebs solution. No effects on basal tone of mesenteries isolated from either male or female rats were observed for any concentration of anandamide.

2.4. Immunohistochemistry for CGRP. The experiments were performed according to [6]. Deeply anaesthetized rats were fixed by transcardiac perfusion with PBS containing 4% w/v paraformaldehyde, and mesenteric vascular beds were dissected. The endogenous peroxidase activity was blocked with 1% H_2O_2, and the preparations were permeabilized with 0.2% Triton X-100. Overnight incubation at room temperature with 1/3,000 anti-CGRP antibody (Sigma Aldrich, St. Louis, MI, USA) and 1 h incubation with 1/200 goat anti-rabbit peroxidase conjugated antibody (Sigma Aldrich, St. Louis, MI, USA) were performed. Several branches of each mesenteric bed were not incubated with the primary antibody to obtain the corresponding controls. Peroxidase

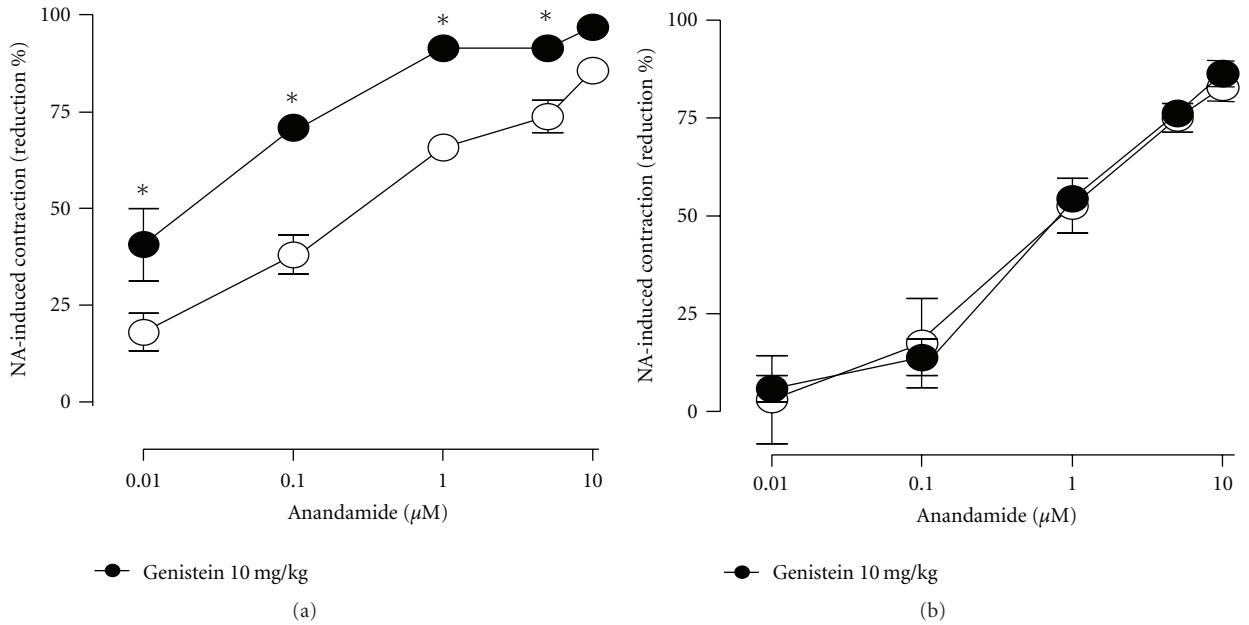

Figure 1: Effects of 3-day oral administration of 10 mg/kg genistein (filled circles) on anandamide-induced reductions of contractile responses to NA in mesenteric vascular beds isolated from female (a) as well as male (b) rats. Vehicles are depicted in open circles. $^*P < 0.05$ when treatment with genistein was compared to the corresponding vehicle.

activity was evidenced with diaminobenzidine in an *Eclipse* 50*i* NIKON light microscope equipped with a video camera Nikon DS-SM. All groups were simultaneously processed to prevent interassay differences. CGRP-immunoreactive fibers were quantified in second arterial branches. Relative area (stained/total area) per field and the difference between anti-CGRP-incubated tissues and the corresponding controls were measured. Morphometric analysis was performed with Image J software (1.34 S National Institutes of Health USA).

2.5. Drugs. (−)-Noradrenaline bitartrate, genistein, and daidzein were obtained from Sigma-Aldrich (St Louis, MI, USA). Fulvestrant (Faslodex) was kindly donated by Astra Zeneca. Anandamide was purchased from Cayman Chemical (Ann Arbor, MI, USA).

2.6. Statistical Analysis. Data are presented as the mean ± SEM ($n = 4$ to 6) of the percent reductions of the initial contraction to NA and were analyzed by two-way analysis of variance followed by Bonferroni's *post hoc t-test*. One-way analysis of variance followed by Dunnett's multiple comparison tests were performed for the immunohistochemical assays as well as for noradrenaline-induced contractions. In all the cases, a $P < 0.05$ was considered as significant.

3. Results

As shown in Figure 1, the endocannabinoid anandamide reduced, in a concentration-dependent manner, the transient contractions elicited by 10 nmol NA in mesenteric beds isolated from either male or female Sprague-Dawley rats. The oral administration of the phytoestrogen genistein (10 mg/kg; daily during 3 days) significantly potentiated the effect of anandamide in mesenteric beds isolated from female but not from male mesenteric beds.

In turn, a 3-day treatment with the soy-derived phytoestrogen daidzein did not modify the anandamide-induced reduction of contractile responses when administered at a dose of 10 mg/kg to either female (Figure 2(a)) or male rats (Figure 2(b)) but did significantly increase the anandamide effects in mesenteries isolated from female rats when dose was scaled up to 20 mg/kg (Figure 2(c)).

The oral administration of the phytoestrogen genistein (10 mg/kg; daily during 3 days) significantly potentiated the effect of anandamide in mesenteric beds isolated from female but not from male mesenteric beds.

Twenty-one days after ovariectomy, the ability of anandamide to decrease the contractile response to NA in mesenteric arteries declined significantly (compare intact females in Figure 1 and untreated OVX females in Figure 3; $P < 0.001$). Figure 3 shows that a 3-day treatment with either 10 mg/kg genistein or 20 mg/kg daidzein could restore anandamide-induced vascular effects in OVX rats. On the other hand, no effects were evidenced by treatment with 10 mg/kg daidzein (Figure 3(b)).

The estrogen receptor antagonist fulvestrant (2.5 mg kg^{-1}, s.c. during 3 days) did not modify *per se* the anandamide-induced reductions of precontracted arteries either in intact (Figure 4(a)) or in OVX (Figure 5(a)) females rats but significantly prevented the potentiation on anandamide-induced effects caused by either 10 mg/kg genistein or, 20 mg/kg daidzein in intact (Figures 4(b) and 4(c)) as well as in OVX female rats (Figures 5(b) and 5(c)). As shown in Figure 6, the density of the CGRP-containing fibers surrounding mesenteric arteries was markedly reduced

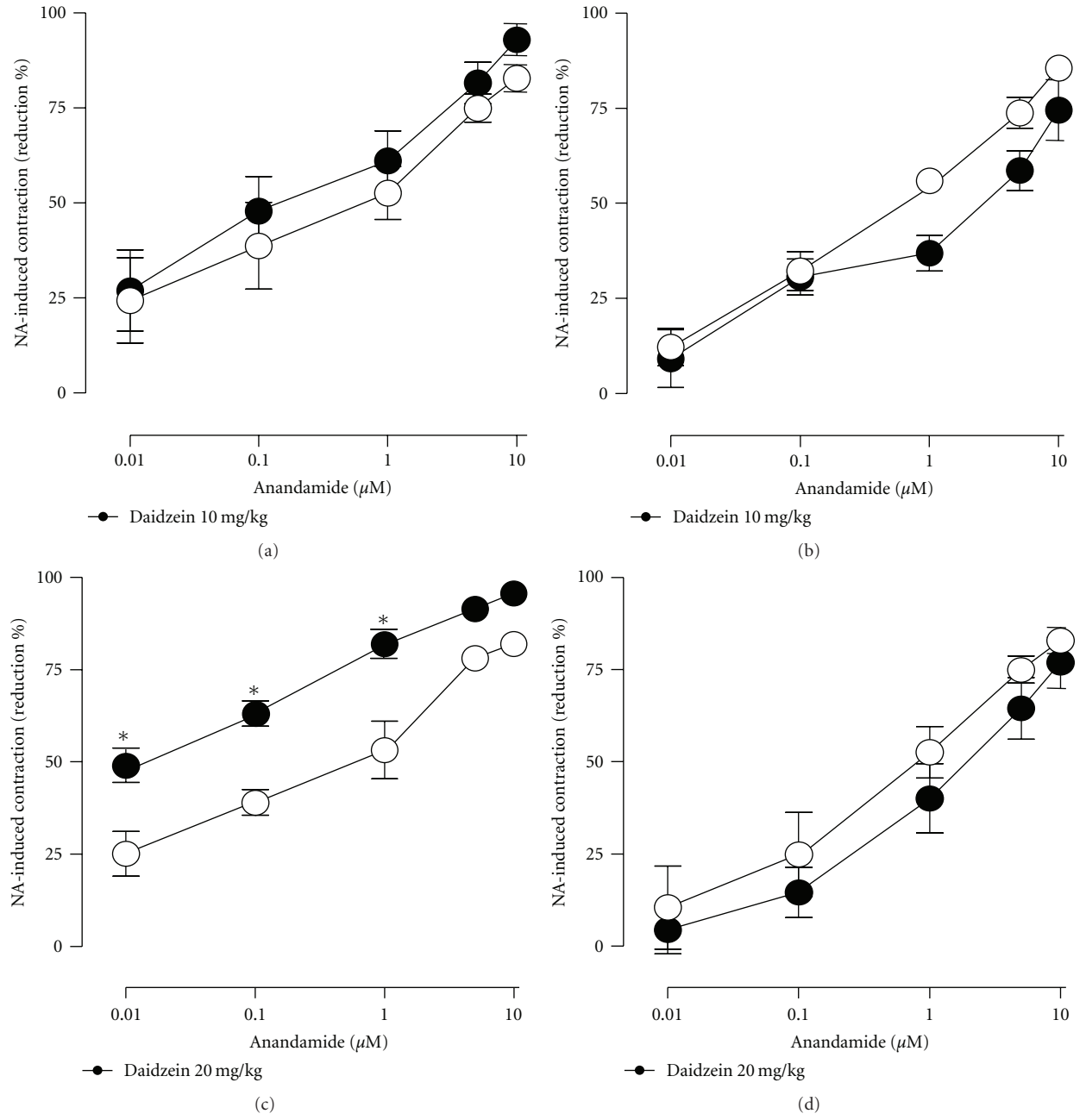

Figure 2: Effects of 3-day oral administration of either 10 mg/kg or 20 mg/kg daidzein (filled circles) on anandamide-induced reductions of contractile responses to NA in mesenteric vascular beds isolated from female (a) and (c) as well as male (b) and (d) rats. Vehicles are depicted in open circles. $^*P < 0.05$ when treatment with daidzein was compared to the corresponding vehicle.

by ovariectomy and significantly restored after a 3-day oral treatment with 10 mg/kg genistein. Moreover, when animals were concomitantly treated with genistein and fulvestrant, the enhancing effect of genistein was not observed. A similar profile was found after a 3-day oral treatment with 20 mg/kg but not with 10 mg/mg daidzein (Figure 7).

4. Discussion

The present study shows that oral administration of the soy-derived phytoestrogens genistein and daidzein daily during 3 days enhanced the decrease in the contractile responses to NA induced by anandamide in mesenteric arteries isolated from female but not from male rats. Taking into account that the anandamide effect is already greater in female mesenteries compared to males [16], the enhancing effect of the phytoestrogens shown here in female rats adds to the overall sex differentiation in this model. The tissue was selected because it represents a group of resistance vessels that greatly contributes to the maintenance of the total peripheral vascular resistance [17, 18]. Precontractions to NA were used to resemble the effects of the adrenergic

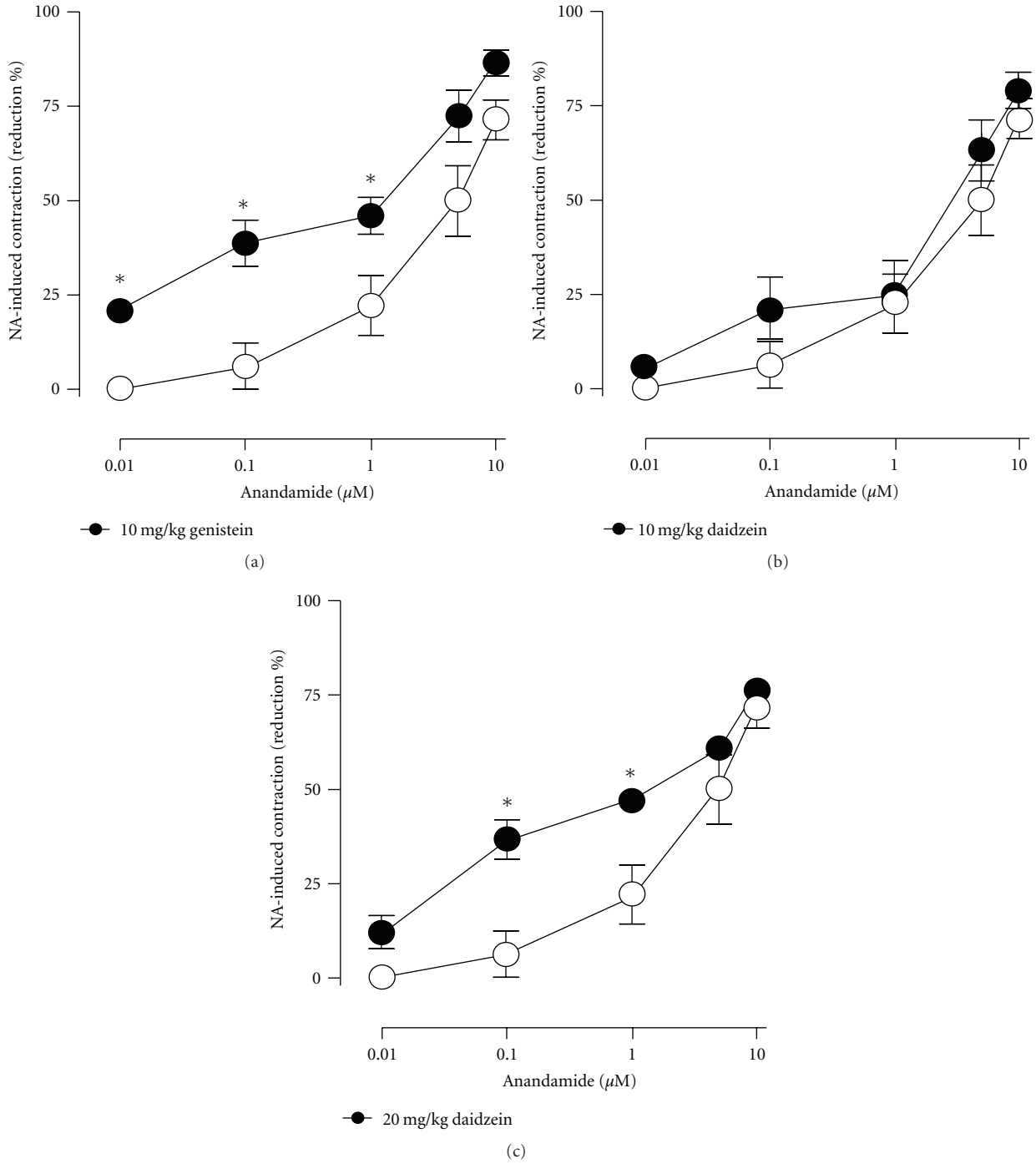

Figure 3: Effects of 3-day administration of 10 mg/kg genistein in (a), 10 mg/kg daidzein in (b), and 20 mg/kg daidzein in (c) on the anandamide-induced reductions of contractile responses to NA in mesenteric beds isolated from ovariectomized female rats. Vehicles are depicted in open circles. $^{*}P < 0.05$ when treatments were compared to the corresponding vehicles.

hyperactivity in vascular tissues that usually precedes the onset of primary hypertension [12].

The observation that the anandamide-induced relaxations in the OVX rats were restored by a 3-day oral administration of phytoestrogens (present results) to the same extent as that produced by 17β-estradiol administration [16] suggests that a common site of action, namely, estrogen receptors (ER), could be involved in both cases. In support of this view is the finding that in intact as well as in OVX female rats the facilitatory effect of phytoestrogens was counteracted by the ER antagonist fulvestrant.

Moreover, a direct effect of phytoestrogens on the contractility to NA is precluded on the basis that no differences were observed in the responsiveness to NA between male

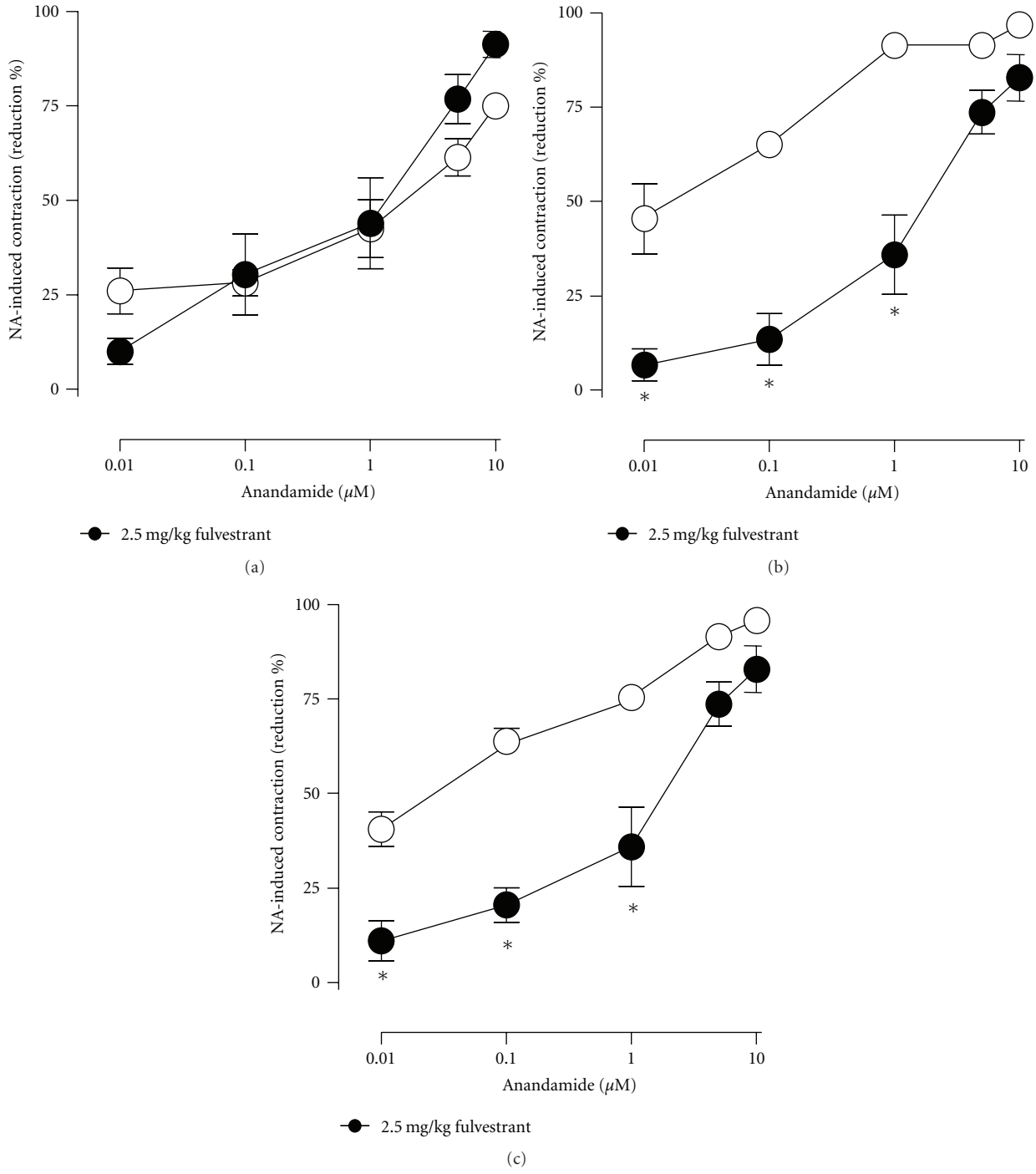

Figure 4: Effects of 3-day s.c. administration of 2.5 mg/kg of fulvestrant on the anandamide-induced reductions of contractile responses to NA in untreated (a), genisteintreated (10 mg/kg; (b)), or daidzein-treated (20 mg/kg; (c)) intact female rats. Either fulvestrant (filled circles) or its vehicle (open circles) were administered concomitantly with the corresponding phytoestrogen treatment. $^{*}P < 0.05$ when phytoestrogen-treated were compared against phytoestrogen plus fulvestrant-treated intact female rats.

and age-matched female rats after treatment with genistein or daidzein ([16] and present results).

