Cardiology Research and Practice

Interactions between CKD and MetS and the Development of CVD

Guest Editors: Ken-ichi Aihara, Masaki Mogi, Rei Shibata, David Bishop-Bailey, and Xin L. Ma

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Editorial Board

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Editorial

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Ken-ichi Aihara,[1] Masaki Mogi,[2] Rei Shibata,[3] David Bishop-Bailey,[4] and Xin L. Ma[5]

[1] *Department of Medicine and Bioregulatory Sciences, The University of Tokushima, Graduate School of Health Biosciences, 3-18-15 Kuramoto-cho, Tokushima 770-8503, Japan*
[2] *Department of Molecular Cardiovascular Biology and Pharmacology, Ehime University Graduate School of Medicine, Shitsukawa, Tohon, Ehime 791-0295, Japan*
[3] *Department of Cardiology, Nagoya University Graduate School of Medicine, 65 Tsurumai, Showa-Ku, Nagoya 466-8550, Japan*
[4] *Department of Translational Medicine and Therapeutics, William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London EC1M6BQ, UK*
[5] *Department of Emergency Medicine, Thomas Jefferson University, Philadelphia, PA 19107, USA*

Correspondence should be addressed to Ken-ichi Aihara, aihara@clin.med.tokushima-u.ac.jp

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1. Introduction

Metabolic syndrome (MetS) consists of a combination of metabolic disorders, including increased abdominal circumference, hyperglycemia, elevated blood pressure, and lipid disorders. MetS is now widely accepted as a crucial risk factor for the development of cardiovascular disease (CVD) and mortality. In addition, persistent proteinuria indicating chronic kidney disease (CKD) is well known as a powerful risk factor for the progression of end-stage renal disease and CVD. In recent years, patients with CKD and MetS appear to be increasing along with increasing incidence of CVD in industrial countries.

In order to ameliorate cardiovascular mortality, it is essential to extend comprehensive treatments for patients with CKD and MetS. Although those disorders may be partly formed by a certain common pathological basis, there is insufficient knowledge of the underlying interplay between the pathological conditions and CVD. For this special issue, we asked front-line researchers and authors to submit original research and review articles on the interactions between CKD and MetS and the development of CVD. Finally, we were able to publish 10 review articles and 4 original research articles that provide pivotal evidence for understanding the pathophysiological relationships among the disorders on a clinical basis and a molecular basis. The following articles will serve very useful treatment strategies for promoting worldwide public health.

2. Review Articles

K. Nitta reviewed the epidemiology of MetS and CKD and focused on the possible linkage between CKD and MetS leading to an increase in cardiovascular events. The author described a fundamental treatment strategy including lifestyle modification and renal protection by renin-angiotensin blockade and/or statins.

D. Vykoukal and M. G. Davies showed influences of MetS on the hemostatic disorders and development of CKD and the outcomes of percutaneous renal intervention in patients with symptomatic atherosclerotic renal and fibromuscular dysplasia renal artery disease.

Y.-J. Sheen and W. H.-H. Sheu summarized the relation between MetS and CKD from epidemiological, biological, and clinical aspects. They clearly revealed the significance of several biomarkers and the importance of MetS as a therapeutic target for preventing CKD.

Since much attention has been paid to the role of oxidative stress in promoting not only the severity of CVD but

also the progression of CKD, E. O. Gosmanova and N.-A. Le focused on the central roles of oxidative stress in the development of CVD and its complications in patients with CKD.

M. Raimundo and J. A. Lopes reviewed in detail the associations between and treatment strategies for CKD, MetS, and CVD. They clearly described clinical evidence and pathophysiology, including insulin resistance, inflammation, endothelial dysfunction, oxidative stress, renal circulation, renin-angiotensin-aldosterone system and sympathetic nervous system, and dietary factors.

Y. Beyazit et al. demonstrated the effect of bone marrow angiotensin II signaling on the initiation and progression of atherosclerosis with inflammation and oxidative stress involving endothelial cells and hematopoietic cells.

M. Mogi and M. Horiuchi showed the cerebrorenal connection mainly from a clinical point of view. They demonstrated that cerebral and glomerular small vessel diseases are based on a common pathogenesis through anatomic and vasoregulatory similarities. These issues indicate that CKD markers may be helpful for predicting the future risk of neuronal diseases such as stroke, dementia, and cognitive impairment.

K. Aihara et al. focused on the interplay between the TGF-β1 signaling pathway and the development of CVD, CKD, and MetS. Understanding the TGF-β1 signaling pathway and appropriate modulation of the biological actions of TGF-β1 is a valuable therapeutic approach to reduce CVD.

Y. Okamoto reviewed the clinical significance of hypoadiponectinemia in cardiovascular diseases and the protective features of adiponectin against cardiovascular remodeling, including cardiac hypertrophy, hypertension, atherosclerosis, and pulmonary artery hypertension.

M. Tesauro et al. showed that adipose tissue secretes bioactive adipokines, including adiponectin, leptin, adipsin, and visfatin, into the whole body circulation. Accumulating evidence about these factors would serve a strategy for protection of both renal and cardiovascular systems.

3. Original Research Articles

Since height is inversely associated with augmentation index indicating arterial stiffness, T. Takenaka et al. showed that not only cigarette smoking but also short height independently contributes to total mortality in hemodialysis patients.

V. B. Djordjević et al. showed that available biomarkers in patients with coronary artery disease with and without statin treatment are C-reactive protein in acute myocardial infarction, triglyceride/apoB in stable angina pectoris, and lipoprotein (a) in unstable angina pectoris.

V. S. Rao et al. showed that among the biological cardiovascular risk markers, oxidized LDL cholesterol is the most powerful predictor of the incidence of MetS in 2316 individuals who were recruited in Phase I of the Indian Atherosclerosis Research Study (IARS).

C. S. Coffey et al. showed that subjects with MetS have higher levels of PAI-1 and t-PA antigen than do subjects without MetS in a population study. Since these factors have been known to increase the risk of cardiovascular disease, they raised the possibility that an accelerated coagulation state is linked with the pathological basis of MetS.

Ken-ichi Aihara
Masaki Mogi
Rei Shibata
David Bishop-Bailey
Xin L. Ma

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Review Article

Possible Link between Metabolic Syndrome and Chronic Kidney Disease in the Development of Cardiovascular Disease

Kosaku Nitta

Department of Medicine, Kidney Center, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan

Correspondence should be addressed to Kosaku Nitta, nitta@kc.twmu.ac.jp

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Metabolic syndrome (MetS) is a clinical syndrome that consists of visceral obesity, dyslipidemia, hypertension, and impaired insulin sensitivity. Although individual components of MetS have been implicated in the development of chronic kidney disease (CKD), few studies have examined the effect of combinations of the components of MetS on the development of CKD and cardiovascular disease (CVD). The prevalence of MetS is increasing worldwide in both developing and developed countries, and early detection and treatment of MetS would be a cost-effective strategy for preventing the development of CKD. Visceral obesity and insulin resistance are two important features of MetS that may be associated with renal damage. Lifestyle modifications, including caloric restriction and exercise, are necessary to treat MetS. Initial antihypertensive therapy should consist of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. An improved understanding of the mechanism responsible for the association between MetS and renal damage should be helpful in determining the treatment regimens directed at cardiovascular and renal protection.

1. Introduction

Chronic kidney disease (CKD) has a major impact on the quality of life of patients, health services, and society. CKD is now also widely accepted as a risk factor for cardiovascular disease (CVD) and mortality [1–3], and recent reports, including those of observations in Japan, support this notion [4–6]. The Kidney Early Evaluation Program (KEEP) screened 6071 eligible persons for CKD and reported that 16% had a reduced estimated glomerular filtration rate (eGFR) and that 44% were obese [7]. A systematic review of 39 studies that included a total of more than a million patients revealed an increased relative risk of all-cause mortality in non-dialysis-dependent CKD patients, and the absolute risk of death appeared to increase exponentially as renal function diminished [8]. Thus, CKD is common among persons who have experienced a stroke and among patients with CVD, diabetes mellitus, and other medical conditions.

In both the Western world [9] and Japan [10], there has been an increase in the prevalence of CKD that has paralleled the increase in prevalence of obesity in recent years. The World Health Organization (WHO) defines normal body weight on the basis of body mass index (BMI) as a BMI of 18.5–24.9, overweight as a BMI ranging from 25 to 29.9, and obesity as a BMI of 30 or more [11]. Obesity was demonstrated to be a predictor of the development of CKD in two large studies of 5897 patients and 11,104 patients, respectively [12, 13]. Analysis of data from the Second National Health and Nutrition Examination Survey (NHANES II) in the United States identified an increased risk of CKD in persons who were morbidly obese [14].

BMI was found to be associated with an increased risk of developing end-stage renal disease (ESRD) in men in a Japanese cohort [15], and a similar positive association between CKD and obesity was demonstrated among men in a population-based study in Singapore [16]. Obesity has not only been suggested to cause renal disease, but it appears to accelerate its progression. A retrospective cohort study of 320,252 healthcare-insured participants in northern California who were followed for 15–35 years revealed that the rate of ESRD increased in a stepwise manner as BMI rose [17]. In that study, the age-, sex-, and race-adjusted rates of ESRD increased from 10 per 100,000 person-years

among those with normal weight (BMI, 18.5 to 24.9) to 108 per 100,000 among whose BMI was greater than 40. High BMI is likely to be a risk factor for the progression of CKD. Metabolic syndrome (MetS) is a clinical syndrome that consists of visceral obesity, dyslipidemia, hypertension, and impaired insulin sensitivity.

2. Epidemiology of MetS and CKD

The relationship between MetS and CKD has recently been examined. Ninomiya et al. performed a slope analysis of the association between the GFR slope and MetS by using a multiple regression model [18]. The results showed that the multivariate-adjusted mean value for the GFR slope decreased significantly in subjects with 4 or more MetS components in comparison with those who had 1 or no components, and the mean of the GFR slope was also significantly lower in subjects with 3 MetS components in the 60 year and over age group. Chen et al. investigated the risk of developing CKD, defined by a Modification of Diet in Renal Disease study (MDRD)-eGFR of less than 60 mL/min per 1.73 m^2, in a cohort of the NHANES III study that included >7800 participants who had normal renal function at baseline and were followed for >21 years [19]. The results showed that the multivariate-adjusted odds ratio (OR) for CKD of the participants with MetS was 2.6 in relation to participants without MetS, and the OR increased from 1.89 to 5.85 as the number of components of MetS that were present increased. Importantly, the relationship persisted after exclusion of diabetes. They also found a 2-fold increase in the risk for microalbuminuria that correlated with the number of components of MetS. Palaniappan et al. demonstrated a higher rate of microalbuminuria in men and women with MetS than in healthy controls [20]. The cutoff point of the urinary albumin-to-creatinine ratio varied in subjects with various CVD risk profiles, and even low-grade albuminuria below the conventional cutoff point for microalbuminuria was associated with increased prevalence of CKD [21]. Kurella et al. performed a longitudinal cohort study and found a higher rate of CKD in MetS even after adjustment for subsequent development of diabetes and hypertension, suggesting that MetS is independently associated with an increased risk for incident CKD in nondiabetic adults [22]. These findings suggest that the onset of renal dysfunction may occur long before the appearance of hypertension or diabetes in patients with MetS.

3. Possible Role of MetS in the Development of CKD

In a population of nondiabetic American Indians with a high prevalence of MetS (38%), MetS was found to be associated with an increased risk of incident CKD, but no adjustment for hypertension status was made in that study [23]. The relationship between MetS and incident CKD was stronger than among members of the population who developed diabetes during the followup period, suggesting that the development of diabetes was a likely mechanism of the increased risk of CKD associated with MetS. The authors also reported a 2.6-fold increased prevalence of CKD among adults with MetS in NHANES III [19].

Microalbuminuria has been described as the earliest manifestation of MetS-associated kidney damage and diabetic nephropathy, and it is associated with insulin resistance independent of diabetes [24]. MetS is often accompanied by increased plasma renin activity, angiotensinogen, angiotensin-converting enzyme activity, and angiotensin II (renin-angiotensin-aldosterone system) and with renal sympathetic activity. Hyperinsulinemia, insulin resistance, and increased plasma angiotensin II levels are potent activators of expression of transforming growth factor-β1, a fibrogenic cytokine that contributes to glomerular injury [25]. Microalbuminuria is attributable to augmented hyperfiltration, a well-recognized glomerular hemodynamic change in patients with MetS [26–29].

The mechanisms by which MetS causes and exacerbates CKD remain a matter of speculation (Figure 1). The hallmark of MetS is insulin resistance. Inflammatory mediators, including tumor necrosis factor (TNF)-α, have been shown to mediate insulin resistance [30]. Adipokines, including TNF-α, IL-6, and resistin, are cytokines secreted by adipose tissue, and their plasma concentrations are elevated in patients with MetS, whereas their plasma adiponectin levels are reduced. These findings may contribute to insulin resistance, and insulin resistance promotes chronic inflammation. Several studies have shown that visceral adipose tissue is a major source of adipokine secretion in MetS [31].

Adiponectin has been shown to be an adipokine that has cardiorenal protective properties [32, 33]. Plasma adiponectin levels are negatively correlated with visceral fat mass, body weight, blood pressure, insulin resistance, inflammatory markers of MetS, and high triglyceride and LDL cholesterol levels, and they are positively correlated with HDL cholesterol levels and weight loss [34]. Hypoadiponectinemia is associated with vascular dysfunction and cardiovascular events in MetS patients who do not have CKD [35]. Thus, adiponectin may be important in preventing some of the deleterious effects that the chronic inflammatory state exerts on various organs, including the kidney. Becker et al. found that low adiponectin levels in patients with mild or moderate renal dysfunction were correlated with cardiovascular events [36], whereas Menon et al. reported finding that all-cause mortality and cardiovascular mortality were paradoxically higher in patients with stage 3 or 4 CKD who had high adiponectin levels [37], suggesting that plasma adiponectin levels are influenced by renal function. Whether adiponectin is renoprotective or cardioprotective in CKD patients with MetS is still unknown.