The fact that, as previously observed for 17β-estradiol [6], the 3-day oral treatment with either 10 mg/kg genistein or 20 mg/kg daidzein restored the decrease in the density of CGRP-containing perivascular fibers in mesenteries isolated from OVX rats could indicate that the modulation of CGRP levels contributes, among other factors, to the ability of phytoestrogens to potentiate the effect of anandamide in the mesenteric vasculature. In addition, this finding is supported on the basis that the presence of fulvestrant completely prevented the enhancing effect of phytoestrogens on CGRP

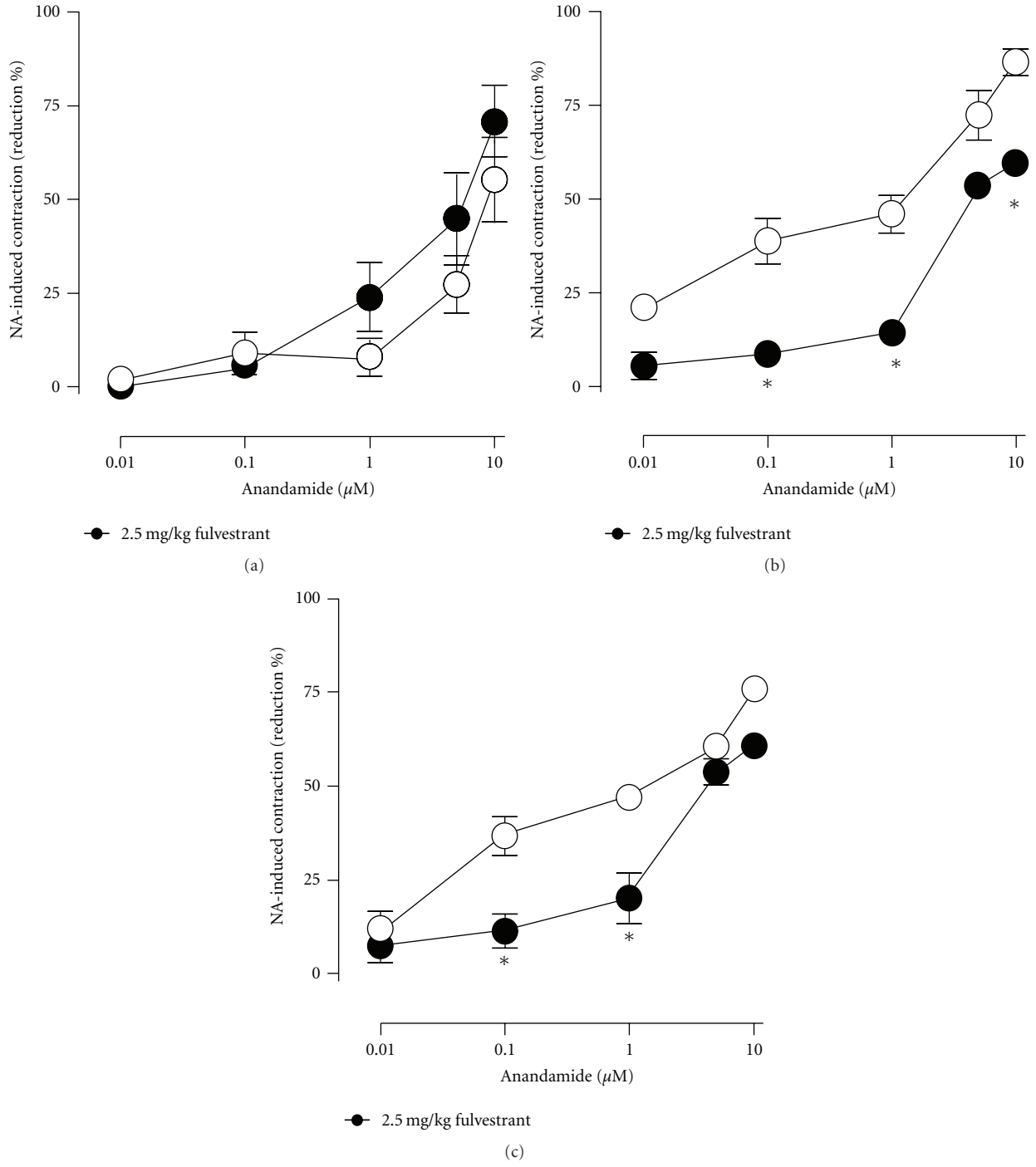

Figure 5: Effects of 3-day s.c. administration of 2.5 mg/kg of fulvestrant on the anandamide-induced reductions of contractile responses to NA in untreated (a), genistein-treated (10 mg/kg; (b)), or daidzein-treated (20 mg/kg; (c)) OVX female rats. Fulvestrant (filled circles) or its vehicle (open circles) were concomitantly administered with the corresponding phytoestrogen treatment. $^*P < 0.05$ when phytoestrogen-treated were compared against phytoestrogen plus fulvestrant-treated OVX female rats.

perivascular levels. This hypothesis agrees with previous evidence showing that mesenteric availability of CGRP underlies the ability of anandamide to reduce the contractile responses to NA in mesenteric arteries [6]. Similarly, a cause-effect relationship between estrogen levels and CGRP arises from the observation that CGRP-containing fibers density is faded after ovariectomy and restored by estradiol treatment in sensory and perivascular neurons [6, 19]. Specifically related to phytoestrogens, it was reported that a diet with fujiflavone P40, a soybean isoflavone product, completely reverses the decrease in the levels of the mRNA coding for CGRP in dorsal root ganglion neurons, as well as the

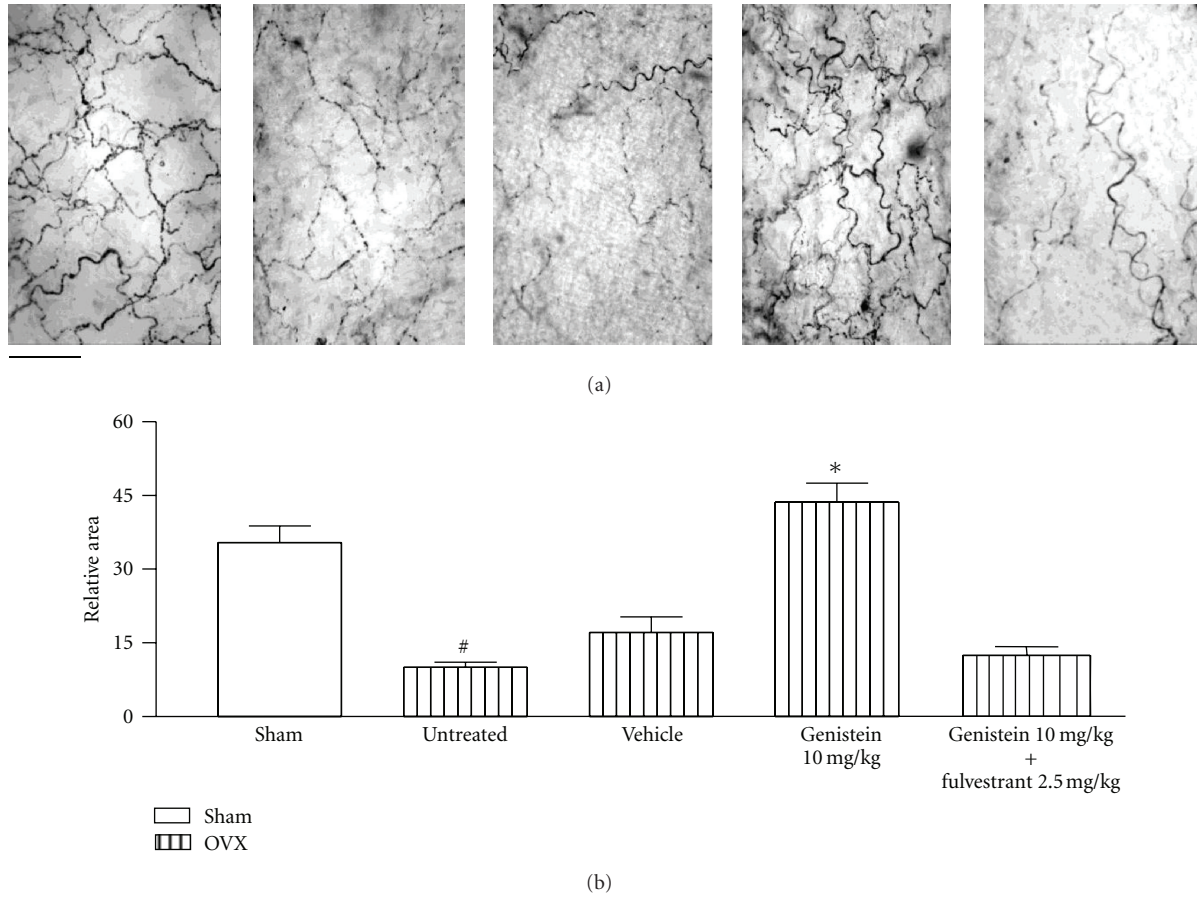

Figure 6: Immunohistochemistry for CGRP. (a) Representative microphotographs of CGRP-immunoreactive fibers surrounding mesenteric arteries in myenteric plexus preparations of sham-operated as well as of OVX female rats. Either genistein (10 mg/kg p.o.) or genistein plus fulvestrant (10 mg/kg p.o. and 2.5 mg/kg s.c., resp.) were administered daily during 3 days. The photomicrographs were captured at 400x magnification; the scale bar indicates 50 μm. (b) Bars represent the mean ± SEM ($n = 4$) of relative morphometric units measured as stained area/total area. Specific immunoreactivity in every tissue was calculated as the difference between anti-CGRP-incubated and nonprimary antibody-incubated samples. $^{\#}P < 0.001$ between sham and untreated-ovariectomized female rats. $^{*}P < 0.01$ between genistein-treated and either genistein plus fulvestrant-treated or the corresponding vehicle-treated OVX rats.

diminutions of the gastric tissue levels of CGRP in OVX rats [20]. In this sense, the lack of effect of oral treatment with 10 mg/kg daidzein agrees with the present observation that 10 mg/kg daidzein did not counteract the decrease in mesenteric CGRP content caused by OVX. This observation is consistent with previous evidence showing that genistein is 10 to 100 times more potent than daidzein and that this difference is linked to a higher affinity of genistein for ER [8], as observed for the modulation of the expression of enzymes that metabolize 17 α-estradiol in cultured MCF-7 cells [21].

On the other hand, the fact that phytoestrogens enhanced anandamide-induced effects selectively in the vasculature of female rats (present results) differs from the potentiation caused by 17β-estradiol in this tissue that is only observed in males [16]. This discrepancy could arise from the fact that the sex-related differences in the rat vasculature, which include variations in the density and distribution of ER subtypes [22], could only become evident when tissues are exposed to compounds, such as genistein and daidzein, that are known to possess a 1000-times lower estrogenic activity than estradiol and are supposed to act as ERbeta partial agonist [8]. In accordance to this, vasodilation to genistein but not to 17β-estradiol is enhanced in postmenopausal women suffering coronary heart disease that express high ERbeta in the vascular wall [23]. However, a more extensive analysis of the estrogen receptor subtypes involved in the vascular effects of anandamide, including variations in the density and distribution of ER subtypes in the mesenteric bed of male and female Sprague-Dawley rats, is necessary to reinforce this possibility.

Moreover, the lack of effect of phytoestrogens in males (present results) could rely on the fact that phytoestrogens modify male gonadal steroids levels [24, 25]. In support of the latter, it was reported that the control of anxiety-related behaviours produced by the systemic administration of phytoestrogens in male rats depends on the gonadal status [26].

At the molecular level, the fatty acid amidohydrolase (FAAH), the major anandamide-hydrolyzing enzyme, is a potential locus for an interaction between oestrogens

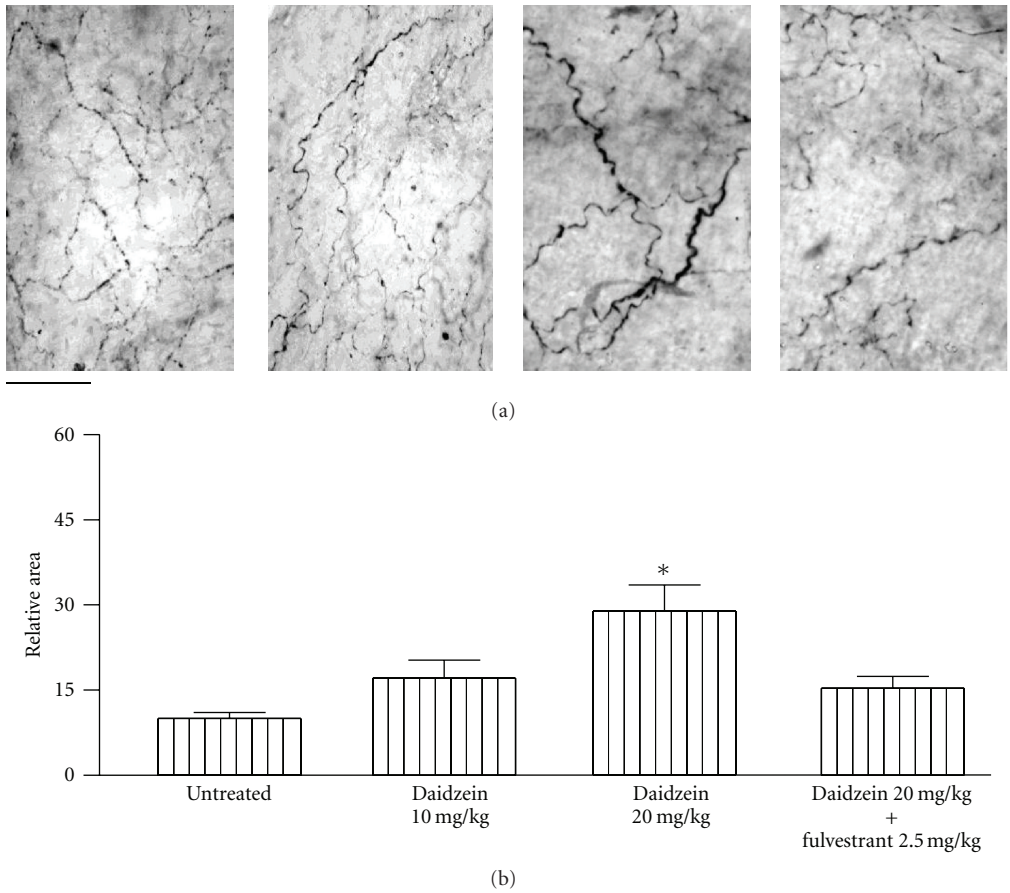

Figure 7: Immunohistochemistry for CGRP. (a) Representative microphotographs of CGRP-immunoreactive fibers surrounding mesenteric arteries in myenteric plexus preparations of OVX female rats. Daidzein (10 mg/kg or 20 mg/kg p.o.) or daidzein plus fulvestrant (20 mg/kg p.o. and 2.5 mg/kg s.c., resp.) were administered daily during 3 days. The photomicrographs were captured at 400x magnification; the scale bar indicates 50 μm. (b) Bars represent the mean ± SEM ($n = 4$) of relative morphometric units measured as stained area/total area. Specific immunoreactivity in every tissue was calculated as the difference between anti-CGRP-incubated and nonprimary antibody-incubated samples. $^*P < 0.01$ between daidzein-treated (20 mg/kg) and either daidzein plus fulvestrant-treated or untreated OVX rats.

and endocannabinoid signalling. The FAAH enzyme possesses an oestrogen response element in its genetic sequence, and translocation of the oestrogen receptor to the nucleus results in inhibition of FAAH transcription that leads to an increase in the anandamide signalling [27]. Since genistein and daidzein inhibit the fatty acid amidohydrolase in vitro [11], the possibility exists that, at least in part, the modulatory effect of phytoestrogens on the anandamide-induced reductions of the contractility to NA could involve the increase of anandamide levels. Nevertheless, this possibility is likely to be precluded since the FAAH inhibitor PMSF is devoid of effects on anandamide-induced vasodilations in the rat mesenteric vascular beds isolated from either sex [16], as well on anandamide actions in other rat tissues, namely, the brain [28].

In conclusion, this is the first evidence that the soy-derived phytoestrogens, genistein and daidzein, modulate positively the reduction of the contractility to NA produced by anandamide in the mesenteric vasculature and supports the hypothesis that the endocannabinoid system could be a target for the beneficial cardiovascular actions of dietary phytoestrogens, as proposed before for estrogens [5].

Finally, the present results give further support to the view that a dietary intervention with an isoflavone-enriched soy extract, acting at the cardiovascular level with minimal impact in the reproductive tract, could have implications for women's cardiovascular health, for example, enhancing the vasorelaxation of small arteries whenever increased adrenergic hyperactivity occurs [23].

Acknowledgments

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Research Article

Do Recommendations for the Management of Hypertension Improve Cardiovascular Outcome? The Canadian Experience

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The Canadian Hypertension Education Program (CHEP) was established in 1999 as a response to the result of a national survey that showed that a high percentage of Canadians were unaware of having hypertension with only 13% of those treated for hypertension having their blood pressure controlled. The CHEP formulates yearly recommendations based on published evidence. A repeat survey in 2006 showed that the percentage of treated hypertensive patients with the blood pressure controlled had risen to 65.7%. Over the first decade of the existence of the CHEP, the number of prescriptions for antihypertensive medications had increased by 84.4% associated with a significant greater decline in the yearly mortality from stroke, heart failure and myocardial infarction and a significant decrease in the hospitalization for stroke and heart failure. Therefore, the introduction of the CHEP and the yearly issue of updated recommendations resulted in a significant increase in the awareness, diagnosis and treatment of hypertension and in a significant reduction in stroke and cardiovascular morbidity and mortality. The CHEP model could serve as a template for its adoption to other regions or countries.

1. Introduction

Hypertension is still a major contributor to mortality worldwide [1], and it is estimated that there are 970 million hypertensives worldwide and it is predicted to increase to 1.56 billion in the year 2025 [2]. The risk for a fail or morbid cardiovascular or cerebral vascular event starts at the systolic blood pressure of 115 mmHg and a diastolic blood pressure of 73 mmHg.

Therefore, it is not surprising that hypertension accounts for about 60% of strokes and 50% of heart failure [3]. Considering that lowering of systolic blood pressure by 10 mmHg and diastolic blood pressure by 5 mmHg reduces the relative risk for a coronary artery event by 23% and a stroke by 40%, it follows that blood pressure is not optimally diagnosed and treated.

There can be several reasons for this lack of diagnosing and proper control of hypertension [4]. The major factors are patient related, for example, poor adherence to treatments, physician-related inertia to properly inform the public of the danger of hypertension and the failure of physicians to diagnose, initiate, and treat blood pressure to achieve the recommended blood pressure goals.

2. The Canadian Situation

A Canadian national survey conducted in Canada from 1985 to 1992 revealed that 45% of individuals were unaware of their blood pressure condition, 22% were aware of having hypertension but remained untreated, 21% were treated but not controlled, and only 13% had their blood pressure treated and controlled to target, that is, less than 140/90 mmHg [5]. These results were disappointing particularly considering the easy access of Canadians to health care, but the Canadian results were similar to some European countries although better results were reported from the United States [6].

As a reaction to these results, the Canadian Hypertension Society established the Canadian Hypertension Education Program which issued the first recommendations for the

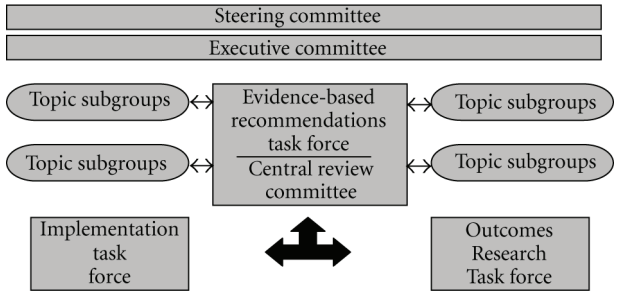

Figure 1: Organization of the Canadian Hypertension Education Program.

management of hypertension in 1999 [7]. The mandate of the Canadian Hypertension Education Program (CHEP) was to reduce the burden of cardiovascular disease in Canada through yearly updating evidence-based recommendations for the management of hypertension, implement the recommendations, regularly evaluate and revise the program, and assess the effect of the recommendations by measuring patient outcomes.

To fulfill these tasks, it required the establishment of a multidisciplinary structure as outlined in Figure 1 [8].

The CHEP is composed of the evidence-based task force which annually reviews and updates the recommendations according to new published information [8].

The implementation task force is responsible for the dissemination of the recommendations by members who have expertise in knowledge translation. Dissemination of information includes the yearly publication of the recommendations in the Canadian Journal of Cardiology which is freely available to every physician, distributing the recommendations to every practice, hospitals, public health system, the pharmaceutical industry, and local small group information meetings with physicians and nurses. Since public awareness is key to the success of improvement in hypertension management, a public education task force has developed information material for patients and the public at large through easy-to-understand pamphlets in several languages, articles in the lay press, public information meetings, and availability of a website (http://www.hypertension.ca/) [9, 10].

The Outcomes Research Task Force is responsible for evaluating and monitoring the effect of the CHEP activities on the public awareness and the management of hypertension at large. This is accomplished through a national surveillance system in collaboration with the Public Health Agency of Canada, the Canadian Institute for Health Research, the Heart and Stroke Foundation of Canada, the Canadian Stroke Network, provincial databases, and a number of other organizations [11]. The data collection includes physical measures and questionnaire surveys, morbidity and mortality data for hypertension, cardiovascular complications, and data on antihypertensive drug prescriptions. Questionnaire surveys are performed every two years to assess the prevalence of hypertension diagnosis and treatment. A national hypertension surveillance program has been initiated and has produced some initial results [11]. All this activity is overseen and directed by the executive and steering committees (Figure 1). Gradually, a number of scientific organizations, health care professionals and public health organizations became involved in the effort to improve hypertension management in Canada.