Activation of the renin-angiotensin-aldosterone system is common in patients with MetS despite sodium retention and a clearly increased extracellular fluid volume [38, 39]. Several mechanisms to explain its activation have been postulated: (a) hemodynamic alterations, including interference with renal blood flow [40]; (b) sympathetic stimulation, which is related to hyperleptinemia, and possibly to hyperinsulinemia and insulin resistance [41]; (c) synthesis of several proteins in the renin-angiotensin-aldosterone system by visceral fat

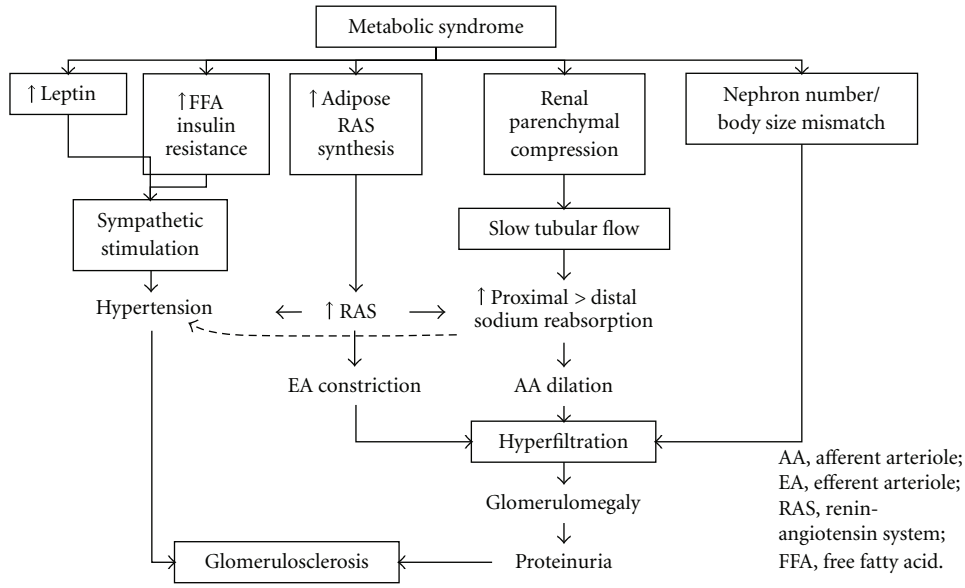

Figure 1: Hemodynamic consequences of obesity leading to hyperfiltration and hypertension.

tissue [42]. A review of these mechanisms has shown that hypertension, increased glomerular pressure, exacerbation of proteinuria, induction of intrarenal inflammatory cytokines and growth factors, and apoptosis are some of the deleterious effects of angiotensin II on the kidney [43]. In addition, angiotensin II may play a role in the regulation of adipokine production in adipose tissue. Since olmesartan, an angiotensin II type 1 receptor blocker, significantly reduced inflammatory cytokines and markers of oxidative stress and increased adiponectin levels in a mouse model of obesity [44], angiotensin II may adversely affect the residual renal function of patients with CKD.

With regard to potential pharmacologic therapies, it is important to note that aldosterone secretion tends to be more pronounced in obese African Americans than in obese American Whites [45]. Obesity and MetS are frequently associated with increased aldosterone levels and impaired sodium excretion [46], and this "double hit" of expanded volume and relative hyperaldosteronism may be particularly important. Several studies have reported a "mild variant of primary aldosteronism" in hypertensive African Americans and that it was even more pronounced in a subgroup with both obesity and MetS [47–49]. The assertion that antialdosterone therapy may not benefit certain races is not based on solid evidence even though there may be differences between the races in the increase in aldosterone levels.

4. CKD as a Risk Factor for CVD

An independent graded association has been observed between lower estimated GFR values and increased risk of death and cardiovascular events in a large community-based population [3]. Although the initial data linking CKD and increased risk of CVD were limited and complicated by multiple confounding variables (Figure 2), CKD is now widely recognized as an independent risk factor for the development of CVD [50]. Indeed, studies of the relationship between CKD and CVD have generated impressive results over the last few years [51]. In many patients with CKD, the risk of death was found to be greater than the risk of progression to ESRD [52, 53]. In recent publications that have evaluated data obtained through the National Kidney Foundation's (NKF), KEEP, and NHANES, CKD was found to be associated with significantly increased rates of myocardial infarction, stroke, and short-term mortality in comparison with the general population (Figure 3) [54]. In studies that stratified the rates of CVD and all-cause mortality according to GFR values, graded increases were seen as GFR decline even after adjusting for age and common confounders, highlighting the need for effective CVD risk reduction early in the course of CKD prior to significant loss of renal filtration function [52, 53].

5. Treatment of CKD Associated with MetS

Each of the components of MetS is capable of independently causing renal injury and increasing the risk of CKD and CVD. A number of therapeutic interventions that target individual components of MetS and associated conditions may have direct benefits on the kidney and heart. Reduction of adipose tissue mass can be achieved with preventive interventions, caloric restriction with or without physical activity. Lifestyle modifications are required to treat MetS. Weight reduction is effective in reducing proteinuria in obese patients [55, 56]. Weight loss also has a protective effect against progression of CKD to ESRD but may no longer be indicated once progression to ESRD has occurred, because renal replacement therapy has a paradoxical effect on survival [57], and a higher BMI has a beneficial effect on the survival in ESRD patients. Bariatric surgery is often performed in

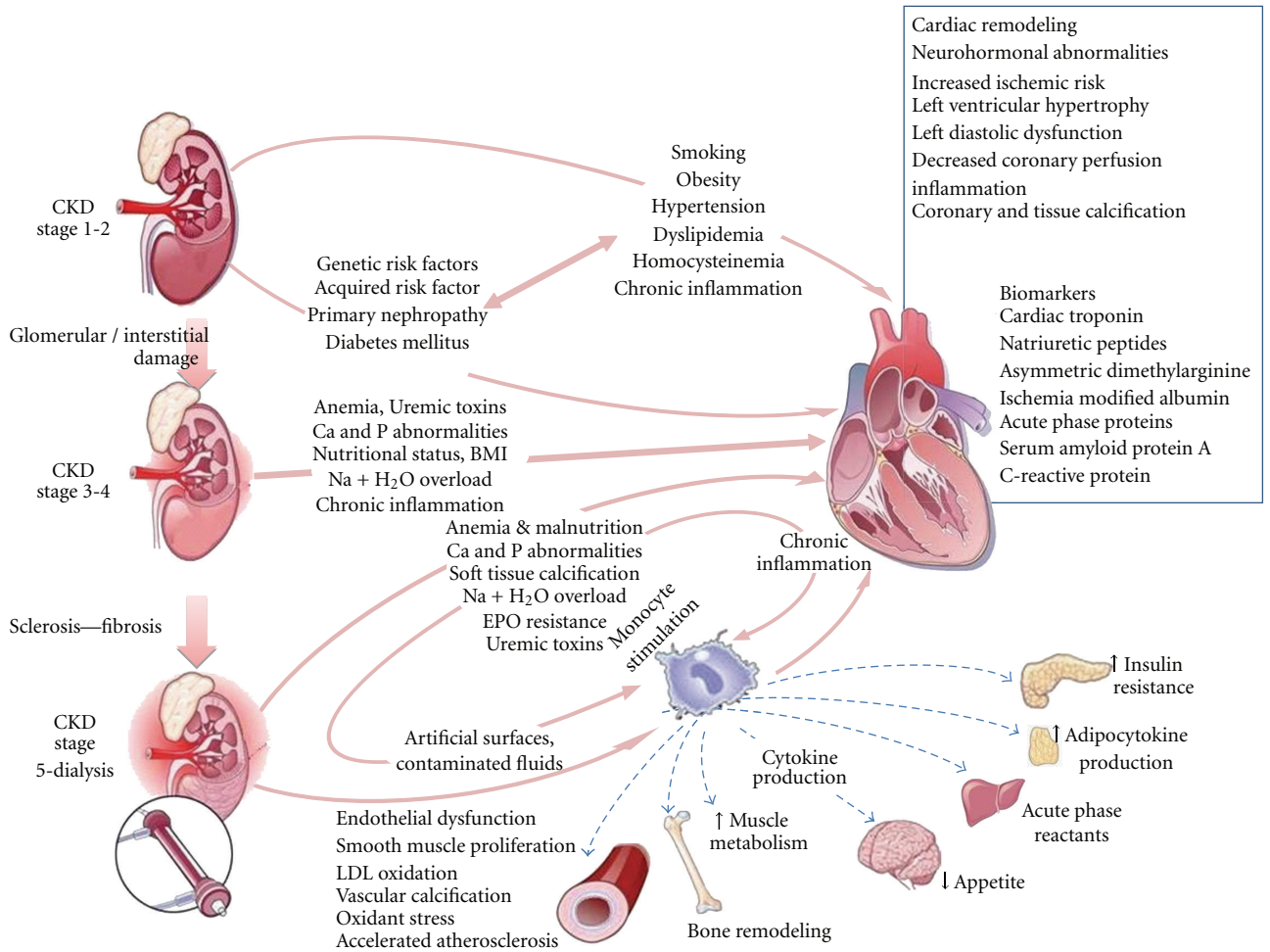

Figure 2: Complex pathogenesis of chronic kidney disease (CKD) and cardiovascular disease (CVD) [50].

cases of extreme obesity (BMI > 40). Navarro-Díaz et al. reported a remarkable improvement in glomerular hyperfiltration following recovery from renal alterations [58]. Exercise training improves various metabolic parameters, including triglyceride and HDL cholesterol levels, resting blood pressure and insulin resistance, in patients with MetS [59], and the improved metabolic profile may reduce risk of CKD and CVD.

Peroxisome proliferators-activated receptors (PPARs)-α agonists (the fibrates) [60] and PPAR-γ agonists (the thiazolidinediones) [61] improve insulin sensitivity, but they are not without risks in CKD patients. Blockade of the renin-angiotensin system is likely to be beneficial, but treatment needs to be individualized according to the degree of renal dysfunction and whether other comorbidities associated with visceral obesity are present. The clinical merit of combination therapy of an angiotensin-converting enzyme inhibitor and an angiotensin receptor blocker remains a matter of debate. HMG-CoA reductase inhibitors seem to be effective in preventing the progression of CKD. Fried et al. found that effective treatment of dyslipidemia decreased proteinuria and retarded the progression of CKD in a meta-analysis [62]. Large randomized controlled trials to examine the effects of each of these interventions on the renal function of patients with MetS are needed before any recommendations can be made.

6. Conclusion and Future Prospects

MetS may be an independent risk factor for CKD and microalbuminuria in addition to being a risk factor for CVD and diabetes. Possible mechanisms by which MetS increases the risk of CKD involve inflammation, hemodynamic effects, and imbalanced adipokine secretion. Cost-effective strategies to prevent CKD and ESRD that are feasible for each individual region are needed. However, few data are available on the beneficial effects of lifestyle and pharmacological interventions in CKD patients with MetS. An improved understanding of the mechanism responsible for the association between MetS and renal damage and large randomized controlled trials of therapeutic regimens designed to prevent the onset and progression of CKD should be helpful in determining which regimen is optimal.

In the next decade, there will be a significant need to conduct randomized controlled trials in order to evaluate

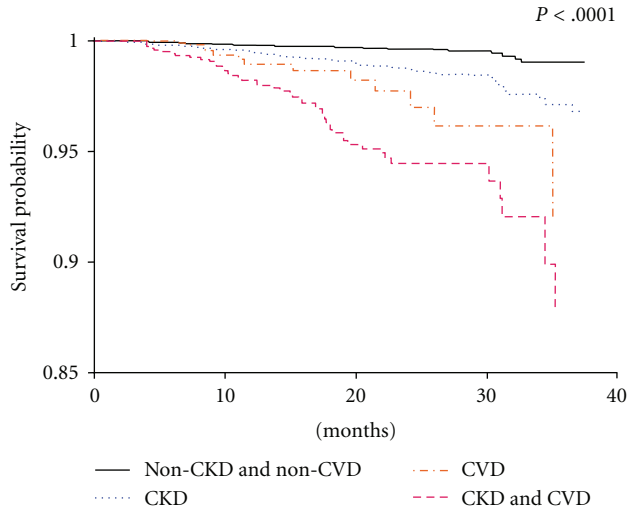

Figure 3: Kapla-Meier curves for all-cause mortality stratified by no chronic kidney disease (CKD)/no cardiovascular disease (CVD), prevalent CKD, CVD, and CVD + CKD from the KEEP Program [54].

the impact of the various proposed therapeutic approaches to MetS. One of the main challenges of such approaches is that the ideal outcomes of interest of such trials need to be carefully selected. The overall goal of these approaches to MetS care is to improve the quality of life. In light of this goal, it will be important to monitor multiple relevant outcomes, such as the incidence and management of CKD and CVD, together with the well-known complications of MetS.

Insulin resistance, a key mechanism of MetS, is considered the hallmark of MetS and is believed to be the underlying reason for the associated systemic metabolic derangements of hypertension and dyslipidemia, which are considered fundamental pathogenetic factors in arteriosclerosis and may contribute directly to renal injury by impairing normal hemodynamic processes through multiple mechanisms [63]. The guidelines of the American Heart Association recommend lifestyle modifications including weight reduction, dietary changes, and physical activity, as first-line therapy for patients with MetS [64].

Initial antihypertensive therapy should consist of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, unless there are contraindications or concomitant diseases with compelling indications for other drugs. Appropriate second-line antihypertensive drugs include a calcium channel blocker or a diuretic. Most patients with MetS will need more than one antihypertensive drug to achieve the target blood pressure values. Combination therapy for multiple cardiovascular risk factors is critical to the successful management of CKD patients with MetS.

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Review Article

Metabolic Syndrome and Outcomes after Renal Intervention

Daynene Vykoukal[1,2] and Mark G. Davies[1,2]

[1] *Department of Cardiovascular Surgery, Methodist DeBakey Heart and Vascular Center, The Methodist Hospital, 6550 Fannin, Smith Tower, Suite 1401, Houston, TX 77030, USA*
[2] *Vascular Biology and Therapeutics Program, The Methodist Hospital Research Institute, Houston, TX 77030, USA*

Correspondence should be addressed to Mark G. Davies, mdavies@tmhs.org

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Metabolic syndrome significantly increases the risk for cardiovascular disease and chronic kidney disease. The increased risk for cardiovascular diseases can partly be caused by a prothrombotic state that exists because of abdominal obesity. Multiple observational studies have consistently shown that increased body mass index as well as insulin resistance and increased fasting insulin levels is associated with chronic kidney disease, even after adjustment for related disorders. Metabolic syndrome appears to be a risk factor for chronic kidney disease, likely due to the combination of dysglycemia and high blood pressure. Metabolic syndrome is associated with markedly reduced renal clinical benefit and increased progression to hemodialysis following endovascular intervention for atherosclerotic renal artery stenosis. Metabolic syndrome is associated with inferior early outcomes for dialysis access procedures.