3. Effectiveness of the Canadian Hypertension Education Program

A national survey which was completed in 1992 showed that almost 50% of Canadians were unaware of having hypertension, 22% who were diagnosed with hypertension were not treated, and of those treated, only 13% had their blood pressure controlled below 140/90 mmHg [5]. The survey was then repeated in 2006 which showed that the proportion of Canadians who were unaware of hypertension had decreased to 16.7% and those treated and had their blood pressure controlled had risen to 65.7% [12]. This improvement was associated with a significant 84.4% increase in the number of prescriptions for antihypertensive drugs [13–15]. There was also an increased use of 2 or more antihypertensive drugs [16]. The largest increase of medications occurred in thiazide diuretics and ace inhibitors, and the smallest increase occurred in beta blockers, consistent with the CHEP recommendations not to use beta blockers as a first-line drug in patients older than 65 years of age [14, 15]. This was paralleled with an increase in hypertension-related physician office visits [14].

The improvement in the management of hypertension resulted in a significant reduction in cardiovascular events and stroke [13]. Since the inception of the CHEP in 1999, there was a significant greater yearly reduction in mortality due to stroke −3%, heart failure −4.3%, and −2.1% for acute myocardial infarctions. Similarly, there was also a significant reduction in the number of hospitalizations for stroke −1.6% and −3.1% for heart failure, but the rate of decline in hospitalization for acute MI remained unchanged, the reason for which is not entirely clear. The decrease in mortality correlated with the increase in the prescription for antihypertensive drugs [13]. The average yearly reductions in mortality due to heart failure, stroke, and acute MI were significantly greater than for noncardiovascular disease deaths or cancer [17]. A recent Canadian population survey confirmed the high rates of treatment and control of hypertension [18].

At the end of the first decade of the existence of the CHEP, certain factors that became important for the sustainability of the CHEP process became apparent and may serve as a guide to implement such a program in other regions or countries [19]. It needs a critical number of experts in the field to reduce individual bias and influence in order to achieve an objective result which at the end should be dictated by up-to-date evidence forming the base of the recommendations and translating data from trials and scientific studies into practical and applicable recommendations. Before issued, consensus on the content on wording of the recommendations has to be achieved.

It also includes the participation of interdisciplinary health teams. In order to be applicable, recommendations should be revised yearly as new information becomes rapidly available. As the overseeing body, academic and government

organizations are involved, which is an important factor for the integrity and credibility of the program. Although the members of the CHEP are all volunteers, certain costs have to be covered, and persistent financial support is important for the continuation of such a program.

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Review Article

Prevalence, Risk Factors, and Management of Prehypertension

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Prehypertension remains an important public health challenge all over the world and appropriate treatments should be adopted to prehypertensive group in different degree effectively. This review aimed to assess the prevalence of Prehypertension and provide effective evidence of the benefits of treating prehypertensive patients. The reasonable evaluation and appropriate intervention of prehypertensive remain need further study.

1. Introduction

Prehypertension was defined as a systolic blood pressure of 120–139 mmHg and/or a diastolic blood pressure of 80–89 mmHg. The concept of prehypertension was introduced as the new guideline for the management of blood pressure by the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JnC-7) [1]. The objectives of defining this classification of blood pressure were to draw the clinical and public healthy attention onthe prevention of people in this range. Prehypertension is a precursor of clinical hypertension and is closely related with the increased incidence of cardiovascular disease [2–4]. Patients with Prehypertension (120–139/80–89 mmHg) have an increased risk of cardiovascular morbidity and mortality compared with patients who have normal blood pressure (<120/80 mmHg). This paper aimed to assess the prevalence of Prehypertension and provide effective evidence of the benefits of treating prehypertensive patients in community.

2. Epidemiology

2.1. High Prevalence of Prehypertension. The National Health and Nutrition Examination Survey (NHANES) 1999-2000 reported that the overall prevalence of prehypertension was 31% all over the world, which was higher in men than in women [5]. A statistical analysis of disease-free adult NHANES participants which was conducted from 1999 to 2006 found that the overall prevalence of PreHTN in disease-free adults was 36.3% [6]. The ATTICA study which included 1514 men and 1528 women found that the prehypertensive population was 39% (43% in men and 35% in women) [7]. The prevalence of prehypertension in India was found more than 45% (of the 2,007 people studied, 47.4% had Prehypertension and 34.7% had hypertension. Prehypertension was found in 46.6% of the men and 49.8% of the women). The data from Korean Nation Health and Nutrition Survey 2001 reported that the estimated age-adjusted prevalence of hypertension and prehypertension was 22.9% (26.9% in men, 20.5% in women) and 31.6% (41.9% in men, 25.9% in women [8]). The Jichi Medical School Cohort Study showed that the prevalence of prehypertension was 34.8% (males) and 31.8% (females) in Japanese general population [9]. Cross-sectional surveys of Shandong and Wuhan Provinces revealed that the prevalence of prehypertension was more than 40% in China [10, 11].

2.2. Risk Factors. Prehypertension is correlated with the recognized traditional cardiovascular risk factors such as obesity, diabetes mellitus, and dyslipidemia. NHANES II 1999-2000 data showed that 64% of individuals with prehypertension had at least another cardiovascular risk factor; persons with Prehypertension were 1.65 times more likely to have at least another adverse risk factor than those with normotension and the percentage increased to 94% in those

aged 60 years or older [12]. Another mortality study of adults aged 30–74 years at the time of the NHANES II examination showed that almost 90% of individuals with prehypertension had at least one other cardiovascular risk factor [13]. Many studies demonstrated that the prehypertensive group had higher levels of blood glucose, total cholesterol, low-density lipoprotein cholesterol, and triglycerides, higher body mass index, and lower levels of high-density lipoprotein cholesterol than the normotensive group [14, 15]. Obesity, abnormalities of glucose metabolism, and insulin resistance were the major factors associated with prehypertension and hypertension [16]. BMI was a strong predictor of prehypertension. The Jichi Medical School Cohort Study which enrolled 4,706 males and 7,342 females of Japanese general population suggested that body mass index (BMI) of more than 23.0 kg/m^2 was the strongest determinant of prehypertension [9]. Prehypertension was more prevalent in diabetic than nondiabetic participants. Compared with nondiabetic participants with normal blood pressure, the hazard ratios of cardiovascular disease were higher for those with both prehypertension and diabetes than for those with prehypertension alone [17].

Other nontraditional cardiovascular risk factors had also been relevant to the development of prehypertension. The prevalence of metabolic syndrome in the prehypertension group was higher than in the normal BP group. Larger waist circumference and body mass index, higher levels of triglycerides, fasting blood glucose, uric acid and ferritin, and lower levels of high-density lipoprotein-cholesterol were more common in subjects with prehypertension than in those with normal BP [18]. Compared to normotensives, prehypertension had higher C-reactive protein, tumor necrosis factor-alpha, amyloid-a, homocysteine levels, and higher white blood cell counts after correcting for multiple comparisons and adjusting for age, body mass index, blood lipids, glucose, food groups consumed, and other potential confounders [19]. It was also found that the prevalence of microalbuminuria in the prehypertension group was higher than in the normal BP group [18]. The nationally representative sample of US adults among 5,827 participants without cardiovascular disease (CVD) and hypertension concluded that prehypertension was associated with higher serum gamma-glutamyltransferase (GGT) levels [20]. In recent years, people pay more attention to whether prehypertension causes change of myocardial structure and function. After adjusting for intergroup differences in age, diabetes, body mass index, smoking, study center, and plasma creatinine, and mean values for left ventricular (LV) measurements were found to be significantly increased in both the prehypertensive and hypertensive groups compared with the normal blood pressure group. LV systolic and diastolic function differed significantly in the hypertensive groups, but not in the prehypertensive participants, compared with the normal blood pressure group [21]. It suggested that the LV structure had been changed during prehypertension period; however, the LV systolic and diastolic function had not been impacted by the change.

2.3. Cardiovascular Disease and Prehypertension. Individuals with prehypertensive levels of blood pressure had an increased risk of developing cardiovascular disease relative to those with optimal levels. The association was pronounced among individuals with diabetes mellitus, and among those with high BMI [22]. It was also found that prehypertension was associated with an increased risk for cardiovascular disease, including myocardial infarction (MI) and coronary artery disease (CAD), but no stroke, with a mean follow-up period of 10 years [23]. The Jichi Medical School Cohort Studys of Japan discovered that prehypertension was associated with a 45% higher risk of cardiovascular events than normal blood pressure after adjusting for traditional cardiovascular risk factors. Prehypertension was associated with an increased 10-year risk of cardiovascular disease; the risk of cardiovascular events with prehypertension during the second 5-year period was elevated in the nonelderly subgroup (<65 years) [9]. A meta-analysis that included approximately 1 million individuals from 61 long-term epidemiological studies demonstrated that mortality from ischemic heart disease and stroke in individuals aged 40–89 years increased in a log-linear relationship together with increases in both systolic/diastolic blood pressure. For each 20 mmHg increase in systolic blood pressure or 10 mmHg increase in diastolic blood pressure over 115/75 mmHg, there was a twofold increase in mortality associated with coronary artery disease and stroke [24]. Longitudinal data from the Framingham Heart study indicated that individuals formerly classified as having "normal" and "high-normal" blood pressure (120–139/80–89 mmHg) were at increased risk of developing full-blown hypertension and cardiovascular disease later in life than those who had an optimal blood pressure (<120/80 mmHg) [25]. The study among 68,438 urban Chinese women aged 40–70 years during an average of 5 years of followup showed that hypertension was associated with high stroke mortality [26].

3. Treatment

3.1. Strategy of Treatment. The relationship between prehypertension and cardiovascular disease aroused widespread concern, and it became an important subject to prevent and intervene. JNC-7 suggested the individuals of prehypertension adopted a healthy lifestyle in order to lower blood pressure and prevent progression to hypertension, with associated reductions in target organ damage and cardiovascular events. 2007 ESH-ESC Practice Guidelines for the Management of Arterial Hypertension emphasized that cardiovascular complications of patients should immediately take drug therapy to reduce the risk of cardiovascular events even in the scope of prehypertensive [27].

3.2. Nonpharmacological Treatments. Prehypertensive blood pressure levels identify individuals with elevated risk of developing hypertension. Prehypertensive patients are not the usual candidates for antihypertensive drug therapy, and prehypertensive individuals should primarily be advised to modify their lifestyle to lower their blood pressure to normal

values (systolic/diastolic blood pressure <120/80 mmHg) to reduce the risk of developing hypertension. Lifestyle modifications were the main treatment recommended by JNC-7 guidelines for the prehypertension patients. The lifestyle modifications included (1) Lose weight, maintain normal body weight, keep body mass index between 18.5 and 24.9 kg/m^2. (2) Adopt DASH eating plan, consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat. (3) Adopt dietary sodium reduction and reduce dietary sodium intake no more than 100 mmol per day (2.4 g sodium or 6 g sodium chloride). (4) Promote physical activity. (5) Attempt moderation of alcohol.

3.3. Dietary Approaches. It is known that obesity, sodium intake, and alcohol consumption factors influence blood pressure. The DASH diet is recommended by physicians for people with hypertension (high blood pressure) or prehypertension. The DASH diet eating plan has been proven to lower blood pressure in studies sponsored by the National Institutes of Health (Dietary Approaches to Stop Hypertension). In addition to being a low-salt (or low-sodium) plan, the DASH diet provides additional benefits to reduce blood pressure. It is based on an eating plan rich in fruits and vegetables, and low-fat or nonfat dairy. DASH dietary pattern is rich in potassium (from fruits and vegetables) and calcium (from dairy), low in total and saturated fat, and contains limited amounts of meats and sweets [28]. Compared with a typical American control diet, the DASH dietary pattern reduced SBP by 5.5 mmHg and DBP by 3.0 mmHg overall. In the participants with prehypertension, corresponding reductions were 3.5 mmHg and 2.1 mmHg. It was also found that the reduction of sodium intake levels below the current recommendation of 100 mmol per day and the DASH diet both lower blood pressure substantially, with greater effects in combination than singly. Long-term health benefits will depend on the ability of people to make long-lasting dietary changes and the increased availability of lower-sodium foods [29].

3.4. Weight Reduction. Increased body weight is a strong risk factor for prehypertension and weight loss is important for the prevention and treatment of prehypertension and hypertension. A lot of clinical trial data document the significant BP-lowering effect of weight loss. A meta-analysis of randomized controlled trials included twenty-five randomized, controlled trials (comprising 34 strata) published between 1966 and 2002 with a total of 4874 participants was performed to estimate the effect of weight reduction on blood pressure overall and in population subgroups in 2003. Blood pressure reductions were −1.05 mmHg (95% CI, −1.43 to −0.66) systolic and −0.92 mmHg (95% CI, −1.28 to −0.55) diastolic when expressed per kilogram of weight loss in this study. It was found that physical exercise with weight reduction reduced blood pressure, decreased cardiovascular risks, and improved abnormal left ventricular relaxation recently [31].

3.5. Salt Intake Reduction. Many surveys reveal the consistent correlation between sodium intake and BP. Numerous trials show that the limit of sodium intake leads to reductions in BP [32, 33]. A long-term followup assessed 10–15 years after the original trial at 10 clinic sites in 1987–90 (TOHP I) and nine sites in 1990–5 (TOHP II) showed the remote effects of dietary sodium reduction for 18 months (TOHP I) or for 36–48 months (TOHP II) on risk of cardiovascular disease. Risk of a cardiovascular event was 25% lower among those in the intervention group compared with the matched group after adjusted for trial, clinic, age, race, and sex, and 30% lower after further adjustment for baseline sodium excretion and weight [34]. The study demonstrated that sodium reduction could reduce long-term risk of cardiovascular events in patients with prehypertension. However, it is difficult to maintain the reduction of sodium intake in the general public.

3.6. Physical Activity. The correlation between habitual physical activity and the development of hypertension have been found in numerous studies. A meta-analysis demonstrated the studies published and indexed between January 1966 and December 1998 concluded that progressive resistance exercise was efficacious for reducing resting systolic and diastolic blood pressure in adults [35]. Another Meta-analysis of randomized, controlled trials evaluated the effect of aerobic exercise on blood pressure. In the random-effect model, it was found that aerobic exercise was associated with a significant reduction in mean systolic and diastolic blood pressure 3.84 mmHg and 2.58 mmHg, respectively [36]. A study evaluated appropriate type and frequency of physical activity for the beneficial effect on blood pressure among Japanese male workers. There was a progressive reduction in the hazards ratios of hypertension with increasing total daily activity (hazards ratio of 0.65 in subjects who walked >8000 steps/day versus <4000 steps/day). Subjects who exercised >3 times/week also showed a significantly lower risk (0.35) of developing hypertension versus those who exercised <3 times/week. In addition, accumulating intermittent bouts of physical activity, as short as 10 min, total 30 min walk sessions may reduce systolic BP in prehypertension.

3.7. Moderation of Alcohol. The recommendation of JNC-7 suggested that the limit consumption to no more than 2 drinks (1 oz or 30 mL ethanol; e.g., 24 oz beer, 10 oz wine, or 3 oz 80-proof whiskey) per day in most men and to no more than 1 drink per day in women and lighter weight persons. The regular consumption of alcohol elevates blood pressure and the global estimates showed that the attributable risk for hypertensive disease from alcohol was 16%. The increase of blood pressure is approximately 1 mmHg for each 10 g alcohol consumed and is largely reversible within 2–4 weeks of abstinence or a substantial reduction in alcohol intake, and this increase of blood pressure occurs irrespective of the type of alcoholic beverage. Maximum cardiovascular benefit occurs at relatively low levels of consumption (i.e., one to two standard drinks a day in men (10–20 g alcohol) and up to

one a day in women (10 g alcohol)). In hypertensive subjects, consumption beyond these levels would be unwise [37].

The reduction of blood pressure is always the comprehensive effect of the lifestyle interventions in the management of prehypertension. The main 6-month results from the PREMIER trial showed that comprehensive behavioral intervention programs improved blood pressure [38].

3.8. Pharmacological Treatments. Whether people without diabetes or chronic kidney disease (CKD) should be given pharmacological treatments or not is still on discussion [39]. The pharmacological treatments could be used on condition that lifestyle modification trial fails to reduce blood pressure to 130/80 mmHg or less according to the JNC-7 guidelines for prehypertension without diabetes or chronic kidney disease (CKD) [1]. The trial of TROPHY study evaluated the effect of the angiotensin II receptor antagonist candesartan cilexetil on the prevention of transition from prehypertension to stage 1 hypertension [40]. Participants were randomly assigned to receive two years of candesartan (Atacand, AstraZeneca) or placebo, followed by two years of placebo for all. When a participant reached the study end point of stage 1 hypertension, treatment with antihypertensive agents was initiated. Both the candesartan group and the placebo group were instructed to make changes in lifestyle to reduce blood pressure throughout the trial. Over a period of four years, stage 1 hypertension developed in nearly two thirds of patients with untreated prehypertension, and the prehypertension treated with candesartan appeared to be well tolerated and reduced the risk of incident hypertension during the study period. Another study evaluated the impact of bovine casein hydrolysate (c12 Peptide) on prehypertension. After four weeks, repeated daily intake of 3.8 g C12 peptide, the systolic, and diastolic BP reduced significantly by about 10 mmHg and 7 mmHg, respectively [41]. The drug intervention in patients with prehypertension is therefore appealing. In the absence of higher baseline risk, the absolute benefit of treatment is presumably small and was not demonstrated to date. These individuals could be candidates to treatment with the aim to prevent the development of full hypertension. The long-lasting effectiveness of nondrug therapies is low outside the controlled conditions of randomized clinical trials, and there is evidences that the use of BP-lowering drugs reduces the incidence of hypertension in individuals with prehypertension by more than 60%. Clinical trials testing the efficacy and safety of BP agents to prevent hypertension in a population-based perspective are required. In the meantime, it is worthy to present the option to start low doses of BP agents for individuals with prehypertension without comorbidities who do not respond to the prescription of lifestyle modification [42].

4. Conclusions

The category of "prehypertension" increases the awareness of the high risk group of hypertension. Individuals with Prehypertension have an increased risk of full-blown hypertension, target organ damage, and cardiovascular-related morbidity and mortality [43]. Despite progress in recent years in the prevention, detection, and treatment of Prehypertension, it remains an important public health challenge that adopts appropriate treatments to prehypertensive group in different degrees effectively. The reasonable evaluation and appropriate intervention of prehypertensive need further study.

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Clinical Study

Medical and Psychological Risk Factors for Incident Hypertension in Type 1 Diabetic African-Americans

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Objective. To determine risk factors for the development of hypertension among African-Americans living with type 1 diabetes. *Methods*. African-Americans with type 1 diabetes (n = 483) participated in a 6-year followup. At both baseline and followup blood pressure was measured twice in both sitting and standing positions using a standard protocol. Patients had a structured clinical interview, ocular examination, retinal photographs, and blood and urine assays and completed the Hostility and Direction of Hostility Questionnaire (HDHQ) and the Beck Depression Inventory (BDI). *Results*. Of the 280 diabetic patients with no hypertension at baseline, 82 (29.3%) subsequently developed hypertension over the 6-year followup. Baseline older age, longer duration of diabetes, family history of hypertension, greater mean arterial blood pressure, overt proteinuria, increasing retinopathy severity, peripheral neuropathy, smoking, and higher hostility scores were significantly associated with the development of hypertension. Multivariate analyses showed that higher hostility scores and overt proteinuria were significantly and independently associated with the development of hypertension in this population. *Conclusions*. The development of hypertension in African-Americans living with type 1 diabetes appears to be multifactorial and includes both medical (overt proteinuria) as well as psychological (high hostility) risk factors.

1. Introduction

Persons living with diabetes have a prevalence of systemic hypertension twice as high as persons without diabetes [1–5]. Hypertension is an important problem in persons living with diabetes because it is strongly associated with the development of the major complications of diabetes—retinopathy, nephropathy, and cardiovascular disease [6–10]. As such, it is a major cause of morbidity and mortality among persons living with diabetes [11, 12]. Hypertension in persons living with diabetes appears to be more common in African-Americans than in whites [5]. For instance, data from the 1976–1980 National Health and Nutrition Examination Survey for mostly type 2 diabetic persons indicate that both systolic and diastolic blood pressures are higher in African Americans compared with whites at ages <54 years [5].

In persons living with diabetes, reducing morbidity and mortality from hypertension is predicated on identifying risk factors associated with the development of hypertension, so that treatment strategies may be implemented. In whites living with type 1 diabetes, medical risk factors reported in association with the development of hypertension include older age, longer duration of diabetes, male gender, smoking, poor glycemic control, and proteinuria [13]. Psychological factors have also been implicated in both the onset and progression of hypertension in the general population [14–17]. For example, in a meta-analysis of the relationship of personality to blood pressure, one of the strongest predictors of developing hypertension was found to be

a high level of anger [15]. Furthermore, there is large literature suggesting that hostility and negative affective states, including depression, may be a risk factor for not only cardiovascular disease but also for hypertension [18–30]. One reason for the association of psychological factors with hypertension may be the exposure to chronic and environmental stressors, particularly for African Americans [17, 27, 31]. There is, however, no longitudinal study examining medical and psychological risk factors for the development of hypertension in a large group of African-Americans living with type 1 diabetes.