1. Introduction

Metabolic syndrome is evolving into a pandemic, contributing to approximately 6-7% for all-cause mortality, 12–17% for cardiovascular disease, and 30–52% for diabetes in the population [1]. In populations free of cardiovascular disease at baseline, cardiovascular morbidity and mortality increases 1.5- to 3-fold in the presence of the metabolic syndrome [2, 3]. Two definitions of metabolic syndrome predominate the literature, the National Cholesterol Education Program (NCEP) and the World Health Organization (WHO). Metabolic syndrome is defined as the presence of 3 or more of the following: (1) waist circumference $\geq$88 cm in women and $\geq$102 cm in men, (2) fasting triglycerides $\geq$150 mg/dL or drug treatment for elevated triglycerides, (3) HDL-cholesterol $<$ 50 mg/dL in women and $<$ 40 mg/dL in men or drug treatment for reduced HDL-cholesterol, (4) BP $\geq$ 130/85 mmHg or use of BP-lowering medication, and (5) fasting glucose $\geq$100 mg/dL or use of glucose-lowering medication, according to the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI), updated National Cholesterol Education Program (NCEP), and Adult Treatment Panel III (ATPIII) criteria [4]. If waist circumference is not available, a body mass index (BMI) $>$ 30 kg/m^2 can be used as a determinant for abdominal obesity [5]. Metabolic syndrome appears to be a risk factor for chronic kidney disease, likely due to the combination of dysglycemia, a prothrombotic state and high blood pressure. This paper examines the relationship between metabolic syndrome and the development of and interventions for renal artery and renal parenchymal disease.

2. Coagulation

The increased risk for cardiovascular diseases could partly be caused by a prothrombotic state that exists because of abdominal obesity. Adipose tissue induces thrombocyte activation by the dysregulated production of adipose tissue-derived hormones, often called adipokines, which have been shown to interfere with platelet function. Enhanced platelet aggregation and activation markers are associated with low adiponectin concentrations [6]. Increased adipose tissue mass induces insulin resistance and systemic low-grade inflammation, also affecting platelet function. It has been demonstrated that adipose tissue directly impairs fibrinolysis

by the production of plasminogen activator inhibitor-1 and possibly thrombin-activatable fibrinolysis inhibitor [7]. Adipose tissue may contribute to enhanced coagulation by direct tissue factor production, but hypercoagulability is likely to be primarily caused by altered hepatic synthesis of the coagulation factors fibrinogen, factor VII, factor VIII, and tissue factor, by releasing free fatty acids and proinflammatory cytokines (tumor necrosis factor-α, interleukin-1β, and interleukin-6) into the portal circulation and by inducing hepatic insulin resistance. Adipose tissue dysfunction could thus play a causal role in the prothrombotic state observed in obesity, by directly and indirectly affecting hemostasis, coagulation, and fibrinolysis [8]. Platelets in type 2 diabetic individuals adhere to vascular endothelium and aggregate more readily than those in healthy people. Loss of sensitivity to the normal homeostatic restraints exercised by prostacyclin (PGI_2) and nitric oxide (NO) generated by the vascular endothelium presents as the major defect in platelet function. Insulin is a natural antagonist of platelet hyperactivity. It sensitizes the platelet to PGI_2 and enhances endothelial generation of $PGI_2$and NO. Thus, the defects in insulin action in diabetes create a milieu of disordered platelet activity conducive to macrovascular and microvascular events. Patients with type 2 diabetes and abdominal fat patterning displayed higher plasma activities of clotting factors VII and VIII as well as increased plasma levels of fibrinogen and von Willebrand factor antigen, when compared with not only healthy normal weight controls, but also with diabetic patients at normal body weight. An altered coagulation state has implications for any surgical or endovascular intervention.

3. Obesity and Kidney Disease

Obesity and the metabolic syndrome significantly increase the risk for cardiovascular disease and chronic kidney disease. Multiple abnormalities that can lead to kidney injury have been identified in overweight and obese people, including insulin resistance, compensatory hyperinsulinemia, inappropriate activation of the renin-angiotensin-aldosterone system, increased oxidative stress, endoplasmic reticulum stress, coagulability, and impaired fibrinolysis. The combined effects of these conditions induce, in the kidneys, impaired pressure natriuresis, glomerular hypertension, endothelial dysfunction, and vasoconstriction, as well as matrix proliferation and expansion. Among the consequences are microalbuminuria, now known to be a surrogate of diffuse endothelial dysfunction as well as a predictor of cardiovascular disease, and chronic kidney disease [9]. Multiple observational studies have consistently shown that increased body mass index as well as insulin resistance and increased fasting insulin levels is associated with chronic kidney disease, even after adjustment for related disorders [10]. Obesity may promote intracellular lipid accumulation in the kidney. Prevalence of a body mass index of at least 35 kg/m^2 among incident dialysis patients has increased by 64% over the past decade, and if these trends continue 20% of all patients will initiate dialysis with this degree of obesity. Weight loss improves glomerular hemodynamics in morbidly obese adults and may retard progression of chronic kidney disease. In contrast, once a patient reaches end-stage renal disease, the degree of adiposity correlates with survival, and weight loss may not necessarily be beneficial [11]. Metabolic syndrome appears to be a risk factor for chronic kidney disease, likely due to the combination of dysglycemia and high blood pressure. Metabolic syndrome is associated with markedly reduced renal clinical benefit and increased progression to hemodialysis following endovascular intervention for atherosclerotic renal artery stenosis.

4. Cardiovascular Risk and Peripheral Vascular Procedures

Patients with peripheral arterial disease and metabolic syndrome have an increased risk for the development of cardiovascular (CV) events, when compared to patients without metabolic syndrome (27% versus 18% and 27% versus 19%, $P < .001$, resp.). In peripheral arterial disease, metabolic syndrome was independently associated with an increased risk of long-term CV events (HR = 1.6; 95% CI 1.2–2.1 and HR = 1.4; 95% CI 1.1–1.8) but not CV mortality [12]. A survey of patients with intermittent claudication and ankle/brachial index (ABI) < 0.90 showed that 52.6% meet the revised version of the Adults Treatment Panel III (rATP III) criteria for metabolic syndrome [13]. In women, metabolic syndrome is associated with an increased risk of future symptomatic peripheral arterial disease. This risk appears to be mediated largely by the effects of inflammation (increased levels of high-sensitivity C-reactive protein) and endothelial activation (increased levels of soluble intercellular adhesion molecule-1). There is currently no data on the impact of metabolic syndrome on outcomes in peripheral interventions. After open aneurysm repair, obesity of any class is independently predictive of wound complications. Class III obesity was also an independent predictor of renal complications and cardiac complications. After EVAR (endovascular aortic/aneurysm repair), obesity (any class) was predictive of wound complications, but not predictive of other complications or death. For the two types of operation, there were fewer complications and deaths after EVAR compared with open repair across all BMI categories, but outcomes were most disparate among the obese [14]. Obesity is associated with extended operation time during EVAR. After controlling for age, gender, and operation type, mortality risk remained lowest in obese class I patients (odds ratio (OR) 0.63, $P = .023$), while morbidity risk was highest in obese class III patients (OR 1.70, $P = .0003$), due to wound infection, thromboembolism, and renal complications [15]. Surgical site infections occur frequently after lower extremity bypass regardless of bypass origin and are associated with early graft failure and sepsis. Obesity predicts postoperative surgical site infections. Mortality risk was greatest in the underweight, followed by morbidly obese and normal-weight patients, while overweight and mild to moderate obesity were associated with the lowest mortality.