We had previously examined and subsequently carried out a 6-year followup of a large group of African-Americans living with type 1 diabetes, the *New Jersey 725* [8, 32, 33]. This 6-year followup provided an opportunity to fill the gap in knowledge about risk factors for the development of hypertension in the 280 African-American men and women with type 1 diabetes free of hypertension at baseline. The purpose of the present study was to examine putative medical and psychological risk factors in relation to the development of hypertension in our African-American diabetic cohort.

2. Methods

2.1. Study Population. Description of the original cohort has been previously reported [32]. Briefly, participants were identified from among 68,455 African-American patients discharged with a primary or secondary diagnosis of diabetes mellitus from 31 hospitals located in the seven counties lying within a 20-mile radius of the New Jersey Medical School, Newark. Approval by Institutional Review Boards at the University of Medicine and Dentistry of New Jersey, New Jersey Medical School, Newark, NJ, USA and at the various hospitals was first obtained. Subsequently, the medical record department at each hospital was given a list of potentially eligible patients and randomly retrieved patients' chart for review by the Principal Investigator (MSR), the study coordinator, and the two research assistants. From the review of 13,615 patient charts, 875 patients with an acute onset of diabetes before 30 years of age and on insulin therapy were found to be eligible. Patients of all ages were included in the study. Excluded were patients with type 2 diabetes, those diagnosed after age 30 whether on insulin or not, and patients with maturity-onset diabetes of youth [34, 35]. Of the 875 eligible patients, 725 (82.9%) were enrolled, 39 (4.4%) could not be traced, and 111 (12.7%) declined to participate [32].

Of the 725 patients, 508 (70.1%) participated in the 6-year follow-up examination, 44 (6.1%) could not be located, 34 (4.7%) refused examination, and 139 (19.2%) had died in the 6-year interval [8]. Excluding patients who had died since baseline, 508 of the 586 (87%) live patients had a 6-year follow-up. There was no contact with participants or data collection between the baseline and the 6-year examinations. At followup, 25 of the 508 (4.9%) participants were no longer receiving insulin and had not received a pancreas transplant. Since these 25 patients may not be truly insulin dependent, they have been excluded, leaving 483 (95.1%) of the 508 patients available for analysis. Comparison between patients on and off insulin at followup has been previously reported [8]. The mean (±SD) time of follow-up was 6.1 ± 0.5 years and median followup 6.0 years. Baseline characteristics of the 483 patients have been previously reported [8].

2.2. Procedures. Patients were examined in the Eye Clinic at University Hospital in Newark, NJ USA. On arrival, informed written consent was obtained. Similar procedures were obtained at both baseline and 6-year follow-up visits. Blood pressure was measured twice in both the sitting and standing positions using a random zero sphygmomanometer according to the Hypertension Detection and Follow-up Program protocol [36, 37]. The technician was trained according to a standardized protocol and was required to meet specified performance levels prior to certification [36]. Patients were sitting at rest for 10 minutes before any blood pressure measurement was made, and the two blood pressure measurements in either position were made at least 5 minutes apart. The averages of the two measurements in each position were used. Patients also underwent a complete eye examination and seven standard stereoscopic Diabetic Retinopathy Study retinal photographs [38]. Also obtained were height and weight.

A structured clinical interview included detailed medical and ophthalmologic histories as well as sociodemographic factors and life-style variables (i.e., self-reported measures of smoking, alcohol consumption, and physical activity). Patients were asked whether their mother or father had hypertension for which they were treated. At baseline, patients ≥18 years of age completed the Beck Depression Inventory (BDI) [39]. The BDI is a 21-item self-report depression inventory which measures depressive symptoms [39]. For each item, there is a 1 to 4 score. The total score is obtained by adding up the scores on each of the 21 questions.

At the second visit, patients ≥18 years of age completed the 51-item Hostility and Direction Hostility Questionnaire (HDHQ) [40]. Each item is answered as either "true" or "false", and a scoring template is used to generate subscales scores which are summed to obtain a total hostility score. The HDHQ has been shown to have high validity and reliability [40].

Color fundus photographs obtained at both baseline and followup were graded for retinopathy severity in a masked fashion by the Wisconsin Fundus Photograph Reading Center in Madison, WI USA. The modified Early Treatment of Diabetic Retinopathy Study (ETDRS) Airlie House classification of retinopathy was used based on the severity level in the worse eye [41, 42]. Level 10 indicates no retinopathy, 20–35 minimal nonproliferative retinopathy, 43–53 moderate nonproliferative retinopathy and levels ≥61 severe proliferative retinopathy [42].

Venous blood was drawn for total glycosylated hemoglobin, using high-pressure liquid chromatography, and high- and low-density lipoprotein cholesterol (HDL-C and LDL-C) and total cholesterol using an enzymatic assay and separation spectrophotometry (Genzyme Diagnostics, Cambridge, MA USA). The normal range for total glycosylated hemoglobin is 4.2–7.0% and the intra-assay coefficient of variation 0.38–1.47%. A 4-hour timed urine collection was

obtained for the measurement of albumin excretion rate (AER) and creatinuria using spectrophotometry (SmithKline Beecham Clinical Laboratory, Philadephia, PA USA).

At both visits, patients' charts of previous hospital admissions and/or medical notes from private physicians were obtained and reviewed by the PI (MSR).

2.3. Definitions. Systemic hypertension was considered present if either the systolic pressure was ≥140 mm Hg and/or the diastolic ≥90 mm Hg, and/or the patient was taking antihypertensive medication [43]. When reviewing medical notes, patients' hypertension status and prescription of antihypertensive medications were confirmed. Antihypertensive medication prescribed by the patient's physician to only protect kidney function, as stated in the patients' medical chart, was not considered as antihypertensive medication. When the blood pressure measurements obtained in either the sitting or standing position differed in the characterization of the patient's hypertensive status as defined above, those measurements were discarded and the blood pressure measurements were repeated. The latter results were used to define the patient's hypertensive status. The 6-year incidence of hypertension was calculated from all patients ($n = 280$) who did not have hypertension at the baseline examination. Patient's age was the age at the time of baseline examination. Age at diagnosis was age at which diabetes was first recorded in the hospital record. Duration of diabetes was time between age at diagnosis and age at baseline. Microproteinuria was present if baseline AER was 20–200 μg/min, and overt proteinuria if baseline AER was >200 μg/min. A patient was considered depressed if at baseline the BDI score was ≥13. BDI cut-off scores of 12 to 14 have been found to have high predictive value as a screening instrument for depressive disorders in both the general population and in diabetic patients [44, 45].

Socioeconomic factors recorded included patient's level of education (for those ≥25 years of age), marital status, employment status, personal income (for those ≥18 years of age), and family income. Patient's socioeconomic status was classified from the Goldthorpe and Hope classification of occupations as middle-high (level 1–22) and lower (level 23–36) class using the occupation of the head of the household [46].

Alcohol abuse was considered present if the patient either currently reported drinking four or more alcohol drinks every day or had a past history of drinking four or more alcohol drinks a day every day for at least 1 year, as also documented from the review of the charts of all past hospital admissions. Smoking status was quantified as packyears calculated using the average number of cigarettes (or cigars) per day multiplied by the number of years the patient smoked until the baseline examination.

2.4. Statistical Tests. Data management and statistical analyses were performed using window-based statistical software (SPSS, Chicago, IL USA, version 17). Patients who did develop hypertension over the 6-year period (or who began using antihypertensive medication during that time, whether or not that treatment was effective), and those who did not were compared with regard to the various known and suspected risk factors. Mean levels of continuous variables were compared between groups with an independent samples t-test, and rates were compared with the χ^2 test. Odds ratios (ORs) and 95% confidence intervals (CIs) were also used to quantify the association between incident hypertension and relevant levels of each risk factor. The statistical significance of the associations was based on the Wald test. Rates are presented for each level of the risk factor, and the OR is computed with reference to the level thought to represent the lowest risk. Multivariate logistic regression analyses were used to identify independent risk factors for incident hypertension. Two risk factors were categorized for analysis because their distribution was skewed (smoking and BDI). Continuous values were used otherwise.

Given the number of incident cases, we selected in the multivariate regression analysis five clinical variables (age, body mass index, smoking history, proteinuria, and family history of hypertension) on the basis of their importance in the literature in addition to the psychological variables (HDHQ and depression) [47]. The first rationale for including these predictors concerns the number of predictors that a regression can support [48]. Babyak suggests that regression modeling proceed with 10–15 incident cases per predictor. Limiting the number of predictors helps to avoid the influence of sampling variation that may be present, improving stability of the results and the likelihood that results will be replicable. The hostility variable was chosen because it represents a unique innovation of this study, and evaluating its independence from known risk factors (particularly depression) was a major goal of the multivariate analysis. The remaining variables were selected so as to maximize consistent reports in the literature; represent a range of causal mechanisms; modifiable over immutable risk factors; and proximal (with regard to hypertension) over more distal risks. All tests are 2-sided (where appropriate) and all use a 0.05 significance level.

3. Results

At baseline, the mean age of the 483 type 1 diabetic African-American patients (288 women and 195 men) was 27.5 ± 10.8 years and mean duration of diabetes 10.4 ± 8.6 years. At baseline, 203 (42.0%) of these patients already had hypertension and were excluded from further analysis. Over the 6-year followup, 82 of the 280 insulin-dependent patients [(29.3%) (95% CI, 24.0–34.9%)] without hypertension at baseline subsequently developed hypertension. At the 6-year followup, 60 patients were on one antihypertensive medication (26 patients on angiotensin-converting enzyme inhibitors (ACE), 6 on calcium channel blockers, 6 on beta-blockers, and 2 on diuretics), and 20 were on a combination of antihypertensive medications. Baseline characteristics of patients with and without hypertension at followup are presented in Table 1.

3.1. Baseline Risk Factors for Hypertension

3.1.1. Bivariate Analyses. The incidence of hypertension increased significantly with increasing age at baseline from

Table 1: Baseline characteristics of patients with and without hypertension* at the six-year followup.

	Hypertension*		
	Present	Absent	
	$N^{\dagger} = 82$	$N^{\dagger} = 198$	$P^{\ddagger}$
	Mean ± SD		
Age (years)	27.0 ± 9.4	24.0 ± 10.0	0.02
Duration of diabetes (years)	10.3 ± 7.6	8.1 ± 7.9	0.03
Body mass index (kg/m^2)	26.6 ± 8.3	25.0 ± 6.5	0.08
Glycosylated hemoglobin (%)	14.6 ± 4.6	13.6 ± 4.3	0.08
Total cholesterol (mg/dL)	213.4 ± 58.5	189.6 ± 40.9	<0.001
Systolic blood pressure (mm Hg)	116.5 ± 11.3	114.1 ± 10.6	0.09
Diastolic blood pressure (mm Hg)	78.1 ± 8.5	75.6 ± 8.6	0.04
Mean arterial blood pressure (mmHg)	86.5 ± 8.5	82.1 ± 9.2	<0.001
Beck Depression Inventory score	11.8 ± 9.0	9.5 ± 9.1	0.08
HDHQ score[§]	20.8 ± 9.1	17.1 ± 7.6	0.001
	$N^{\dagger}$ (%)	$N^{\dagger}$ (%)	$P^{\|\|}$
Gender			0.89
male	31 (38.3)	74 (37.4)	
Proteinuria[¶]			0.001
none	48 (60.8)	152 (78.4)	
micro-	19 (24.1)	33 (17.0)	
overt	12 (15.2)	9 (4.6)	
Retinopathy severity[#]			<0.001
none	32 (39.5)	111 (56.1)	
minimal	25 (30.9)	74 (37.4)	
moderate	13 (16.0)	9 (4.5)	
severe	11 (13.6)	4 (2.0)	
Peripheral neuropathy			0.001
yes	45 (55.6)	67 (33.8)	
Stroke			0.77
yes	3 (3.7)	6 (3.0)	
Heart disease			0.34
yes	10 (12.3)	17 (8.6)	
Total Cholesterol/HDL-C** ≥4.5			0.15
yes	49 (73.1)	146 (81.6)	
Smoking			0.03
ever	43 (53.1)	77 (38.9)	
Family history of hypertension			0.05
yes	47 (59.5)	88 (46.6)	

* Systolic ≥140 and/or diastolic ≥90 mm Hg or use of antihypertensive medication; † N may vary due to missing data; ‡ t-test; § Hostility and Direction of Hostility Questionnaire [40]; || chi-square test; ¶ albumin excretion rate: none <20 μg/min, micro- 20–200 μg/min, overt >200 μg/min; # Early Treatment of Diabetic Retinopathy Study severity level [42]; ** high-density lipoprotein cholesterol.

13.6% in those <10 years of age to 40.9% in those >30 years of age (test for trend, $P < 0.01$). The incidence of hypertension also increased with longer baseline duration of diabetes from 19.8% in patients with ≤5 years of diabetes to 40.0% in those with >20 years of diabetes duration (test for trend, $P < 0.01$). There was no significant association with gender.

The 6-year incidence of hypertension was significantly associated with baseline longer duration of diabetes ($P = 0.02$), more years of smoking ($P = 0.008$), a family history of hypertension ($P = 0.04$), higher mean arterial blood pressure ($P = 0.001$), overt proteinuria ($P = 0.001$), moderate to severe diabetic retinopathy ($P < 0.001$), peripheral neuropathy ($P = 0.001$), and a higher HDHQ score ($P = 0.001$) (Table 2).

There was no significant association between developing hypertension and baseline body mass index ($P = 0.46$),

Table 2: Six-year incidence of hypertension* by baseline characteristics: bivariate analysis.

Baseline characteristics	No. at risk†	Crude (%)	OR (95% CI)‡	P‖
Glycosylated hemoglobin (%)¶				0.11
<10.4	64	31.3	1.0	
10.41–13.45	74	23.0	0.66 (0.31–1.40)	
13.46–16.2	68	23.5	0.68 (0.31–1.46)	
>16.2	74	39.2	1.42 (0.70-2.87)	
Retinopathy severity				<0.001
none	143	22.4	1.0	
minimal	100	26.0	1.22 (0.67–2.21)	
moderate	22	59.1	5.01 (1.96–12.78)	
severe	15	73.3	9.54 (2.84–31.99)	
Proteinuria#				0.001
none	200	24.0	1.0	
micro-	52	36.5	1.82 (0.95–3.50)	
overt	22	59.1	4.57 (1.84–11.36)	
Peripheral neuropathy				0.001
no	167	21.6	1.0	
yes	113	40.7	2.50 (1.48–4.23)	
Total cholesterol/HDL-C**				0.16
<4.5	196	25.5	1.0	
≥4.5	51	35.3	1.59 (0.83–3.08)	
HDHQ score¶††				0.001
0–12	71	18.3	1.0	
13–16	51	27.5	1.69 (0.71–3.99)	
17–23	62	30.6	1.97 (0.88–4.42)	
≥24	63	44.4	3.57 (1.64–7.79)	
BDI score ≥13‡‡				0.20
no	159	27.7	1.0	
yes	63	36.5	1.50 (0.81–2.79)	
Smoking (packyears)¶				0.008
0	160	24.4	1.0	
<5	44	29.5	1.34 (0.64–2.81)	
5–14	40	32.5	1.53 (0.72–3.26)	
≥15	36	47.2	2.85 (1.35–6.03)	
Body mass index (Kg/m^2)				.46
<25	153	27.5	1	
>25	127	31.5	1.22 (0.73–2.04)	
Duration of diabetes (years)¶				.02
<5	111	20.7	1	
5–9	69	36.2	2.17 (1.10–4.26)	
10–17	57	28.1	1.49 (0.71–3.12)	
≥18	43	41.9	2.76 (1.29–5.89)	
Family history of hypertension				.04
no	133	24.1	1	
yes	136	35.3	1.72 (1.01–2.93)	
Mean arterial blood pressure (mmHg)‖‖				.001
<82.2	113	23.9	1	
82.3–90.5	105	22.9	0.94 (0.50–1.77)	
>90.5	62	50.0	3.19 (1.65–6.16)	

Table 2: Continued.

Baseline characteristics	No. at risk†	Crude (%)	OR (95% CI)‡	P‖
Education				0.32
≤high school	75	37.3	1	
≥college	71	29.6	0.71 (0.35–1.41)	
Socioeconomic status				0.30
middle-high	133	26.3	1	
lower	147	32.0	1.32 (0.78–2.21)	
Alcohol abuse				0.09
no	240	24.6	1	
yes	19	42.1	2.23 (0.86–5.81)	

* Systolic ≥140 or diastolic ≥90 mm Hg or antihypertensive medication; † number at risk may vary due to missing data; ‡ odds ratio (95% confidence interval); ‖ test for trend, using Cochran Armitage trend test; ¶ quartiles; # albumin excretion rate: none <20 μg/min; micro- 20–200 μg/min; overt >200 μg/min; ** high-density lipoprotein cholesterol; †† HDHQ: Hostility and Direction of Hostility Questionnaire score [40]; ‡‡ Beck Depression Inventory score ≥13 at visit 1 [39]; ‖ tertiles.

Table 3: Six-year incidence of hypertension* by baseline characteristics: multivariate analysis.

Characteristic	OR (95% CI)†	P‡
Age (per year)	0.99 (0.95–1.04)	0.88
Body mass index (per Kg/m^2)	1.02 (0.98–1.07)	0.37
Smoking (packyears)§		0.67
0	1.0	
<5	0.98 (0.43–2.24)	
5–14	1.20 (0.50–2.89)	
≥15	2.04 (0.74–5.62)	
Family history of hypertension‖	1.63 (0.87–3.05)	0.13
Proteinuria¶		0.16
none	1.0	
micro-	1.39 (0.63–3.09)	
overt	3.00 (1.03–8.73)	
HDHQ score	1.06 (1.02–1.10)	0.001

* Systolic ≥140 or diastolic ≥90 mm Hg or antihypertensive medication; † odds ratio (95% confidence interval); ‡ P values; § quartiles; ‖ present versus absent; ¶ microalbuminuria versus none and overt proteinuria versus none.

Table 4: Six-year incidence of hypertension* by baseline characteristics: multivariate analysis.

Characteristic	OR (95% CI)†	P‡
Age (per year)	1.00 (0.95–1.05)	0.99
Body mass index (per Kg/m^2)	1.04 (0.99–1.09)	0.09
Smoking (packyears)§		0.51
0	1.0	
<5	0.71 (0.27–1.89)	
5–14	0.89 (0.34–3.32)	
≥15	1.93 (0.66–5.64)	
Family history of hypertension‖	1.54 (0.78–3.04)	0.21
Proteinuria¶		0.05
none	1.0	
micro-	1.74 (0.73–4.19)	
overt	3.75 (1.26–11.16)	
HDHQ score	1.08 (1.03–1.13)	0.002
BDI score ≥13**	0.64 (0.29–1.43)	0.28

* Systolic ≥140 or diastolic ≥90 mm Hg or antihypertensive medication; † odds ratio (95% confidence interval); ‡ P values; § quartiles; ‖ present versus absent; ¶ microalbuminuria versus none and overt proteinuria versus none; # Hostility and Direction of Hostility Questionnaire score [40]; ** Beck Depression Inventory score ≥13 at visit 1: depressed versus not depressed [39].

insulin dose ($P = 0.14$), level of education ($P = 0.30$), socioeconomic status ($P = 0.32$), alcohol abuse ($P = 0.09$), blood total cholesterol levels ($P = 0.23$), total cholesterol/HDL-C ($P = 0.16$), glycosylated hemoglobin values ($P = 0.11$), or being depressed ($P = 0.20$).

3.1.2. Multivariate Analyses. Multivariate logistic regression was used to evaluate the relative contribution of the baseline risk factors to the development of hypertension. Higher HDHQ scores and overt proteinuria were significantly and independently associated with the 6-year incidence of hypertension in this population (Table 3). This result was obtained whether or not depression was included in the model, suggesting that hostility makes a contribution to incident hypertension that is independent of depression (Table 4). The set of predictors produced a significant improvement in fit (χ^2 (14) = 33.0, $P = 0.003$) over an intercept-only model, and the Hosmer-Lemeshow statistic was consistent with good overall fit (χ^2 (8) = 9.7, $P = 0.29$). The model also showed good discrimination, as indexed by ROC analysis (AUC = 0.65, 95% CI = 0.56, 0.73); however, while there was excellent specificity (92.3%), sensitivity was low (36.7%). Interestingly, while age, family history of hypertension, and years of smoking showed significant bivariate associations with incident hypertension, these factors did not make an independent contribution.

The analyses show a significant and independent association between baseline overt proteinuria and incident hypertension whether or not depression was included in the model (Tables 3 and 4). The association between

proteinuria and hypertension suggests a causal pathway in which proteinuria precedes hypertension. To support this causal inference, we conducted a logistic regression analysis, otherwise parallel to that shown above, in which baseline hypertension was used as predictor of incident proteinuria. Results showed a statistically and clinically similar 6-year incidence of overt proteinuria in patients with (14.5%) or without (12.3%) hypertension at baseline, even after adjusting for family history of hypertension. Thus, while overt proteinuria is a risk factor for the 6-year incidence of hypertension, hypertension is not a risk factor for the 6-year incidence of overt proteinuria.