5. Interventions and Renal Fibromuscular Dysplasia

Hypertension is one of the criteria for metabolic syndrome and one cause of treatable hypertension in women is fibromuscular dysplasia (FMD) [16]. Percutaneous endovascular intervention for clinically symptomatic fibromuscular dysplasia in the renal arteries is technically successful and safe. There are excellent assisted patency and low restenosis rates with immediate clinical benefit for most patients and continued long-term results up to 5 years [17]. Using proportional hazard analysis, the predictors of long-term clinical benefit were duration of hypertension <8 years, creatinine <1.5 mg/dL, ipsilateral kidney size, functional status of the contralateral kidney, a fasting blood sugar <110 mg/dL*, triglycerides <150 mg/dL*, and HDL > 50 mg/dL* (*components of metabolic syndrome) [17]. Neither age < 50 years nor administration of statins appeared to be significant. The diagnosis of metabolic syndrome did not affect outcomes. It appears, however, that the presence of existing renal pathology and markers of metabolic syndrome is associated with recurrence of hypertensive symptoms [17].

6. Interventions and Renal Atherosclerotic Disease

Endovascular therapy for symptomatic atherosclerotic renal artery stenosis is common and effective in the well-selected patient [18, 19]. The proportion of patients with symptomatic renal artery disease who will have metabolic syndrome is similar to that described for symptomatic peripheral vascular disease [20]. These patients will more often be female, but there is no significant difference in presenting symptoms. Despite the presence of obesity and the risks associated with metabolic syndrome, perioperative mortality and morbidity are equivalent to those without metabolic syndrome. Patients with metabolic syndrome have equivalent survival and cumulative patency. However, the metabolic syndrome group has a lower 5-year freedom from restenosis and lower 5-year retained clinical benefit (freedom from recurrent hypertension or worsening renal insufficiency) (Figure 1). However, a higher number of patients progress to hemodialysis (3% versus 13%, no metabolic syndrome versus metabolic syndrome; $P < .01$). Individually, the components of metabolic syndrome do not influence outcomes [20].

7. Dialysis Access

The average BMI of incident dialysis patients in USA has risen by 13% since 1995, mirroring the expanding obesity epidemic in USA. This increase in patient weight has resulted in an increased number of dialysis patients who are obese (BMI > 30). The impact of BMI on dialysis access outcomes has been difficult to elucidate, with some studies showing inferior outcomes for dialysis access procedures among obese patients, while others do not detect a BMI-associated outcome effect. When determining the route of dialysis access in the obese, proper consideration must be given to peritoneal dialysis (PD). While the placement of PD catheters in obese individuals may be technically challenging, there is no decrease in catheter use or catheter survival in obese patients compared to the nonobese. Obese PD patients do have higher catheter-exit site infection rates and a tendency toward poor wound healing. Placement of autologous fistulae and prosthetic grafts in the obese follows the same guidelines as in the nonobese. However, in the case of autologous fistulae, superficialization (i.e., removing subcutaneous fat to decrease the depth of the vein and allow cannulization) is more common in these patients and will delay primary access. There is no data on the impact of metabolic syndrome on the functionality and longevity of dialysis access sites.

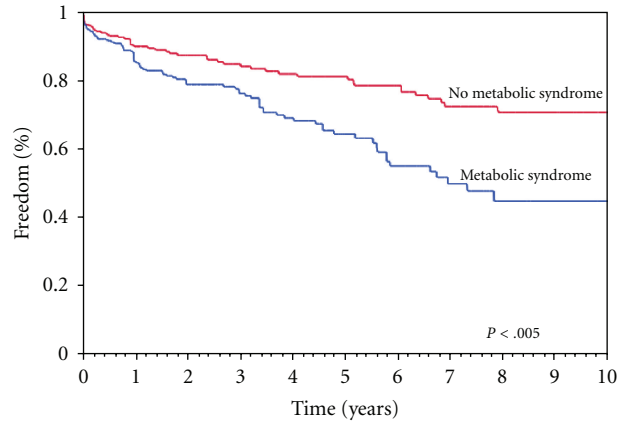

Figure 1: Kaplan-Meier analysis of freedom from renal-related morbidity (persistent increase in creatinine >20% of baseline, progression to hemodialysis, death from renal-related causes) for the patients with and without MetS. Values are mean.

Metabolic syndrome influences the development of chronic renal insufficiency and does influence the outcomes of percutaneous renal intervention in patients with symptomatic atherosclerotic renal and FMD renal artery disease. In addition, the presence of obesity, as well as metabolic syndrome, alters the paradigms for obtaining dialysis access for those with end-stage renal disease and complicates the ability to achieve successful and durable access.

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Review Article

Metabolic Syndrome and Renal Injury

Yi-Jing Sheen[1] and Wayne Huey-Herng Sheu[2]

[1] *Division of Endocrinology and Metabolism, Department of Internal Medicine, Taichung Hospital Department of Health, Executive Yuan, No. 199, Sec. 1, Sanmin Road, Taichung 403, Taiwan*
[2] *Division of Endocrinology and Metabolism, Department of Internal Medicine, Taichung Veterans General Hospital, No. 160, Sec. 3, Taichung-Kang Road, Taichung 407, Taiwan*

Correspondence should be addressed to Wayne Huey-Herng Sheu, whhsheu@vghtc.gov.tw

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Both metabolic syndrome (MetS) and chronic kidney disease (CKD) are major global health issues. Current clinical markers used to reflect renal injury include albuminuria and estimated glomerular filtration rate (eGFR). Given the same eGFR level, urine albumin might be a better risk marker to predict progression of CKD and future development of cardiovascular diseases (CVDs). Serum Cystatin C is emerging as a new biomarker for early detection of renal injury associated with MetS and cardiovascular risk. In addition to each component, MetS per se influences the incidence and prognosis of renal injury and the odds ratios increased with the increase in the number of metabolic abnormalities. Hyperinsulinemia, activation of rennin-angiotensin-aldosterone system, increase of oxidative stress, and inflammatory cytokines are proposed to be the plausible biological link between MetS and CKD. Weight control, stick control of blood pressure, glucose, and lipids disorders may lead to lessening renal injury and even the subsequent CVD.

1. Introduction

MetS, a complicated clinicopathological entity with clustering of CVD and metabolic risk factors, includes central obesity, hypertension, dyslipidemia, and glucose intolerance. It has been pervasively recognized that individuals with MetS are associated with the increased risks of type 2 diabetes and CVD [1–3]. Abdominal fat plays an important role in MetS, because it is predictive of sensitivity to insulin [4, 5]. It has been reported that obesity adversely affects renal function and may be associated with morbidity and mortality in patients with CKD [4]. Recent evidence also indicated that presence of MetS is associated with an increased risk of developing CKD [6, 7]. As a matter of fact, both MetS and CKD are major global health issues with regard to the increasing prevalence of obesity and aging society [8–11]. What is more alarming is the fact that the prevalence of end-stage renal disease has more than doubled in the recent ten years [9]. Although the relationship between MetS and CKD was established, the detailed understanding of quantitative association between MetS and its components implicated in kidney damage is still limited. In this paper, we will review the following issues:

(1) epidemiological association between MetS and CKD incidence and/or progression,

(2) reliable markers of MetS associated with renal injury,

(3) plausible biologic links between MetS and CKD,

(4) impact of treating the MetS on the risk of renal injury or CKD progress.

2. Epidemiological Association between MetS and CKD Incidence and/or Progression

The association between MetS and CKD in different populations varies with odds ratio (OR) ranging from 0.93 to 2.60 according to our review (Table 1). In a group of 118,924 nondiabetic Chinese patients with a mean followup for 3.7 years, Sun et al. reported that multivariable adjusted HR for CKD in subjects with MetS (ATP-III-MetS) was 1.30 (95% CI, 1.24–1.36) and 1.37 (95% CI, 1.30–1.44), evaluated

by proteinuria and eGFR, respectively [12]. In American Indians without diabetes, it is reported that adjusted hazard ratio for incident CKD (measured by using eGFR and urinary albumin-creatinine ratio) was 1.3 (95% CI, 1.1–1.6) [7]. In a survey conducted in nondiabetic native Americans (the intertribal heart project), the MetS was associated with a twofold increase on prevalence of microalbuminuria [13]. In The Third National Health and Nutrition Examination Survey (NHANES III), independent excess risks for CKD were hypertension, low HDL cholesterol, hypertriglyceridaemia, fasting hyperglycemia, and large waist circumference after adjustment for several confounding factors [14]. Notably, the ORs of CKD (eGFR $< 60\,\text{mL/min}$ per $1.73\,\text{m}^2$) were 2.60 (95% CI, 1.68–4.03) and 1.89 (95% CI, 1.34–2.67) in patients with or without MetS, respectively. This study also found that even mildly elevated blood pressure or mild hyperglycemia may portend an increased risk of CKD and microalbuminuria. Remarkablely, high blood pressure was the most powerful predictor of CKD in patients with MetS and with the OR of 2.66 (95% CI, 1.62–4.35) [14, 15]. In Atherosclerosis Risk in Communities (ARIC) study, a 9-year follow-up survey of 10,096 nondiabetic patients, the OR was 1.43 (95% CI, 1.18–1.73) for the development of CKD in subjects with MetS [16]. Furthermore, the OR was 1.24 (95% CI, 1.01–1.51) even after being adjusted for the subsequent development of diabetes and hypertension [16]. Accordingly, it is suggested that diabetes and hypertension were responsible for the renal injury progress. In addition, previous studies also suggested that dyslipidemia may also affect the prognosis of CKD [17–20]. Observations in the Modification Diet Renal Disease (MDRD) cohort indicated that low high-density lipoprotein (HDL) cholesterol predicts faster CKD progression [14, 21].

The findings of several previous studies conducted different ethnicities have that MetS per se affected CKD. A population-based study of native American adults resulted in multivariate-adjusted ORs of CKD for patients with 0 or 1 component of the MetS; patients with 2, 3, 4, and 5 components of CKD had multivariate-adjusted ORs of 2.21 (CI, 1.16 to 4.24), 3.38 (CI, 1.48 to 7.69), 4.23 (CI, 2.06 to 8.63), and 5.85 (CI, 3.11 to 11.0), respectively. The corresponding multivariate-adjusted ORs of microalbuminuria for patients with 3, 4, and 5 components were 1.62 (CI, 1.10 to 2.38), 2.45 (CI, 1.55 to 3.85), and 3.19 (CI, 1.96 to 5.19), respectively [14]. Another study in the US showed that the OR for microalbuminuria was 1.8 for one MetS component, 1.8 (95% CI, 1.0 to 3.2) for two components, and 2.3 (95% CI, 1.1 to 4.9) for three or more components (versus no traits) after controlling age, sex, smoking, body mass index, education, and family histories of diabetes and kidney disease [13]. A cross-sectional survey of Chinese adults resulted that the multivariate-adjusted ORs (95% CI) of CKD in participants with and without the MetS were 1.64 (1.16–2.32) and 1.36 (1.07–1.73). Compared to participants without any component of the MetS, the multivariate-adjusted ORs (95% CI) of CKD were 1.51 (1.02, 2.23), 1.50 (0.97, 2.32), 2.13 (1.30, 3.50), and 2.72 (1.50, 4.93) for those with 1, 2, 3, and 4 or 5 components, respectively. The corresponding multivariate-adjusted ORs (95% CI) of elevated serum creatinine were 1.11 (0.88, 1.40), 1.39 (1.07, 2.04), 1.47 (1.06, 2.04), and 2.00 (1.32, 3.03), respectively [26].

In summary, high blood pressure and hyperglycemia seem to be the most powerful predictors of CKD in subjects with MetS. Several population-based studies supported the effect of MetS on CKD even after adjusting for the influences of diabetes and hypertension. Although the ORs of renal injury in different ethnicities were varied widely (Table 1), all these results suggested that OR was higher in patients with MetS than those without even adjusting for age and gender. Furthermore, previous studies also suggested that the ORs of renal injury increased with the increase in the number of metabolic abnormalities, and the findings seem to be independent of ethnicity. These findings suggest that MetS per se is an important causative factor for CKD.