4. Discussion

In the present study, we found that a high percentage (29.3%) of 280 African-Americans with type 1 diabetes, who had no hypertension at baseline, subsequently developed hypertension over a 6-year follow-up period. Baseline psychological (high HDHQ score) and medical (overt proteinuria) risk factors were found to be independent predictors for the development of hypertension in this cohort.

In white persons with type 1 diabetes, the 10-year incidence of hypertension was also found to be a high (25.9%) by Klein et al., albeit a lower rate than the 6-year incidence of 29.3% in our type 1 diabetic African-Americans [13]. It has been similarly reported that African-Americans with type 2 diabetes have a higher risk for developing hypertension than their white type 2 counterparts [5]. The apparent higher risk of hypertension in African-Americans compared with whites, particularly in those with diabetes, is incompletely understood though it is noteworthy that the etiology of hypertension is generally thought to be multifactorial and to include medical, lifestyle, psychological, and genetic factors [13, 17, 31, 49].

To the best of our knowledge, risk factors associated with the development of hypertension have not been previously examined in a large cohort of African Americans living with type 1 diabetes. When we examined possible medical risk factors, we found that baseline overt proteinuria was the only independent medical risk factor associated with developing hypertension in our African-American patients. In type 1 diabetic whites baseline proteinuria was also reported to be an independent predictor for developing hypertension [7, 13, 49]. While the time relationship between hypertension and proteinuria is not always clear, our data indicate that in this cohort overt proteinuria precedes rather than follows the development of hypertension since patients with and those without hypertension at baseline have a similar risk of having overt proteinuria at the 6-year followup (see results) [50]. It is noteworthy that a high 37% of our African American patients with <5 years duration of diabetes at baseline had developed proteinuria at the 6-year follow-up [51]. Not only are African Americans living with type 1 diabetes at a particularly high risk for diabetic nephropathy, but they also develop this complication relatively early after diagnosis of diabetes [51]. Thus, evaluating kidney function early after diagnosis of diabetes, and regularly thereafter, is critically important in African Americans living with type 1 diabetes in order to reduce morbidity and mortality from the disease [9, 12, 51].

Because African-Americans as a group are more likely to experience chronic sociocultural stressor, we were particularly interested in determining the respective role of psychological risk factors for hypertension [17, 27, 31, 52]. Our data show that a high hostility score on the HDHQ was significantly and independently associated with developing hypertension, even after adjusting for the traditional medical risk factors as well as for depression. While HDHQ and BDI measures showed significant levels of association ($r = 0.37$, df = 394, $P < 0.001$), that aspect of hostility which is related to incident hypertension does not appear to be related to depression, as depression was not associated with incident hypertension in this population (Table 3). Our data are in accord with a large literature suggesting that hostility may be a risk factor for cardiovascular disease and hypertension [14–31]. For example, Suarez and Williams showed that both men and women with high hostility scores on the Cooke Medley Hostility scale responded to a solvable anagram task—during which they were harassed—with greater diastolic blood pressure, greater forearm blood flow, and prolonged systolic blood pressure [23, 53]. They went on to demonstrate that high hostility individuals also had significantly enhanced and prolonged plasma norepinephrine and cortisol responses compared to low hostility subjects [54].

Also akin to the hostility findings of the present study is a 4-year follow-up study of 537 normotensive Finnish men [55]. In that study, each 1-point increase in anger-out on the Spielberger Anger Expression scale was associated with a 12% increase in the risk of developing hypertension [55]. Similarly, Bleil et al. found in 237 men with untreated hypertension that trait anger, anger temperament, and a propensity to express anger outwardly (anger-out) on the Spielberger scale were associated with heightened carotid atherosclerosis as measured by B-scan ultrasonography [56]. African-Americans may be more likely than whites to experience chronic sociocultural stressors and associated suppressed anger. For instance, in African-Americans living in high-stress areas in Detroit, suppressed anger was shown to be associated with elevated blood pressure [57].

In the present study, baseline years of smoking were significantly associated with the development of hypertension on bivariate analyses as previously reported in other studies [58, 59]. In a recent study, smoking in persons with mental illness was significantly associated with the development of hypertension [57]. Smoking is a known risk factor for cardiovascular disease, including coronary disease and stroke [60]. In this regard, it is noteworthy that smoking has been reported to increase arterial stiffness, promote atherosclerosis and inflammation, and lead to alteration in blood rheology [61]. However, smoking was no longer significant in the multivariate analyses because of its significant association with both the HDHQ score and proteinuria (data not shown). Similarly, age, family history of hypertension, and body mass index were not independent risk factors for incident hypertension because of their significant association with overt proteinuria (data not shown).

Strengths of the present study include that the sample is a large cohort of African-Americans living with type 1 diabetes; patients were followed for a mean of 6 years; both medical, lifestyle, and psychological risk factors were examined; a detailed medical history was obtained; standardized questionnaires were used to evaluate psychological factors; retinopathy severity was graded in a masked fashion on two separate occasions.

Limitations of the present study include that we did not have African-Americans without diabetes serving as a control group. Furthermore, at the time of followup, 139 patients had died, and many patients included in the study were young. Therefore, the incidence of hypertension may be underestimated. Also blood pressure measurements were made on one single rather than on two separate visits, and there were no at-home or ambulatory measures of blood pressure [37]. Thus, the possibility of hypertension status misclassification exists. However, blood pressure was obtained by a certified technician using a standardized protocol and the random zero sphygmomanometer, a period of resting time was observed before and in between measurements, and measurements were repeated when there was a discrepancy in the results. Also, we used the cutoff score of $\geq$140 and/or $\geq$90 mm Hg for systolic and diastolic hypertension, respectively, which is higher than the target blood pressure of <130/80 mm Hg recommended for hypertensive patients with diabetes [37]. Due to time constraints, a battery of anger and anxiety measures was not administered. HDHQ scores measure trait rather than state hostility and thus are unlikely to be unduly impacted by diabetic complications. Finally, our patients were initially recruited from among patients admitted to hospital at some time during their life and may thus have more severe disease than persons living with type 1 diabetes but were never admitted to hospital. Thus, we cannot conclude that our findings can be generalized beyond the population that was studied.

In summary, as far as we are aware, this is the first study reporting incidence rates of and risk factors for the development of hypertension in a large population of African-Americans living with type 1 diabetes. The results show that both medical risk factors—overt proteinuria—and psychological risk factors—high hostility score—may play a role. Thus, the results suggest the possibility of a multifactorial model for the development of hypertension in type 1 diabetic African-Americans. The potential impact of the findings in terms of clinical intervention might include the early identification of modifiable risk factors, which may be helpful in reducing the morbidity and mortality associated with diabetes.

Abbreviations

AER: Albumin excretion rate
BDI: Beck Depression Inventory
CI: Confidence interval
HDHQ: Hostility and Direction of Hostility Questionnaire
OR: Odds ratio
SD: Standard deviation.

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Conflict of Interests

The authors declare there are no Conflict of Interests.

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Review Article

Changes in the Perceived Epidemiology of Primary Hyperaldosteronism

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Primary aldosteronism has been considered a rare disease in the past years, affecting 1% of the hypertensive population. Subsequently, growing evidence of its higher prevalence is present in literature, although the estimates of disease range from 5 up to 20%, as in type 2 diabetes and resistant hypertension. The main reasons for these variations are associated with the selection of patients and diagnostic procedures. If we consider that hypertension is present in about 20% of the adult population, primary aldosteronism can no longer be considered a rare disease. Patients with primary aldosteronism have a high incidence of cardiovascular, cerebrovascular and kidney complications. The identification of these patients has therefore a practical value on therapy, and to control morbidities derived from vascular damage. The ability to identify the prevalence of a disease depends on the number of subjects studied and the methods of investigation. Epidemiological studies are affected by these two problems: there is not consensus on patients who need to be investigated, although testing is recommended in subjects with resistant hypertension and diabetes. The question of how to determine aldosterone and renin levels is open, particularly if pharmacological wash-out is difficult to perform because of inadequate blood pressure control.

1. Introduction

The history of primary aldosteronism (PA) is that of an uncommon cause of hypertension until up to 15 years ago. In 1954, Conn studied a 34-year-old female with high blood pressure, severe hypokalemia, and mild hypernatremia, discovering an averaged 22-fold higher mineralcorticoid activity per day in comparison with normotensive controls: this clinical condition reversed after the removal of a right adrenal mass. Thereafter, Conn stated in his presidential address "*It is believed that these studies delineate a new clinical syndrome which is designated as primary aldosteronism*." Primary aldosteronism, as defined by Conn in 1955 [1], was widely thought to be present in approximately 1% of hypertensive patients [2, 3]. Today primary aldosteronism can be defined as a group of different disorders (Table 1), "*in which aldosterone production is inappropriately high, relatively autonomous from the renin-angiotensin system, and non suppressible by sodium loading*" [4]. Several studies suggest that PA is the most common cause of secondary hypertension, although the prevalence is variable from 5 to 20%, depending on patient selection and methods of diagnosis. There are changes in the perceived epidemiology of the disease because as Gordon observed "*normokalemic primary aldosteronism has been known for 50 years, always there, but not recognized because patients were not tested for it*" [5]. Recent studies highlight that only a minority of patients with PA presents with hypokalemia and normokalemic hypertension is the most common presentation of the disease, particularly in the case of idiopathic hyperaldosteronism (IHA). Variability in the prevalence of PA can be due to differences in aldosterone to renin ratio (ARR) cutoff values, defects in the use of functional tests, or suboptimal sampling conditions such as the maintenance of some medications or bias in the selection of patients. Strong evidence supports the hypothesis that aldosterone plays a pivotal role in hypertension, even if the classical diagnosis of primary aldosteronism cannot be made. Finally, is the diagnosis of aldosteronism essential in the strategies we need to adopt in treating high blood pressure and related comorbidities?

Table 1: Subtypes of primary aldosteronism [6].

Aldosterone-producing adenoma (APA)—35% of cases
Bilateral idiopathic hyperplasia (IHA)—60% of cases
Primary unilateral adrenal hyperplasia—2% of cases
Pure aldosterone-producing adrenocortical carcinoma—<1% of cases
Familial hyperaldosteronism
Type I = glucocorticoid remediable aldosteronism—<1% of cases.
Type II = familial APA or IHA—<2% of cases.
Ectopic aldosterone-producing adenoma or carcinoma—<0.1% of cases

2. Materials and Methods

2.1. Data Sources and Searches. We conducted a search on the PubMed database for epidemiological studies on primary aldosteronism using terms to identify clinical settings as follows: ([Primary Aldosteronism] AND [epidemiology] AND [hospital setting] OR [general population] OR [essential hypertension] OR [refractory hypertension] OR [diabetes] OR [aldosterone antagonist] OR [angiotensin II receptor antagonist] OR [angiotensin converting enzyme inhibitors]). The search was limited to articles published up to February 2011. A subsequent search was performed for clinical trials using terms for identification as follows: ([aldosteronism] AND [target organ damage] OR [heart] OR [kidney] OR [endothelium] OR [mesangium]). Clinical trials with an active treatment period of ≥4 weeks were included.

3. Aldosterone and Hypertension

Mineralcorticoid antagonists are extremely efficient in the treatment of hypertension [7]. Eplerenone is able to reduce blood pressure in unselected patients with mild to moderate hypertension [8], with an add-on effect if patients are treated with ACEi [9], and its effect on uncontrolled hypertensive patients on ACE-I or ARB was not predicted by the baseline value of aldosterone/PRA (ARR) ratio [10]. Of note, aldosterone receptor antagonists need to be used with care, because they can induce an increase of potassium especially if renal function is impaired. In the case of renin angiotensin aldosterone system (RAAS) inhibition monotherapy, mineralcorticoid antagonists increase the level of potassium marginally but, in the case of dual RAAS inhibition, when associated with ACEi/ARB, a higher incidence of serum potassium >5.5 mmol/L has been reported in up to 5.6% of patients [11]. Amiloride blocks the epithelial-sodium channel (ENaC) as an indirect aldosterone antagonist, opposing the upregulating action of mineralocorticoids on this transport and, consequently, reduces the sodium and fluid overload. The addition of amiloride in the therapy for resistant hypertension can induce a significant blood pressure decrease in low-renin hypertensive patients [12]. Is it aldosteronism or inappropriately high levels of aldosterone?

A method for answering this question is another question: are aldosterone levels able to predict future hypertension, supporting a causal role? The Framingham Offspring Study reported that serum aldosterone levels predicted the development of hypertension in normotensive subjects [13] and high ARR is predictive of the worsening of hypertension. The study of Newton-Cheh and coworkers [14] analyzed the 3-year followup of 607 normotensive individuals participating in the Framingham study, revealing that 34.2% experienced BP progression and 16% developed hypertension. Dividing patients into quartiles of ARR, the upper quartile was associated with an 89% increased risk of blood pressure progression and a 53% increased risk of hypertension. They also observed that ARR was hereditary and a modest correlation with chromosome 11p was reported. The effect of aldosterone is not associated exclusively with sodium retention, but with a multitude of profibrotic and proinflammatory effects, and its blockade induces a 40% reduction of urinary excretion of type IV collagen [15] and of glomerular mesangial injury [16]. From these considerations, we proceed to the concept that aldosterone per se has a critical role in a significant number of patients with hypertension.

4. Epidemiology of Primary Aldosteronism

If we consider the relationship between primary aldosteronism and hypertension, we are moving into the field of awareness that increased levels of aldosterone in relation to normal range are an important cause of secondary hypertension (Table 2). How frequent is primary aldosteronism? The Harvey Lecture of Conn held in 1967 reports "*While we were theorizing about the possible existence of normokalemic primary aldosteronism and before we have actually described it, we had suggested on the basis of autopsy report and other indirect evidence, that primary aldosteronism could actually involve as many as 20 percent of people with "essential hypertension." Although our own work in this regard is far from complete, it appears that the determined value will not be as high as predicted. At present 10 percent appear to be more realistic*" [17].

At the beginning of the 1990s, Gordon et al. reported that 12% of 52 individuals enrolled in a hypertensive drug trial were positive for primary aldosteronism. The diagnosis was made after the determination of ARR and by using a suppression test, namely, fludrocortisone acetate administration plus oral salt loading. Remarkably, none of the 6 patients in this study presented hypokalemia. The study concluded that "*The incidence of primary aldosteronism is probably much higher than the 1% currently quoted in texts, with earlier, normokalemic forms accounting for the majority of cases*" [18].

Table 2: Epidemiology study on primary aldosteronism.

Author	Ref.	Clinical setting	Number of Patients	Type of study	Diagnostic Criteria	Confirmatory test for PA	Prevalence
Conn 1967	[17]	Hypothesis					10%
Fishman et al. 1969	[2]	Hospital	90 EH	Prospective	Increased aldosterone or suppressed PRA levels	No	<1%
Gordon et al. 1990	[18]	Hospital	52 EH	Prospective	ARR	Yes	12%
Gordon et al. 1994	[19]	Hospital	199 EH	Prospective	ARR	Yes	8.5–12%
Fardella et al. 2000	[20]	Hospital	305 EH 205 NT	Prospective	ARR > 25	Yes	9.5%
Newton-Cheh et al. 2008	[14]	General pract.	3326 EH	Retrospective	Aldosterone/plasma renin > 26 ng/L mU/L	No	7.9–31.1%
Olivieri et al. 2004	[21]	General pract.	412 EH	Prospective	Aldosterone/active renin > 32 pg/mL	No	32.4%
Rossi et al. 2006	[22]	Hospital	1125 EH	Prospective	ARR > 25	Yes	11.2%
Williams et al. 2006	[23]	Hospital	347 EH	Prospective	ARR > 25	Yes	3.4%
Calhoun et al. 2002	[24]	Hospital—RH	88 EH	Prospective	PRA < 1 ng/mL/h u.Aldosterone > 12 pg/24 h	Yes	20%
Gallay 2001	[25]	Hospital—RH	90 EH	prospective	ARR > 100	Yes	19%
Strauch et al. 2003	[26]	Hospital—RH	402 EH	prospective	ARR > 100	Yes	19%
Di Murro et al. 2010	[27]	Hospital—OSA	325 EH	prospective	ARR > 40	Yes	33.9%
Mukherjee et al. 2010	[28]	Hospital—diabetes	100 EH	prospective	ARR > 550 Aldosterone = pmol/L	Yes	13%
Unpierrez et al. 2007	[29]	Hospital—diabetes	100 EH	prospective	ARR > 30	Yes	14%

RH: resistant hypertension; OSA: obstructive apnea syndrome; EH: essential hypertension; NT: normotensive patients; ARR: aldosterone/plasma renin activity.

One year later, in 1994, the same authors reported in 199 patients referred to the Hypertension Clinic of Brisbane a prevalence of 8.5% up to probably 12% [19]. The characteristics of these patients were hypertension and normokalemia; that is, the diagnosis was made in patients without a clinical suspicion of primary aldosteronism. The cutoff value of serum aldosterone/plasma renin activity ratio (SA/PRA = ng/dL/ng/mL/h) could be a bias in the diagnosis of PA. Some years later, Fardella et al. [20] used two cutoffs for SA/PRA ratio: a ratio greater than 25 was defined as a high level, while a ratio greater than 50 corresponded to a very high level. Diagnosis of probable PA was made for an SA/PRA ratio >25 without other criteria, while diagnosis of highly probable PA was established for a ratio higher than 50. To confirm the diagnosis, the fludrocortisone test was performed while the differentiation test for glucocorticoid-remediable aldosteronism (GRA) was made using the dexamethasone test, with determination of 18-hydroxicortisol and genetic detection of the chimeric gene responsible for GRA (aminoacid substitution S288G and V320A in the CYP11B1 gene). The study was based on 305 unselected essential hypertensive (EH) patients and 205 normotensive controls. Hypertensive patients showed higher levels of SA and SA/PRA ratio than controls. In EH patients, the diagnosis of primary aldosteronism was made for 29 patients, corresponding to 9.5%; 13 patients had very high SA/PRA ratio and fludrocortisone testing confirmed the diagnosis in all of them; the other 16 patients were defined at the beginning as probable PA. The diagnosis of probable PA was made on a total of 31 patients corresponding to 10.2%. Probable PA was defined as normal aldosterone levels but SA/PRA ratio >25 or elevated aldosterone levels and normal SA/PRA ratio. Fludrocortisone testing confirmed the diagnosis of PA in 16 patients. 34.5% of patients with PA had a positive dexamethasone test, but elevated 18-hydroxycortisol levels were present in only 2 subjects. In all of the 29 patients with PA, plasma potassium was normal, demonstrating that hypokalemia can no longer be considered as a requisite for the diagnosis of primary aldosteronism. In normotensive controls, PA was diagnosed in 3 cases (1.46%). In summary, the Fardella study demonstrated a prevalence of 9.5% of PA in unselected EH and reported the limited utility of dexamethasone test in discriminating GRA. Their conclusions pointed to the need for a routine determination of SA and PRA in all essential hypertensive patients and that serial determination of 18-hydroxycortisol levels should be performed in positive cases.

This study was performed in a university setting; therefore, the difference with the general population can be considerable.

More recently, the Framingham Offspring Study [14] reported aldosterone/plasma-renin concentration ratio exceeding 26 ng/L per mU/L in 7.9% and 23.1% of untreated hypertensive men and woman, respectively, and in 24.6% and 31.1% of men and woman on β-blockers. In this study, ARR was measured only once, sodium intake was not standardized, and suppression tests were not executed;

therefore, a limit to this epidemiological observation was present, although it does reflect a large community-based investigation.

The Bussolengo Study [21] was carried out in a primary care setting. A sampling of 1462 patients referred by general practitioners, aged 35–74 years, were randomly selected and studied. 412 patients were identified as hypertensive (28.2%) and 287 gave their consent to blood analysis (69.6%). Direct active renin and aldosterone were measured in these hypertensive subjects. The aldosterone/active renin ratio (AARR) was considered positive for values >32 pg/mL, which corresponded to ARR > 50 ng/dL/ng/mL/h. This last cutoff has a relatively high sensitivity and specificity for the diagnosis of aldosteronism [30]. About one of three patients (32.4%) had an elevated AARR. The study cannot demonstrate clearly the prevalence of hyperaldosteronism in a general hypertensive population, because confirmatory tests were not performed and a prudent practice could be the repetition of AARR, but the suggestion that a large population can reap benefits from antialdosterone drug therapy does arise.

A large study was carried out by Rossi et al. [22] on 1125 hypertensive patients referred to 14 specialized hypertension clinics throughout Italy. Plasma renin activity and plasma aldosterone were measured at baseline and again 60 minutes after administration of 50 mg of captopril. The subjects then had a saline suppression test, and 126 patients were identified as presumed PA, corresponding to 11.2%. Taking into account patients with primary aldosteronism, an aldosterone producing adenoma (APA) was found in 54 of them, 43% of cases, with the remainder considered to have idiopathic hyperaldosteronism (IHA). Different results on PA prevalence were reported by Williams and coworkers [23]. They observed a low prevalence of primary aldosteronism in a group of 347 hypertensive volunteers: they analyzed ARR, plasma, and urine aldosterone, on different salt diet regimens. Only 3.4% of patients were diagnosed with PA. The large difference in prevalence with the other studies brings to light the question of patient selection, because subjects with plasma potassium <3.5 mEq/L were excluded, as well as patients with diastolic BP > 110 mmHg while on two or more medications. The analysis of these two last studies follows up on the question suggested by Kaplan [31]: is there really an unrecognized epidemic of aldosteronism? The Rossi study could be limited by a number of problems, as Kaplan observes, one of them being related to the fact that only one set of ARR was performed; on the other hand, the Williams study could have the bias that patients were excluded from the study on the basis of low plasma potassium and resistant hypertension. The bias of patient selection in the Williams study could be reasonably evoked, because it is clearly demonstrated that primary aldosteronism is more prevalent in essential hypertensives classified as stage 2 and 3 JNC VI [32].

Three years after Kaplan's observations, a recent study by Rossi [33] demonstrated that ARR has a good reproducibility, contrary to the previously claimed poor reproducibility [34].

As Gordon observes in answering the question "primary aldosteronism—actual epidemics or false alarm?," "*Epidemics is an inappropriate term*", but, at the same time, PA is not a "false alarm," because "*false alarm suggests that we can all relax again and get back to our real work*" [5]. In summary, the question of primary aldosteronism prevalence remains open. It seems reasonable to assert that PA can be present in up to 15–20% of hypertensive patients, depending on the population and methods of diagnosis used, as hereafter reported.

5. Primary Aldosteronism and Resistant Hypertension

Are there subgroups of essential hypertensive patients that more frequently can be diagnosed as affected by primary aldosteronism? The study of Mosso and coworkers [32] reports that the prevalence of PA confirmed with suppression test was diagnosed in 6.1% of 609 patients treated in primary care centers. Dividing all patients into groups based on blood pressure values and relating them to a control group, primary aldosteronism prevalence was 1.55% in normal subjects, 1.99% in Stage 1 hypertension JCN IV (SBP 140 to 159 mmHg, DBP 90 to 99 mmHg), 8.02% in Stage 2 (SBP 160 to 179 mmHg, DBP 100 to 109 mmHg), and 13.2% in Stage 3 (SBP > 180 mmHg, DBP > 110 mmHg) hypertension. Those having PA were younger and took a larger number of drugs for BP control. Of interest is the fact that only 1 out of 29 PA patients had mild hypokalemia, and the researchers explained the low frequency of reduced serum potassium levels as the result of screening and referral of these patients to secondary centers. Estimating the prevalence of hypokalemic PA close to 1.5%, they reported a total prevalence of 7.5%. But the point is that 13.2% of patients at hypertension Stage 3 JNC IV had PA. Calhoun and coworkers have studied 88 patients referred to a university clinic for resistant hypertension (hypertensive subjects requiring 3 or more different antihypertensive medications at pharmacologically effective doses) [24]. 20% of them had primary aldosteronism on the basis of suppressed plasma renin activity (PRA < 1.0 ng/mL/h) and high urinary aldosterone (>12 pg/24 h), in the presence of a high-sodium diet (>200 mEq/24 h). They were treated with spironolactone with a consistent and significant reduction of BP ($-26 \pm 15.7/-12 \pm 12.6$ mmHg). Gallay in Seattle reported a prevalence of PA in 17% of patients with resistant hypertension [25]; similarly, Strauch et al. in Europe [26] and Eide and colleagues have reported primary aldosteronism in 23% of patients with RH [35].

Although cause-and-effect has not been confirmed, it appears that the increased occurrence of primary aldosteronism may be linked to the increasing incidence of sleep apnea syndrome and obesity.

Di Murro and colleagues [27] reported a prevalence of 33.9% of primary aldosteronism in hypertensive patients with sleep apnea syndrome. Pratt-Ubunama and coworkers reported 85% prevalence of obstructive apnea syndrome (OSA) in resistant hypertensive patients, and serum aldosterone levels were higher than in patients with OSA without resistant hypertension [36]. Patients with upper body or

visceral obesity frequently have elevated plasma aldosterone levels, but the mechanism is unknown. An increased aldosterone secretion could be secondary to a decreased secretion of atrial natriuretic peptide, which seems to be reduced in the case of obesity [37].

6. Primary Aldosteronism and Diabetes

Type 2 diabetic patients are frequently affected by hypertension, and approximately 50–75% fail to achieve satisfactory blood pressure control [38]. This is one cause of the high incidence of cardiovascular complications, such as heart failure, stroke, and kidney disease. A close relationship between aldosterone and insulin resistance has been demonstrated: hyperinsulinemia stimulates the production of aldosterone, and an excess of mineralocorticoids can cause the resistant hypertension observed in diabetic patients. Mukherjee and coworkers [28] have studied prospectively 100 Asian type 2 diabetic patients with uncontrolled hypertension and have analyzed ARR ratio. Those with a ratio >550 pmol/L/ng/mL/h underwent a confirmatory saline test, and, in the case of high aldosterone levels, imaging investigations and adrenal vein sampling were performed. Thirteen patients (13%) were diagnosed with primary aldosteronism; their blood pressure was significantly higher, 46% had plasma potassium levels lower than 3.5 mmol/L, and 62% of them had a surgically correctable form of PA. The limitation of this study was linked to the difficulties in safely withdrawing antihypertensive medications; therefore, a false negative ratio could be present and the saline test to indentify these was not performed on all patients. Consequently, a higher prevalence of PA may have been present in this population. Another report by Umpierrez and colleagues [29] screened 100 patients with type 2 diabetes and resistant hypertension, measuring ARR and performing confirmatory salt load tests in subjects with a ratio >30 ng/dL/ng/mL/h. They observed an increased ARR in 34% of patients, and 14% of them had primary aldosteronism. These results have a potentially great impact, because, for each 10 mmHg decrease of systolic BP, there is a 13% reduction of microvascular complications, a 12% decreased risk of fatal and nonfatal myocardial infarction, and a 17% decreased risk of death [39]. From these data arises the recommendation to investigate primary aldosteronism in all patients with type 2 diabetes and resistant hypertension, because its identification could have a tremendous impact on achieving BP control and consequently on decreasing cardiovascular complications and mortality.

7. Primary Aldosteronism and Target Organ Damage

The detection of primary aldosteronism is central in the study of essential hypertension for at least two reasons: the first is linked to therapeutic strategies, such as the indication for surgical procedures in the presence of adenoma or the use of mineralcorticoid antagonists. The second is the observation that cardiovascular and cerebrovascular complications may be more common in the case of PA.

Milliez and colleagues reported that the stroke rate was 12.9% in PA subjects, compared to 3.4% observed in a control group matched for age, gender, and blood pressure levels [40]. They also observed a higher incidence of myocardial infarction and atrial fibrillation in PA subjects. Catena and coworkers [41] have studied 54 patients with PA and compared left ventricular mass (LVM) and function before and after treatment with a group of 274 patients with essential hypertension. At baseline, the groups were similar in clinical characteristics and blood pressure control, but significantly higher LVMi were observed in patients with aldosteronism. Decreased diastolic function was also reported. After one year of treatment, significant reductions of blood pressure and LVMi were present, and after an average period of 6.4 years of followup, LV mass further decreased, but not BP. The percentage reduction of LVMi was higher in patients with idiopathic hyperaldosteronism who underwent medical therapy than in the adenoma-producing aldosterone group, who were surgically treated. The cardiac changes observed in the period between one year and the end of study lead us to suppose that factors other than volume stress, which can result from the renal effects of aldosterone, or blood pressure are responsible for these changes. The activation of cardiac receptors might play a role in left ventricle hypertrophy and remodeling. It is known that interactions of aldosterone with angiotensin, endothelin, or bradykinin activate inflammatory cells and fibroblast proliferation, leading to collagen synthesis. Independently of blood pressure, aldosterone exerts detrimental effects on small vessels, such as pronounced fibrosis, and on heart geometry and function. The result of an increased fibrosis [42] explains the failure in diastolic function.

Clinical outcome in terms of myocardial infarction, stroke, revascularization procedures, and sustained arrhythmias was analyzed by the same authors after 7.4 years [43]. Before the beginning of treatment, at basal time, a history of cardiovascular events was present in 34% of patients with PA, significantly higher than the 11% registered in essential hypertension group. After treatment, at the end of followup, endpoint was reached in 19% of patients with PA, and 18% of essential hypertensives, demonstrating the importance of correction of hyperaldosteronism.

Of interest is the study of the German Conn's Registry [44]: a population of 553 patients with PA was investigated, of which 56.1% had hypokalemia. They differed from normokalemic patients because of higher BP levels, but therapeutic strategies were not different between the groups. Aldosterone was significantly higher in patients with low potassium levels, and a correlation with the prevalence of vascular comorbidities was observed. The prevalence rate for cardiovascular events, such as angina or cardiac insufficiency, was higher in the hypokalemic group.

A larger work [45], the Ludwigshafen Risk and Cardiovascular Health (LURIC) study, analyzes comorbidity and survival in a group of 3153 patients with ischemic heart disease who underwent coronary angiography. The study evaluated ARR, and 3.1% of patients had a ratio >50. After the division in quartiles on the basis of plasma aldosterone concentration, hazard ratio (HR) of all-cause death was higher

for quartiles with higher ARR. In fully adjusted analysis, patients of the fourth quartile had an increased risk of fatal stroke (HR = 7.02). Again, this study addresses the question of primary aldosteronism or elevated levels of aldosterone and points out the need to consider mineralcorticoid antagonists in medical treatment strategies. Some populations benefit from aldosterone antagonist therapy: this is true not only for hypertensive patients with primary aldosteronism, but also in patients with heart failure and chronic kidney disease. However, patients in these last two groups must be carefully observed for the development of potentially fatal hyperkalemia. The RALES trial demonstrates that, when added to ACEi, aldosterone receptor antagonists decreased mortality by 30% in NYHA class III and IV over a period of 24 months [46]. The addition of eplerenone or spironolactone in diabetic patients with proteinuria to ACEi or angiotensin receptor antagonists seems to reduce protein excretion, which is a causative factor of kidney disease progression [47].

8. Summary

The prevalence of primary aldosteronism cannot be precisely determined at this time. It is significantly more common than previously thought, representing probably the most common cause of secondary hypertension. Changes in the perceived epidemiology of PA are the consequence of increased investigations in normokalemic hypertensive patients, and this represents an evolution from the historical definition of the disease. Using plasma aldosterone to plasma renin activity ratio followed by aldosterone suppression tests, the prevalence in hypertensive patients can be estimated in the range of 5–12%. A higher prevalence up to 15–20% is highly probable in selected patients, such as those with type 2 diabetes and refractory high blood pressure or sleep apnea syndrome. In these populations, the study of aldosterone should be considered as routine in the flowchart of diagnostic procedures and hypokalemia should not be a determinant in the screening process. The identification of primary aldosteronism has a significant prognostic value, because these patients are subject to increased cardiovascular risk, which can be reduced by proper medical or surgical treatment, depending on the cause, be it idiopathic or due to adenoma.

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Research Article

Hypertension, Periodontal Disease, and Potassium Intake in Nonsmoking, Nondrinker African Women on No Medication

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The purpose of this cross-sectional study was to investigate the association of periodontitis and/or tooth loss with hypertension by excluding the common confounders. Eighty-one Tanzanian women who were aged 46–58 years, nonsmokers, nonalcoholic drinkers, and on no medication underwent clinical examination. Multiple-regression analysis showed that the severity of periodontitis was significantly correlated with increased systolic blood pressure and diastolic blood pressure. Simple-regression analysis indicated that the severity of periodontitis was inversely correlated with 24-hour urinary excretion of potassium ($r = -0.579$, $P = 0.0004$) and also inversely with the frequency of intakes of green vegetables ($r = -0.232$, $P = 0.031$) and fruits ($r = -0.217$, $P = 0.0043$). Low-potassium intake in the diet mostly accompanied by low dietary fiber intake increases BP as well as periodontal inflammation. Potassium intake may be an important factor linking periodontitis and hypertension in middle-aged nonsmoking and nonalcoholic women on no medication, although chronic inflammation such as periodontitis may cause hypertension through a more direct mechanism.

1. Introduction

Periodontitis, which affects a large number of adults globally, is epidemiologically related to atherosclerotic vascular diseases and metabolic syndrome [1, 2]. Periodontitis as chronic inflammation destroys the supporting structure of the teeth and increases the level of C-reactive protein (CRP) [3–5]. Recent attention has focused on elevated serum CRP, a marker of systemic inflammation, as a strong and independent risk factor or predictor of hypertension (HT) [6]. The systemic response to periodontal infection is a possible pathway underlying the observed association between periodontitis and increased risk for HT.

Epidemiological systematic examinations about the noted relationship between periodontitis and vascular diseases should be conducted among healthy subjects who have never smoked [7] because smoking is regarded as a strong confounder and may spuriously inflate the association between periodontitis and vascular diseases. Alcohol consumption is also one of the risk factors that can lead to the development of not only HT [8] but also periodontitis [9]. In nonsmoking menopausal Japanese women, tooth loss but not periodontitis was proven to be significantly associated with an increased risk of HT [10]. Medical care is also a confounding variable that strongly affects epidemiological studies in developed countries such as Japan, where epidemiological analysis on the association between vascular diseases and oral health may be complicated by the common use of certain antihypertensive medications that affect not only blood pressure (BP) but also oral health status [11]. In order to avoid these confounders, we selected middle-aged African women on no medication, who were nonsmokers and did not consume

Table 1: Basic characteristics of participants.

Parameter	Women ($n = 81$)
Age (year)	52.09 ± 3.92
SBP (mmHg)	139.93 ± 26.60
DBP (mmHg)	80.33 ± 20.80
BMI	28.57 ± 6.69
Total-C	5.33 ± 1.23
TG	1.63 ± 0.93
HDL- C	1.34 ± 0.39
HbA1c	5.22 ± 1.43
Vegetables (days/week)	4.20 ± 2.32
Fruit (days/week)	3.74 ± 1.47
Periodontitis	2.37 ± 0.66
Tooth loss	3.70 ± 3.81

Values are presented as mean ± standard deviation (SD). BMI: Body Mass Index (body weight/height^2, kg/m^2), Total-C: serum total cholesterol (mmol/L), TG: triglycerides (mmol/L), HDL-C: high-density-lipoprotein cholesterol (mmol/L), and HbA1c: glycosylated hemoglobin (%). Vegetable and fruit intakes are expressed as the number of days per week when they were consumed. Periodontitis: the average CPTIN of each tooth. Tooth loss: number of teeth lost.

alcoholic drinks, and investigated the possible association of periodontitis and tooth loss with the risk factors for HT in the present study.

2. Methods

2.1. Study Design and Subjects. The present study was conducted in Tanzania according to the protocol for Cardiovascular Diseases and Alimentary Comparison (CARDIAC) Study coordinated by the World Health Organization (WHO) [12–14]. We previously reported associations between HT and its traditional risk factors such as body mass index (BMI), salt intake, and Na/K ratio in the CARDIAC study in Tanzania [14–18]. One hundred women aged 46–58, living in Temeke, Dar es Salaam, were randomly selected from an administrative list and invited to participate in the study by letter. Detailed oral examination was limited to women because of the higher prevalence of smokers and alcohol drinkers among men, who were therefore considered not suitable for analysis of the association of oral health with dietary factors [7]. Eighty-one women responded to the invitation for BP and anthropometrical measurements, 24-hour urine collection, blood sampling, dental examination, and lifestyle questionnaires. This study was approved by the Institutional Ethical Review Board of Muhimbili University College of Health Science. Written informed consent was obtained in accordance with the institutional rules.

2.2. Health Examination. In order to eliminate observer bias, BP was measured using a centrally calibrated automatic BP measurement system used for the CARDIAC Study (Khi machine) [12, 13]. BP was measured 3 times for each subject, and the average of the 3 measurements was used in this analysis. Blood was sampled after a 10–14 h fast. Urinary bags (U-container N, Ono Medical Company Osaka, Japan) were used for collecting 24-hour urine and the validity was confirmed by checking creatinine excretion [13]. Blood and urine samples for the CARDIAC Study were analyzed centrally at the former WHO Collaborating Center for Research on Primary Prevention of Cardiovascular Diseases, Graduate School of Human and Environmental Studies, Kyoto University, Kyoto, Japan. Details of other health examination methods were described in previous reports on the protocol and findings of the CARDIAC study in Tanzania [14].

2.3. Oral Examination. A single examiner (M.Y.) carried out, without knowing other health-related data, the oral examination including tooth count and the assessment of periodontitis, which was measured according to the WHO community periodontal index of treatment needs (CPITN). The specially designed WHO periodontal probe with a sensing force of not over 20 g was utilized. The ten teeth examined were 17, 16, 11, 26, 27, 47, 46, 31, 36, and 37; for each tooth, the highest index found was recorded according to the following scale: (0) periodontal health; (1) gingival bleeding; (2) calculus detected during probing; (3) pocket 4 to 5 mm deep; and (4) pocket 6 mm deep and over. Periodontal condition was reported as the average CPTIN condition of each tooth, the scoring for which is well established and regarded as the global standard measurement for epidemiological and screening studies on periodontitis [19–21].

2.4. Statistical Analysis. Data were analyzed using the program Statview 5 for microcomputers from the SAS Institute Inc. Simple correlation analysis using the Pearson method allowed the assessment of univariate relationships. The variables were regarded as normally distributed.

3. Results

In this study, we assessed the association of tooth loss and periodontitis with BP, and the traditional risk factors of HT in 81 women aged 46–58 years, whose basic characteristics are shown in Table 1. None of the subjects in this population was found to be using or have used drugs that affect lipid metabolism, BP, or blood sugar. Additionally, they had never smoked and never drunk alcohol because of their local Islamic religious discipline and culture.

In multiple-regression analysis, the severity of periodontitis was significantly correlated with systolic BP (SBP) ($r = 0.288$, $P = 0.018$) and diastolic BP (DBP) ($r = 0.293$, $P = 0.015$), and tooth loss (the number of teeth missing) was also significantly correlated with SBP ($r = 0.308$, $P = 0.010$) and DBP ($r = 0.417, P = 0.0005$) (Table 2). These results indicate that periodontitis and tooth loss are significantly and independently associated with increases in BP in nonsmoking middle-aged Tanzanian women. In addition, to assess the association between HT and periodontitis, participants were divided into 3 groups. The severely hypertensive (SBP > 180 or DBP > 110) group had a significant difference in the severity of periodontitis (CPITN, 2.82 ± 0.64; mean ± standard deviation (SD)) from the normal to borderline hypertensive BP (SBP < 160 or DBP < 100) group (2.29 ± 0.61, $P < 0.05$).

Table 2: Multiple-regression analysis of BP, periodontitis, tooth loss, and traditional risk factors possibly related to hypertension in middle-aged women.

Parameter	Systolic blood pressure (mmHg)		Diastolic blood pressure (mmHg)	
	β	P value	β	P value
Age (year)	0.103	0.364	0.051	0.649
BMI	0.270	0.024†	0.299	0.012†
Total-C	0.074	0.602	0.125	0.374
TG	0.187	0.545	0.099	0.452
HDL-C	0.081	0.165	−0.056	0.668
HbA1c	0.259	0.190	0.139	0.194
Periodontitis	0.288	0.018†	0.293	0.015†
Tooth loss	0.308	0.010†	0.417	0.0005‡

Values are regression coefficients (β) and P values. †$P < 0.05$, ‡$P < 0.001$.
Multiple correlation coefficient $|R| = 0.609$ for systolic blood pressure, $|R| = 0.621$ for diastolic blood pressure.

Table 3: Simple correlation coefficients between periodontitis and tooth loss with traditional risk factors possibly related to hypertension in middle-aged women.

	Periodontitis			Tooth loss	
Versus	r	P value	Versus	r	P value
NaCl (g/day)†	−0.179	0.329	NaCl (g/day)	−0.112	0.547
KCl (g/day)†	−0.579	0.0004§	KCl (g/day)	−0.204	0.265
Na/K	0.160	0.385	Na/K	0.081	0.660
Mg (mg/day)	−0.336	0.060	Mg (mg/day)	−0.273	0.131
Total-C	0.002	0.986	Total-C	−0.102	0.400
TG	−0.007	0.951	TG	−0.083	0.495
HDL-C	0.059	0.627	HDL-C	−0.114	0.345
BMI	−0.160	0.184	BMI	−0.271	0.022‡
HbA1c	−0.071	0.558	HbA1c	−0.158	0.189

Values are correlation coefficients (r), ‡$P < 0.05$, §$P < 0.001$.
24-hour urine ($n = 32$), blood chemistry and BMI ($n = 81$), and †24-hour urinary sodium and potassium excretions were measured and the intakes were estimated as the amount of chloride salt.

Next, we tested the association of periodontitis and tooth loss with traditional risk factors for HT in women (Table 3). There was a strong inverse correlation of 24-hour urinary excretion of potassium (Y; amount estimated as KCL) with severity of periodontitis (X) ($Y = 3.144 - .433X$; $r = -0.579$, and $r^2 = 0.34$, $P < 0.0004$), but not with tooth loss. No other risk factors were correlated significantly with periodontitis. On the other hand, tooth loss was significantly correlated with BMI ($r = -0.271$, $P = 0.022$) but not with the 24-hour urinary excretion of potassium. Since 24-hour urinary excretion was closely related to dietary intake of potassium-rich vegetables and fruit [22], these results suggest that nutritional factors, particularly potassium intake, were associated with periodontitis but not with tooth loss.

Therefore, we further assessed the relationship between dietary factors and periodontitis. There were significant negative correlations of the intakes of green vegetables ($r = -0.232$, $P = 0.031$) and fruit ($r = -0.217$, $P = 0.043$) with the severity of periodontitis in women (Table 4). These results indicate that the intake of potassium-rich foods, such as green vegetables and fruit, is associated with periodontitis. The intake of skimmed milk, but not whole milk, was significantly inversely correlated with the severity of periodontitis. This might be related to the preference for skimmed milk among vegetarians.

4. Discussion

In this study, we demonstrated that periodontitis and tooth loss were significantly associated with an increased risk of HT in middle-aged African women on no medication without any direct influence of smoking and drinking alcohol. HT is associated with increased levels of the markers of inflammation, including CRP and proinflammatory cytokines [6]. Periodontitis as chronic bacterial infection by Gram-negative bacteria is also associated with increased levels of inflammation-related markers such as CRP in circulation [3–5]. Recent studies suggest that everyday events such as chewing and brushing of teeth contribute more significantly to the cumulative exposure of the vascular system to oral bacteria [23]. Periodontal pathogens were identified in carotid atheromatous plaques obtained by endarterectomy from patients [24]. In periodontitis, bacteremia and/or endotoxemia may trigger a systemic inflammatory response that, in turn, may cause endothelial dysfunction and thus increase BP and accelerate atherosclerosis.

Table 4: Simple correlation coefficients between periodontitis and dietary intakes expressed by the frequency or the amount.

	Periodontitis	
Versus	r	P value
Vegetables (days/week)	−0.232	0.031†
Fruit (days/week)	−0.217	0.043†
Skimmed milk (mL/day)	−0.304	0.004†
Whole milk (mL/day)	−0.097	0.375
Coconut milk (mL/day)	0.119	0.273
Meat (days/week)	0.058	0.598
Fish (days/week)	0.052	0.637

Values are correlation coefficients (r), †$P < 0.05$.

One possible pathway is that periodontal infection induces systemic inflammation contributing to the development of HT. Endothelial dysfunction through periodontal infection-inflammation pathway [3, 25] might be the link between periodontitis and HT. The emerging evidence on the positive association of other inflammatory disorders, such as systemic lupus erythematosus [26] and rheumatoid arthritis [27], with increased HT risk, supports this as a plausible mechanism. The second pathway is that periodontitis might be associated with HT-related nutrients and foods. In this study, the severity of periodontitis but not the number of teeth lost was significantly and strongly associated only with daily potassium intake among the traditional risk factors related to HT, including nutrients, cholesterols, obesity, and diabetes. Moreover, we found that periodontitis was associated with less intake of potassium-containing foods, fruit, and vegetables. These results suggest that high consumption of potassium, possibly reducing the risk of HT, might decrease periodontitis severity and partially explain the association between periodontitis and HT.

The mechanisms on the possible causative links of periodontitis with potassium intake could be speculated. Firstly, potassium intake checked by 24-hour urinary excretion is associated with the consumption of vegetables and fruit [22], which may beneficially influence oral health [28]. Secondly, the tissue destruction in periodontitis is considered to be caused mainly by an aberrant inflammatory response involving prolonged release of neutrophil enzymes and reactive oxygen species. Potassium is reported to inhibit reactive oxygen species formation by human white blood cells [29] as well as to protect against hypertensive vascular injury and cardiac dysfunction, though, reducing reactive oxygen species in salt-induced experimental hypertension [30]. Vegetables and fruit are primary dietary sources of antioxidants, such as vitamins C and E. Intake of potassium-rich vegetables and fruit might help to prevent periodontitis by reducing free radicals and oxidative stress in periodontal tissue.

Previously, we reported that the mean levels of 8-hydroxydeoxyguanosine (8-OHdG), a marker of oxidative DNA damage in 24-hour urine samples, were significantly higher in hypertensive subjects than in normotensive subjects in Tanzania [31]. Our results suggested that a beneficial effect of the intake of potassium-rich vegetables and fruit on HT and periodontitis might be related to their roles in inflammation or oxidative stress, and that 24-hour urinary excretion of potassium might be a good biomarker for the risk evaluation of periodontitis as well as HT. The possibility that people with severe periodontitis who lose more teeth tend to eat less vegetables to absorb potassium, and therefore have higher BP, may be excluded because 24-hour urinary potassium excretion was significantly inversely related only with periodontitis but not with tooth loss.

Several limitations in the present study should be considered. First, the cross-sectional design basically precludes any causal inferences about the role of potassium intake between periodontitis and HT. Second, our analysis was carried out only once. Nevertheless, this study has several strengths. First, we controlled other major traditional risk factors, including potential confounders such as age, gender, race, diabetes, hypercholesterolemia, BMI, smoking, and alcohol consumption. The age range was limited to 46–58 years old to avoid the aging influence on HT and periodontitis. Second, the subjects were particularly suitable for the investigation of dietary influence on BP and oral health because they were on no medication and neither consumed alcohol nor smoked. Both of these are well-known confounders causing periodontitis as well as risk factors of HT. Third, to avoid examiner bias, oral examination was performed by a single examiner who was unaware of other health examination data. In addition, to provide an adequate assessment of the severity of periodontitis, CPITN was used as recommended by the WHO. CPITN score has become widely accepted as the method of choice for epidemiological and screening studies for periodontitis [19–21]. Fourth, nutritional assessments were carried out using not only a food frequency questionnaire but also biomarkers from 24-hour urine samples from African Muslim women whose dietary customs did not vary on a daily basis.

5. Conclusion

The present study demonstrated the association among dietary potassium intake, periodontitis, and HT. Low-potassium intake in the diet mostly accompanied by low dietary fiber intake increases BP as well as periodontal inflammation. Moreover, periodontitis may raise BP through chronic inflammatory and oxidative stress mechanisms. Therefore, oral health is important in reducing the risk of HT, and traditional dietary customs of consuming more potassium from vegetables and fruit are expected to decrease the risk of HT and periodontitis, both presently deteriorating the quality of life in the elderly, although this expectation remains to be proven by long-term intervention trials.

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Review Article

Associations between Ambulatory Blood Pressure Parameters and Cerebral White Matter Lesions

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Silent cerebral white matter lesions (WMLs) are a common finding on magnetic resonance imaging of the brain in the elderly. However, in patients with hypertension, WMLs tend to occur earlier in life and appear to be more severe. There is a body of evidence that supports the idea that WMLs in asymptomatic hypertensive patients should be considered a silent early marker of brain damage. It is known that ambulatory blood pressure monitoring (ABPM) correlates more closely with hypertension-related organ damage than office blood pressure. This paper focuses on the associations between blood pressure parameters obtained by 24-hour ABMP and cerebral WMLs.

1. Introduction

On ageing, a nonmodifiable cardiovascular risk factor, hypertension becomes the most important modifiable risk factor for developing cerebrovascular disease, including stroke, cerebral small vessel disease (lacunar infarcts, white matter lesions, microbleeds), and cognitive impairment or vascular dementia.

Silent cerebral white matter lesions (WMLs) are a common finding on brain magnetic resonance imaging (MRI) in the elderly. However, in patients with hypertension, WMLS tend to occur earlier in life and appear to be more severe. There is a body of evidence that supports the idea that WML in asymptomatic hypertensive patients should be considered a silent early marker of brain damage. Cerebral WMLS are an important prognostic factor for stroke, cognitive impairment, dementia, and death [1]. Although the pathogenesis of cerebral WML remains controversial, older age and hypertension are constantly reported to be the main risk factors [2, 3] (Figure 1). Hypertensive patients have a higher rate and extension of cerebral WML compared with normotensives [2, 4]. In addition, it has been shown that treated, controlled hypertensive patients have a lower prevalence of WML than both untreated and treated but not controlled hypertensive patients [4]. Data from interventional and prospective observational studies also suggest that appropriate antihypertensive treatment could efficiently prevent the development of WML and slow their progression [5, 6].

Twenty-four hour ambulatory blood pressure monitoring (ABPM) has become an important tool for improving the diagnostic and management of hypertension. It is known that ABPM more closely correlates with hypertension-related organ damage and has a closer association with cardiovascular events than office blood pressure (BP) [7]. The information provided by 24-hour ABPM includes daytime and nighttime BP profiles, day-night BP difference, morning blood pressure rise, and blood pressure variability. Studies have found associations between 24-hour ABPM parameters and hypertensive target organ damage, such as left ventricular hypertrophy, microalbuminuria, intima media thickness, retinal changes, pulse wave velocity, and silent brain damage (lacunar infarct, WML) (Figure 2) [8, 9]. We review current evidence on the relationship between 24-hour ABPM parameters and WML.

2. Relationship between 24-Hour, Daytime, and Nighttime ABP Values and Cerebral WML

The association between hypertension and WML has been established in cross-sectional [2, 4, 10–12] and longitudinal

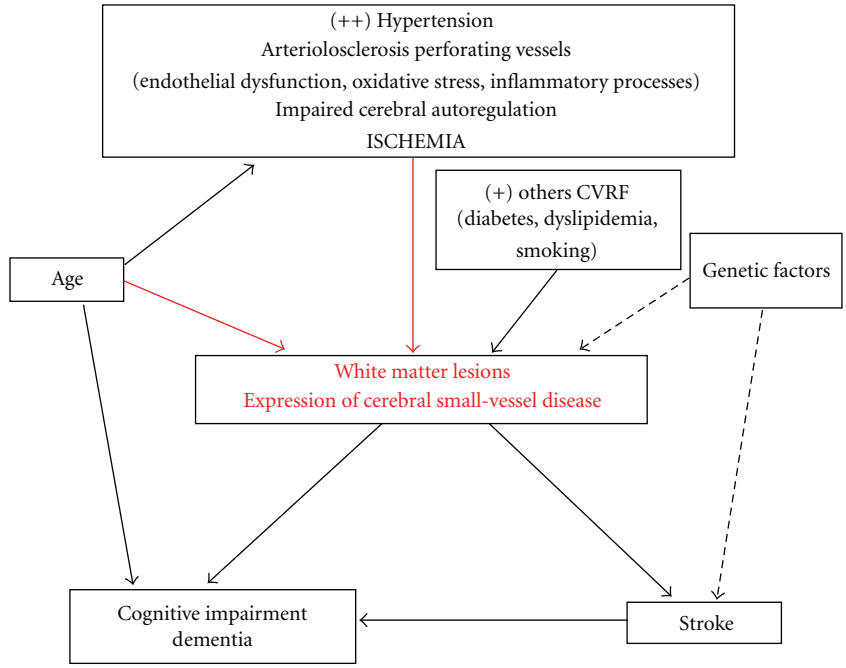

Figure 1: Pathogenesis and clinical significance of cerebral white matter lesions.

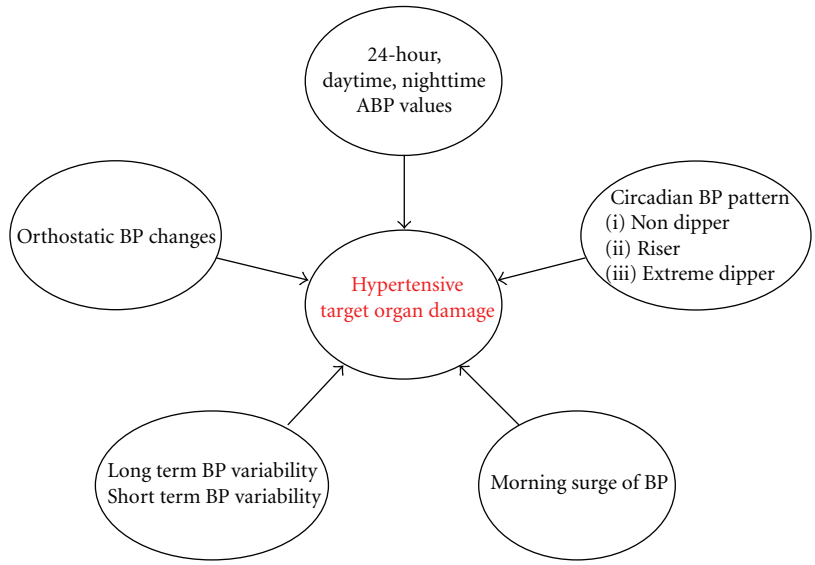

Figure 2: Associations among different ambulatory blood pressure parameters and hypertensive target organ damage.

studies [13–15]. However, some reports have suggested that this relationship is only evident when 24-hour ABPM is used to assess BP. Goldstein et al. [16] found a correlation between WML and office systolic, but not diastolic, BP, in a group of elderly normotensive subjects. Conversely, the severity of WML correlated with both systolic and diastolic BP measured by ABPM. In a group of mixed normotensives, "white coat" hypertensives, and sustained hypertensives, Shimada et al. [12] found a correlation between the number of lacunae and periventricular hyperintensities with 24-hour BP, but not with office BP. Sierra et al. [17] found a correlation between WML and both clinic BP and 24-hour ABPM in 66 untreated middle-aged hypertensive patients. In this study also higher BP values (including office, 24-hour, daytime were and nighttime estimates) in hypertensive patients with WML compared with those without [17] found.

In a recent study of 210 asymptomatic hypertensive patients (mean age: 52.5 ± 12.5 years) it was found that higher 24-hour, daytime, and nighttime BP levels were independently associated with WML volume (MRI semiautomatic volume quantification) [18]. WML volume and ABP levels,

whether daytime, nighttime, or 24-h, were continuous, without evidence of distinct thresholds, and continued down to BP levels within the normotensive range. The authors suggest that this dose effect of BP on WML, though cross-sectional, is supportive of a causal relationship between increasing BP levels and the development of WML.

One longitudinal study assessed the BP-WML relationship using ABPM [19] in 155 healthy elderly individuals (range: 55–79 years; mean age: 66.2) who were followed for five years, at which time a second 24-hour ABPM was performed in 121 subjects. The initial cross-sectional findings showed that in a sample of healthy subjects with relatively low BP levels (mean: 116.9/71.1 mmHg), men and women with casual BP in the upper ranges had a higher WML severity rating. Subjects whose casual or waking systolic BP remained high for five years relative to the group were more likely to exhibit higher WML volume during both phases of the study than the remaining study subjects, especially those whose initial low BP remained low.

Some studies have also shown an association between higher PP values (including office and ambulatory 24-hour, daytime, and nighttime estimates), a measure of arterial stiffness, and WML [17, 20]. In addition, it has recently been shown that brachial BP is associated with WML in the elderly [21].

3. Circadian Blood Pressure Patterns and Cerebral WML

The natural circadian BP rhythm typically includes a nocturnal decrease of 10–20% in BP compared with daytime, waking values. However, there is a moderate-to-marked loss of this reduction in nighttime BP in between 25% and 35% of hypertensive patients, a phenomenon that has been associated with excessive cardiac, vascular, renal, and cerebrovascular target organ damage [22].

Yamamoto et al. [23] studied 105 patients with lacunar infarcts who were followed for 3.2 ± 2.6 years and found that a high mean ambulatory BP, especially nighttime BP, and a reduced nocturnal BP dip, adversely affected the development of silent ischemic lesions (lacunar infarcts and WML) and symptomatic stroke.

In the aforementioned study by Goldstein et al. [16] of 144 healthy elderly individuals aged 55–79 years, it was found that subjects with the highest WML severity rating had higher casual, waking, and sleeping systolic BP, higher waking diastolic BP, higher waking systolic BP variability, and a smaller nocturnal fall in systolic and diastolic BP than individuals with less severe WML ratings. Sander et al. [24] studied 227 healthy subjects aged >55 years (44% hypertensive; 12% diabetic patients) and found that subjects with WML were significantly older, had a greater frequency of a history of hypertension, and had an elevated mean systolic daytime BP, a reduced systolic circadian BP variation, and an increased incidence of pathological nighttime BP increases. They found a significant correlation between systolic circadian BP variation and the extent of WML. Multiple regression analysis showed that this parameter was best correlated with the extent of WML. Kario et al. [25], in a study of 131 elderly hypertensives (aged ≥60 years), found that both nondippers and extreme dippers had significantly more silent cerebrovascular damage (measuring both lacunar infarcts and WML) than dippers. Similarly, Shimada et al. [26], who studied asymptomatic elderly hypertensives, observed no differences in cerebral abnormalities (lacunar infarct and WML) between the normotensive group and the dipping hypertensive group. However, hypertensive dippers had higher ambulatory BP than normotensive individuals and a larger BP reduction from day to night than both the normotensive and hypertensive nondipping groups. These findings suggest that a dipping profile may inhibit the development of cerebrovascular abnormalities.

One reason why marked nocturnal BP fall may be associated with cerebrovascular disease is that the lower BP limit of BP in the self-regulation of cerebral blood flow is shifted upward, especially in elderly hypertensive patients with brain damage. Marked nighttime BP falls could lead to an excessive reduction in cerebral perfusion. In the study by Kario et al. [25], some patients had been treated before the study, and a greater fall in nocturnal BP due to antihypertensive medication might have accelerated brain ischemia. Atherosclerosis may also be a link between excess nocturnal BP fall and cerebrovascular damage. In the same study [25], although both nondippers and extreme dippers suffered more extensive cerebrovascular damage (lacunar infarcts and WML) than dippers, there were no significant differences between extreme dippers and dippers in terms of cardiac hypertrophy and renal damage, whereas these types of target organ damage were more frequent in nondippers than in dippers. It appears that nondippers show greater hypertensive target organ damage than extreme dippers do. Therefore, as the authors suggest, sustained high BP over prolonged periods seems to be the most important determinant of hypertensive end-organ damage, whereas marked nocturnal BP falls may be more specifically related to cerebrovascular damage. Birns et al. [27] studied 88 hypertensive patients (mean age: 65 years) who were on antihypertensive therapy and optimally controlled, with preexisting hypertensive cerebrovascular disease (WML) and without a history of stroke, transient ischemic attack or syncope in the previous three months. Mean daytime/nighttime systolic BP values were 136.2 mmHg and 127.8 mmHg, respectively, and mean daytime/nighttime diastolic BP values were 77.7 mmHg and 71.1 mmHg, respectively. In the study it was found that a physiological fall in nighttime BP in these hypertensives was associated with greater WML volume which, in turn, correlated with impairments in reaction time and verbal fluency. However, the cross-sectional design could not establish causality, and therefore further studies are necessary.

In contrast, circadian rhythms were not related to WML in a small group of 66 middle-aged (mean age: 54 years) never-treated hypertensive patients [17], while in a group of 86 newly diagnosed hypertensive individuals (mean age 57.4 years; range 40–80), no relationship between diurnal BP rhythm and WML was found [20].

It is clear that the relationships between office, waking, and sleeping BP and cerebral vascular disease vary according to patient characteristics (age, normotensive/hypertensive,

asymptomatic/clinical cerebrovascular disease), the methodology used to evaluate WML volumes, and whether patients are receiving antihypertensive drug therapy. However, a body of evidence supports the idea that, in addition to increased daytime BP, raised sleeping BP and abnormal nocturnal BP reduction are associated with more severe WML.

The studies mentioned have not determined whether nondipping is the cause or consequence of cerebrovascular disease. Reductions in nocturnal BP falls might be secondary to site-specific cerebral injuries resulting in impaired central autonomic nervous system functioning. Kario and Shimada [28] presented a 79-year-old hypertensive patient whose diurnal BP pattern changed after a minor ischemic stroke (small lacunar infarct), suggesting that abnormal diurnal BP might originate from minor cerebrovascular ischemia. Some reports have shown that the level and variation of BP and/or heart rate might change in patients with overt cerebrovascular disease [29]. Korpelainen et al. [29] studied 40 brain infarction patients and 5 healthy controls and found that, in addition to increased sympathetic activity, brain infarction also seems to cause parasympathetic hypofunction. Goldstein et al. [16] investigated diurnal BP variation and subcortical MRI-T2 hyperintensities in 144 healthy individuals aged 55 to 79 years. Individuals with a higher prevalence of hyperintensities in the insular subcortex, which plays an important role in cerebral self-regulation, had higher 24-hour BP. In a study of a homogeneous sample of never-treated hypertensive patients aged 50–60 years, after exclusion for known risk factors for cerebrovascular damage such as diabetes or significant alcohol intake, it was found that subjects with WML had a blunted fall in nocturnal heart rate compared with those without WML [17].

Although some data seem to suggest that chronic ischemia caused by hypertension leads to disrupted diurnal BP variations through the impairment of cerebral self-regulation, resulting in nondipping in sleeping BP, most studies have been cross-sectional and, therefore, the direction of the relationship observed between some parameters and WML remains unclear. Larger, longitudinal studies will be needed to establish causality.

4. Blood Pressure Variability and Cerebral WML

Although BP variability has been associated with target organ damage in hypertension [30], the relationship with cerebral alterations remains unclear. Goldstein et al. [16] suggested a higher standard deviation of waking systolic BP in patients with more severe WML. In the aforementioned study by Kario et al. [25], it was found that extreme dippers had greater BP variability (standard deviation of waking systolic BP) and more WML and lacunar infarcts than dippers.

In one study it was found that asymptomatic middle-aged hypertensives with WML had significantly higher values of long-term systolic BP variability (standard deviation of 24-hour BP) measured by continuous beat-to-beat monitoring and ABPM, compared to those without WML. However, the differences were not independent of BP elevation and the significance was not maintained after adjustment for 24-hour systolic BP. There were no differences in short-term systolic BP variability or short-term or long-term diastolic BP variability in patients with and without WML [31]. Short-term BP variability was obtained by calculating the mean standard deviations of mean systolic and diastolic BP values for each 48 half-hour period (within half-hour standard deviation). Long-term variability was calculated by obtaining the mean 48 half-hour systolic and diastolic BP mean values and calculating the standard deviation of the mean (among half-hour standard deviation).

The two major determinants of BP variability are age and high BP, which are also major cardiovascular risk factors. Therefore, the significant impact of BP variability on cardiovascular disease seems to depend partly on age and high BP. Puisieux et al. [32] retrospectively reviewed computed tomography scans and 24-hour ABPM in 79 patients (mean age: 83 years) and found that higher WML scores were associated with increased blood pressure variability. To evaluate short-term BP variation, they determined the variability of systolic and diastolic BP (within-subject standard deviation of all readings over a 24-hour period), the coefficient of variability (variability of BP/mean BP), and the maximal BP variation (difference between the maximum and minimum 24-hour BP). Higher WML scores were associated with higher systolic BP in 24-hour, diurnal and nocturnal periods, higher maximal variation of systolic BP, greater variability of 24-hour diurnal and nocturnal systolic BP, and a greater coefficient of variability of systolic BP during sleep. They concluded that elevations and short-term variations in systolic BP may contribute to the pathogenesis of WML in the elderly. However, 50 of the 79 patients were suffering from dementia (30 Alzheimer's disease and 18 vascular dementia).

The longitudinal epidemiological Honolulu-Asia Aging Study of the risk factors for cardiovascular disease showed that midlife office systolic BP variability was associated with WML detected in late life in 585 males [33]. Excess systolic BP variability was defined as greater than average increases in BP measurements from up to 3 examinations over 6 years. The mechanism for these relationships is unknown. The authors suggest that a possible explanation could involve chronic periods of higher and lower systolic BP levels that overcome the self-regulation that maintains the blood flow in the cranial vessels. This variability could result in periods of relative ischemia in vulnerable areas. In fact, the deeper white matter tissues are supplied by terminal vessels in the brain and lack sufficient anastomoses with other vessels, and these tissues might be at higher risk from systolic BP variation.

5. Orthostatic Blood Pressure Changes and WML

In healthy subjects, BP variation due to posture-dependent changes is minimal due to self-regulation. In most hypertensive patients without autonomic nervous dysfunction, BP posture-dependent changes are also minimal. Orthostatic hypotension, often found in elderly hypertensives, is recognized as a risk for falls, syncope, cardiovascular events, and death [34–38].

Matsubayashi et al. [39] studied 334 community-dwelling adults aged >75 years and found that both postural hypotension and postural hypertension were closely related to WML and poorer neurobehavioral function scores. Subjects with more advanced WML had exaggerated postural changes in BP. Postural hypotension was defined as a reduction in systolic BP ≥20 mmHg and postural hypertension as an increase in systolic BP ≥20 mmHg using differences between the mean of two measurements of systolic BP while subjects were standing and supine, respectively.

Kario et al. [40] performed a head-up tilting test on elderly subjects with sustained hypertension as indicated by 24-hour ABPM. They were classified as having orthostatic hypertension (orthostatic increase in systolic BP of ≥20 mmHg ($n = 26$)), orthostatic hypotension (orthostatic systolic BP reduction of ≥20 mmHg ($n = 23$)), or being normal (neither pattern ($n = 192$)). The results showed that silent lacunar infarcts were more common in patients with orthostatic hypotension and hypertension than in normal subjects. Patients with orthostatic hypotension and hypertension had significantly greater BP variability (standard deviation of waking systolic BP) than normal subjects. The associations between orthostatic BP change and silent cerebrovascular disease remained significant after controlling for confounders, including ambulatory BP values.

These U-shaped associations between orthostatic BP changes and the prevalence of silent lacunar infarctions are consistent with recent data from the prospective, population-based ARIC study [41], in which it was found that orthostatic systolic BP and diastolic BP reductions were associated with an increased incidence of thrombotic and cardioembolic strokes in a linear fashion. In addition, both orthostatic systolic BP reductions and increases were associated with an increased incidence of lacunar strokes.

Postprandial hypotension has also been related to silent WML. Kohara et al. [42] evaluated BP changes after a meal by 24-hour ABPM in 70 hospitalized essential hypertensive patients aged ≥50 years. They found that the prevalence and severity of both lacunar infarcts and WML were significantly related to postprandial hypotension.

6. Morning Surge in Blood Pressure and Silent Cerebrovascular Disease

Normal morning BP surge is a physiological phenomenon, but an exaggerated morning BP surge is a cardiovascular risk. The association between the degree of morning BP surge and cardiovascular risk is not linear but rather has a threshold [9]. Cross-sectional studies have shown associations between target organ damage (left ventricular hypertrophy, microalbuminuria, intima media thickness, pulse wave velocity, silent lacunar infarcts) and morning surge in BP [9]. Vascular diseases of both the small and large arteries are considered to be not only consequences but also the leading cause of exaggerated morning BP surge, giving rise to a vicious cycle in the cardiovascular continuum [9]. Different pressor factors (aging, hypertension, glucose abnormality, alcohol intake, smoking, psychological stress, physical stress) are associated with morning BP surge. Diurnal variation and activation of neurohumoral factors that regulate the vascular tonus and cardiac output, such as the renin-angiotensin and sympathetic nervous systems, are suggested to be involved in diurnal BP variation and morning BP surge [9].

No studies have yet investigated the relationship between morning surge in BP and WML. However, in one study of 191 hypertensives (mean age: 76 years), an association between a higher morning surge in BP and silent lacunar infarcts, another form of hypertensive-cerebral small vessel disease [43] was found. Morning surge in BP was defined by subtracting mean systolic BP during the one hour with the lowest sleeping BP from mean systolic BP during the two hours after waking. Subjects were classified into 2 groups according to the morning surge in BP, with a cutoff value of 55 mmHg. The study compared the incidence of silent brain infarcts and overt stroke between the two groups and found that the group with a higher morning surge group showed a higher prevalence of silent brain infarcts after matching for age and 24-hour ambulatory BP (70% versus 49%; $P = 0.01$). In addition, patients were followed for a mean of 41 months, and a higher morning BP surge was associated with stroke risk independently of ambulatory BP, nocturnal BP falls, and silent infarct. In this study, 51% of the patients in the morning surge group were classified as extreme dippers. When a combination of dipping status (extreme-dippers, dippers, nondippers, and risers) and morning surge in BP was included in the same Cox regression analysis model, stroke risk was significantly associated with both morning surge in BP and with riser status [43]. In the model, extreme dipper status was not significantly associated with stroke risk independently of morning surge. The authors suggest that the fall in BP during the night appears to be of less importance than the morning surge. The mechanism underlying the increased stroke risk of extreme-dippers might depend on either an excessive morning surge of BP or on cerebral hypoperfusion due to low nocturnal BP.

7. Conclusions

On ageing, hypertension becomes the most important factor for cerebral WMLs, which are an important prognostic factor for stroke, cognitive impairment, dementia, and death. Strong evidence supports the idea that cerebral WMLs in hypertensive patients should be considered a silent early marker of brain damage.

The pathogenesis of WML remains unclear, but the main current hypothesis concerning the association between high BP and WML is that long-standing hypertension causes lipohyalinosis of the media and thickening of the vessel walls, with narrowing of the lumen of the small perforating arteries and arterioles that nourish the deep white matter. Low BP has also been reported to be a risk factor for WML.

As with other hypertensive target organ damage, ABPM 24-hour values also are related to the presence and severity of cerebral WML. In addition, in most studies an association between different forms of higher BP variability of BP and WML. However most of these studies have been cross-sectional has been found and, therefore, the relationship observed between some parameters and the presence of

WML is an association whose direction remains speculative. Larger, longitudinal studies will be required to establish causality.

Various mechanisms may be involved in the association between BP variability and target organ damage and cardiovascular disease. In addition to augmented mechanical stress on the cardiovascular system, leading to cardiovascular remodeling, increased variability of blood flow due to augmented BP variability increases sheer stress on endothelial cells, thereby advancing atherosclerosis, as does sheer stress-induced platelet activation at atherosclerotic stenotic sites. Neurohumoral activation, which is increased in subjects with increased BP variability, may also increase the risk of developing target organ damage and, therefore, cardiovascular disease.

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Research Article

Arginase Inhibitor in the Pharmacological Correction of Endothelial Dysfunction

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This paper is about a way of correction of endothelial dysfunction with the inhibitor of arginase: L-norvaline. There is an imbalance between vasoconstriction and vasodilatation factors of endothelium on the basis of endothelial dysfunction. Among vasodilatation agents, nitrogen oxide plays the basic role. Amino acid L-arginine serves as a source of molecules of nitrogen oxide in an organism. Because of the high activity of arginase enzyme which catalyzes the hydrolysis of L-arginine into ornithine and urea, the bioavailability of nitrogen oxide decreases. The inhibitors of arginase suppress the activity of the given enzyme, raising and production of nitrogen oxide, preventing the development of endothelial dysfunction.

1. Introduction

The reasons and pathogenesis of cardiovascular diseases have always been the object of steadfast attention as the given pathology remains a principal cause of death rate of people. The list of the most frequent diseases of heart and vessels include ischemic illness of heart, arterial hypertension, cerebrovascular diseases. In the pathogenesis of these disorders, the basic role belongs to endothelial dysfunction [1].

Endothelial dysfunction is the first stage of development of heart and vessel illnesses. It is known that endothelium is capable of excreting factors of vasodilatation which relax smooth muscles of a vascular wall and lead to vasodilatation. On the other hand, there are endothelium factors of vasoconstriction. As a whole, on endothelial dysfunction, an imbalance between these factors production and vasoconstriction agents' prevalence takes place [2]. In addition endothelial dysfunction, which can lead to the breakdown of the blood-brain barrier and impair cerebral autoregulation and prothrombotic changes, is believed to be important in mediating leukoaraiosis. The normal cerebral endothelium plays a crucial role in the regulation of cerebral blood flow and autoregulation and in the blood-brain barrier. In addition, in health, it presents an anticoagulant phenotype to blood. Upon stimulation by numerous agents, the endothelium undergoes changes that allow it to participate in the inflammatory response; this is known as endothelial cell activation (ECA) [3]. One of the changes of ECA is increased vascular permeability, and it is thought that the entry of serum proteins into the vascular wall and perivascular neural parenchyma may produce toxic effects [4].

Endothelial dysfunctions may also give rise to molecular events involving a shift in the O(2) and CO(2) trafficking system in the red blood cells, which will result in special complex microcirculation disturbances in the white matter of the brain [5]. Also slight chronic hypoperfusion or an endothelial dysfunction may lead indirectly to a malfunction of the molecular crosstalk between the nucleus and the mitochondria [6].

The basic vasodilatation agent is considered to be a molecule of nitrogen oxide (NO). Differently, endothelial dysfunction is infringement of NO synthesis. In normally functioning endothelium, there is a constant NO production with the help of endothelial NO synthase (eNOS) from L-arginine. It refers to group of semi-irreplaceable amino acids and plays an important role in organism vital activity. Not so long ago it has been established that L-arginine is the predecessor of the NO possessing a wide spectrum of bioregulation influences. NO production infringement on endothelial dysfunctions is associated with reduction of availability of L-arginine stocks for eNOS, acceleration of NO metabolism, or a combination of both [7]. Thus, the basic source of NO is L-arginine which arrives in an organism with food. Because of the high activity of arginase—the enzyme destroying L-arginine in a mucous membrane of thin intestine, 40% of arginine arriving with food is destroyed in the course of absorption, and its remaining quantity arrives into a portal vein. Accepting the fact that 90% of L-arginine is connect with protein , it is possible to consider that only 50% of alimentary arginine goes into system circulation. The arginase is an enzyme of urea cycle that hydrolyzes L-arginine to ornithine and urea. There are two isoforms of this enzyme. Arginase I is constitutive, and "extrahepatic" arginase (arginase II) is induced in vessel endothelium cells by lipopolysaccharides and interferon.

An other way of L-arginine catabolism proceeds with the formation of NO and citrulline. This process is catalyzed by another enzyme—NO synthase (NOS)—which exists in three isoforms: two constitutive, endothelial (eNOS) and neuronal (nNOS), and one induced (iNOS). They carry out the joining of molecular oxygen to nitrogen atom from terminal guanidine group of L-arginine. In the regulation of cardiovascular system, eNOS plays a leading role. Arginase and NOS compete for a common substratum—L-arginine. However, activity of arginase exceeds NOS activity by thousand times. Hence, basic part of L-arginine turns into ornithine and urea, thereby creating NO deficiency. In turn the lack of NO, as already has been mentioned earlier, leads to the development of endothelial dysfunction and to an increase of cardiovascular pathology development risk.

Thus, there is obviously a necessity of suppressing high activity of arginase the decrease to risk and frequency of development of illnesses of heart and vessels. With that aim now arginase inhibitors of substances of a natural origin [8] are investigated. Among substances of this group, L-norvaline attracts the greatest interest, being nonselective inhibitor of arginase which is able to suppress activity of given enzyme, to raise endogenous stocks of L-arginine, and also to increase production of NO, promoting normal functioning of vessels endothelium [9].

The purpose of the present research was studying L-norvaline endothelium-protective properties in L-NAME- and hyperhomocysteinemin-induced endothelial dysfunction.

2. Materials and Methods

Experiments were led on white rat males of Wistar line in mass of 200–250 grams.

NO synthase blocker, N-nitro-L-arginine methyl ester (L-NAME), was inducted intraperitoneally (i.p.) in a dose of 25 mg/kg/day, once a day for 7 days. For simulation of hyperhomocysteinemia, an amino acid methionine was given intragastrically in a dose of 3 g/kg/day once a day for 7 days. A solution of methionine is intragastrically introduced ex tempore with polysorbate Tween-80 and 1% starch solution. The data gained from intragastric introductionof an equivalent amount of polysorbate solution Tween-80 was used as control.

L-norvaline was given i.p. in a dose of 10 mg/kg once a day for 7 days.

Animals have been partitioned into groups, each including 10 rats: (1) intact, (2) Tween-80; (3) L-NAME, (4) methionine, (5) L-NAME + L-norvaline 10 mg/kg, and (6) methionine + L-norvaline 10 mg/kg.

On the day 8 from the initiation of experiments under anaesthetic (chloral hydrate 300 mg/kg), a catheter in the left carotid artery for recording of indexes of blood pressure (BP) was entered. Bolus introduction of pharmacological agents was made into a femoral vein. Hemodynamic indexes were the systolic arterial pressure (SAP), a diastolic arterial pressure (DAP), and cardiac contraction rate metered continuously with a hardware-software complex "Biopac". Besides BP measuring, a series of the functional trials was led in introduced succession: (1) endothelium-dependent vasorelaxation test (intravenous entering of a solution of acetylcholine (AH) in a dose of 40 mkg/kg); (2) endothelium-independent vasorelaxation test (intravenous entering of a solution of sodium nitroprusside (NP) in a dose of 30 mkg/kg) [10–12].

Level of endothelial dysfunction in the experimental animals and also the level of its correction by researched drugs were valued on coefficient of endothelial dysfunction (CED). This coefficient risobtained by the following formula: $CED = SBP_{NP}/SBP_{AH}$, where SBP_{NP} is the area of triangle above a BP recovery curve at a functional test with NP entering and $SBP_{AH}$is the area of triangle above a BP recovery curve at a functional test with AH entering. Points of a smaller cathetus of this triangle are the points of BP before the test and a point of maximum reduction of a BP, and the bigger cathetus is the time of BP restoration [10–12].

The results were expressed as the mean (M) ± the standard error of mean (m). Differences were considered significant at $P < .05$.

3. Results

NOS blockade caused by a seven-day introduction of L-NAME led to an arterial hypertension (SAP: 190,3 ± 6,7 mm hg, DAP: 145,0 ± 3,9 mm hg). Simultaneous L-NAME and L-norvaline introduction did not lead to a decrease in indicators of BP reference values (Table 1). Daily introduction of methionine under the designated scheme did not cause authentic change of arterial pressure (Table 2). Introduction of L-norvaline i.p. also did not influence indicators of haemodynamics (Table 1).

For objectification of endothelial dysfunction correction estimations arising on modelling of deficiency of NO by

Table 1: Dynamics of blood pressure indicators on modeling of NO deficiency and its correction with L-norvaline (M ± m, $n = 10$).

Groups of animals	Functional tests	SAP, mm hg	DAP, mm hg	Area of vascular reaction	CED
Intact	Before test	137,7 ± 3,7	101,9 ± 4,3		
	AH	84,3 ± 4,5	38,7 ± 2,8	1268,0 ± 74,8	1,1 ± 0,1
	NP	83,0 ± 3,7	42,1 ± 4,4	1375,3 ± 93,7	
L-NAME 25 mg/kg	Before test	190,3 ± 6,7*	145,0 ± 3,9*		
	AH	110,6 ± 5,2*	82,8 ± 6,6*	695,3 ± 87,6*	5,4 ± 0,6*
	NP	88,7 ± 4,7	50,8 ± 4,2	3322,7 ± 116,7*	
L-NAME 25 mg/kg + L-norvaline 10 mg/kg	Before test	180 ± 4,7*	144,6 ± 10,2*		
	AH	106,7 ± 4,9*	56,1 ± 1,8*	1360,6 ± 126,9*	2,1 ± 0,2**
	NP	129,3 ± 5,1**	64,6 ± 2,5**	2827,2 ± 429,1**	

* $P < .05$ in comparison with intact group of animals; ** $P < .05$ in comparison with L-NAME group.

Table 2: Influence of methionine and L-norvaline on indicators of haemodynamics and coefficient of endothelial dysfunction in modeling of the homocysteine-induced NO deficiency (M ± m, $n = 10$).

Groups of animals	Functional tests	SAP, mm hg	DAP, mm hg	Area of vascular reaction	CED
Tween-80	Before test	129,2 ± 4,3	82,4 ± 5,9		
	AH	74,1 ± 2,9	39,4 ± 3,1	1124,2 ± 63,7	0,9 ± 0,2
	NP	67,2 ± 5,1	42,9 ± 5,4	1011,8 ± 94,6	
Methionine 3 g/kg	Before test	118,9 ± 10,1	76,6 ± 7,2		
	AH	80,1 ± 2,9	41,4 ± 2,3	854,6 ± 61,4*	3,3 ± 0,3*
	NP	72,3 ± 6,7	45,9 ± 4,3	2820,2 ± 210,4*	
Methionine 3 g/kg + L-norvaline 10 mg/kg	Before test	129,4 ± 2,8**	72,6 ± 5,4**		
	AH	91,0 ± 3,1	47,1 ± 1,8**	920,9 ± 7,8*	1,4 ± 0,1**
	NP	123,8 ± 4,5	63,4 ± 5,0**	1214,7 ± 128,4**	

* $P < .05$ in comparison with intact group of animals; ** $P < .05$ in comparison with metionine group.

L-NAME and methionine introduction, the special coefficient of endothelial dysfunction (CED) [12] is applied in our laboratory. It characterizes the endothelial dysfunction degree.

In each animal in each group, CED was measured. After modeling of NOS blockade, In the group of animals receiving L-NAME, CED was equal to 5,4 ± 0,6 while in group of intact animals CED was 1,1 ± 0,1. In the animals receiving L-norvaline against introduction of L-NAME, CED was 2,1 ± 0,2, coming a value close to that group of intact animals (Table 1). In animals receiving methionine, CED was 3,3 ± 0,3. In the animals receiving Tween-80 CED was equal to 0,9 ± 0,2, and in animals receiving L-norvaline against methionine, CED was 1,4 ± 0,1 (Table 2).

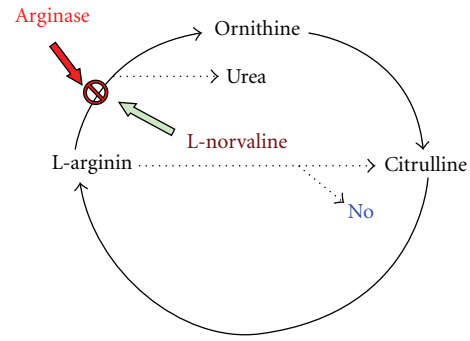

Figure 1: The mechanism of action of arginase inhibitors.

4. Discussion

In conditions of normally functioning endothelium, the balance between vasoconstriction and vasodilatation factors is supported. The basic vasodilatation agent in endothelium is NO. Infringement of the given balance leads to development of endothelial dysfunction. L-arginine serves as a source of NO in a cell. Inhibitors of arginase, suppressing activity of the given enzyme, promote NO biosynthesis increase, preventing the development of endothelial dysfunction. Application of L-norvaline promotes suppression of activity of arginase enzyme which allows for a raise in L-arginine stocks. Expressed endothelium-protective action is provided first of all with increase in stocks of endogenous L-arginine by infringement of its hydrolysis into ornithine and urea (Figure 1), which proves to be true by obvious decrease of CED in animals. In connection with the aforesaid, it is possible to speak about endothelium-protective action of the given group of substances and the prospect for their combined application with L-arginine and the preparations traditionally applied for cardiovascular disease treatment.

5. Conclusion

The present research shows expressed endothelium-protective property of arginase inhibitor, L-norvaline, characterized by decrease of coefficient of endothelial dysfunction and the approached its application to a group of intact animals. In other words, L-norvaline prevents the development of systemic endothelial dysfunctions in L-NAME- and methionine-induced NO deficiency.

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