3. Reliable Markers of the Renal Injury

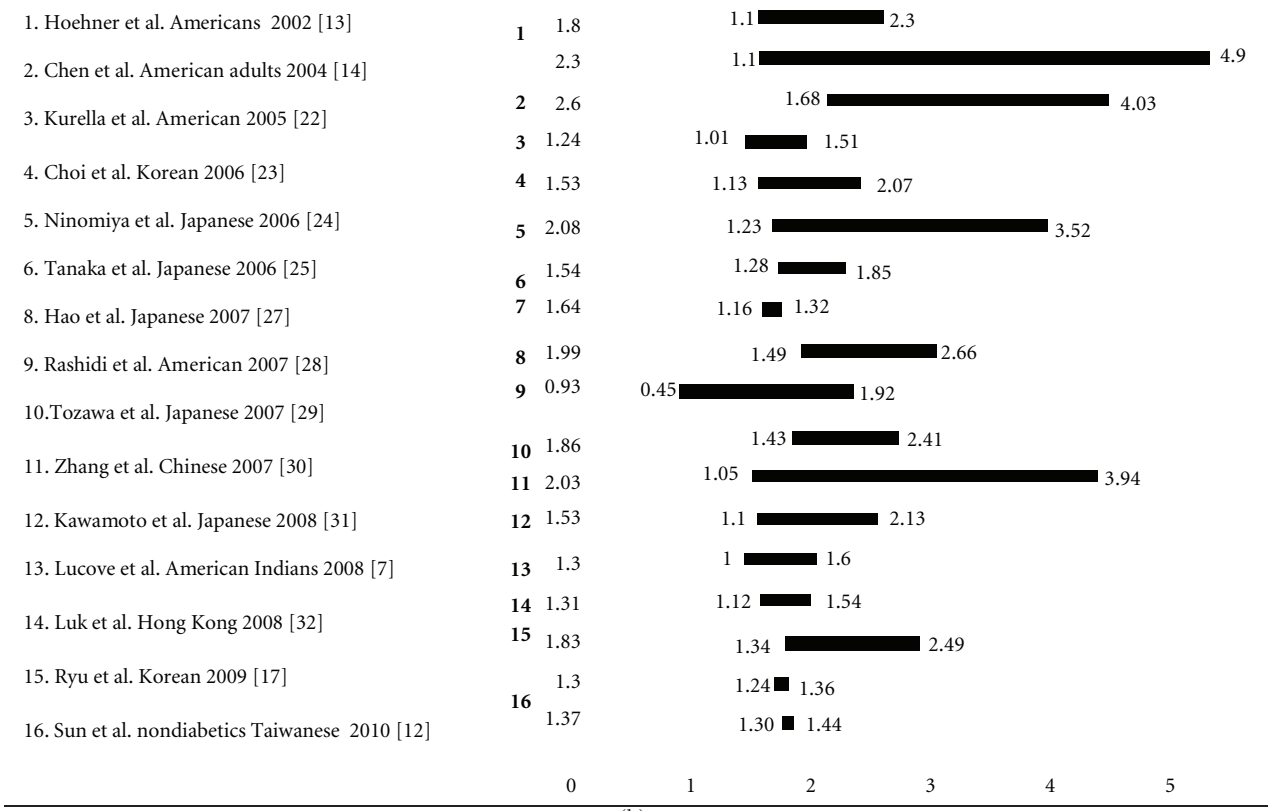
3.1. The Definitions of Metabolic Syndrome. In 1988, "Syndrome X" was introduced by Reaven, who proposed that insulin resistance plays a crucial role in glucose intolerance, hyperinsulinemia, hypertension, increased plasma triglyceride (TG), and decreased HDL cholesterol, all of which are associated with atherosclerosis and increased risk of coronary artery disease [1, 33]. The potential causes of insulin resistance include the unhealthy life style, obesity, and male, genetic, and environmental factors [34–37]. World Health Organization (WHO) designated the clustering of the cardiovascular and metabolic risk factors as "MetS" [38]. Other diagnostic criteria of MetS include National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP III) [2, 39] and International Diabetes Federation (IDF) [40]. Each diagnostic criterion has its essential criteria, for example, central obesity is a prerequisite for the MetS according to the IDF criteria, but microalbuminuria is considered a criterion only by the WHO. Recently, a cross-sectional epidemiological study of Taiwan population had reported that the adjusted ORs of microalbuminuria based on five different definitions of MetS are varied (Table 2) [41]. Insulin resistance is considered to be the key mechanism of MetS [1, 42–44], but it is difficult to be quantified. In order to increase predictive power, some experts suggest that more related biomarkers may be needed, such as high-sensitivity C-reactive protein, uric acid, and other inflammation marker [36, 45–48].

3.2. The Reliable Markers of the Renal Injury. In general, biomarkers are used for diagnosis, severity classification, and outcome prediction. We will discuss two traditional biomarkers, eGFR and urine albumin, and one new marker serum cystatin C [6, 7, 9, 14, 23, 27, 50–55]. Which of them is the most reliable and powerful marker in evaluating patients with MetS remains controversial.

3.2.1. eGFR. Among individuals with CKD, the stages are defined based on the level of GFR, which is estimated by a formula based on the value of creatinine [56]. CKD shares

Table 1: OR of CKD in MetS: population-based studies.

(a)



(b)

Study	Ethnicity	Adjusted risk factors		OR (95% CI)
(1) Hoehner et al. 2002 [13]	Americans	Age	+	1.8 (1.1–2.3)~2.3 (1.1–4.9) difference insulin resistance syndrome trait powerful traits hypertension, impair fasting glucose
		Sex	+	
		HTN		
		DM		
(2) Chen et al. 2004 [14]	American adults	Age	+	2.60 (1.68–4.03)
		Sex	+	
		HTN		
		DM		
(3) Kurella et al. 2005 [22]	Americans	Age	+	1.24 (1.01–1.51)
		Sex	+	
		HTN	+	
		DM	+	
(4) Choi et al. 2006 [23]	Korean	Age	+	1.53 (1.13–2.07) Powerful traits TG and waist circumference
		Sex	+	
		HTN	+	
		DM		
(5) Ninomiya et al. 2006 [24]	Japanese	Age	+	2.08 (1.23–3.52)
		Sex	+	
		HTN		
		DM		

(b) Continued.

Study	Ethnicity	Adjusted risk factors		OR (95% CI)
(6) Tanaka et al. 2006 [25]	Japanese	Age	+	1.54 (1.28–1.85)
		Sex	+	
		HTN		
		DM		
(7) Chen et al. 2007 [26]	Chinese adults	Age	+	1.64 (1.16–1.32)
		Sex	+	
		HTN		
		DM		
(8) Hao et al. 2007 [27]	Japanese	Age	+	1.99 (1.49–2.66)
		Sex	+	
		HTN		
		DM		
(9) Rashidi et al. 2007 [28]	Americans	Age	+	0.93 (0.45–1.92)
		Sex	+	
		HTN	+	
		DM		
(10) Tozawa et al. 2007 [29]	Japanese	Age	+	1.86 (1.43–2.41)
		Sex	+	
		HTN		
		DM		
(11) Zhang et al. 2007 [30]	Chinese	Age	+	2.03 (1.05–3.94)
		Sex	+	
		HTN	+	
		DM	+	
(12) Kawamoto et al. 2008 [31]	Japanese	Age	+	1.53 (1.1–2.13)
		Sex	+	
		HTN	+	
		DM	+	
(13) Lucove et al. 2008 [7]	American Indians	Age	+	1.3 (1.0–1.6)
		Sex	+	
		HTN		
		DM		
(14) Luk et al. 2008 [32]	Hong Kong	Age	+	1.31 (1.12–1.54) Powerful traits central obesity, hypertriglyceridemia, hypertension, and low BMI were independent predictors for CKD.
		Sex	+	
		HTN		
		DM		
(15) Ryu et al. 2009 [17]	Korean	Age	+	1.83 (1.34–2.49) Powerful traits increased TG and LDL cholesterol levels were associated with significantly increased risk of CKD
		Sex	+	
		HTN	+	
		DM	+	
(16) Sun et al. 2010 [12]	nondiabetc Taiwanese	Age	+	ATP-III-MetS1.3 (1.24–1.36) IDF –MetS 1.37 (1.30–1.44)
		Sex	+	
		HTN	+	
		DM	+	

Table 2: Definitions of metabolic syndrome and adjusted ORs of associated microalbuminuria.

	WHO 1998 [38]		EGIR 1999 [49]		NCEP ATP III 2001 [39]		IDF 2005 [40]		AHA 2005 [2]	
Essential criteria Definition of MetS	IFG, IGT, or IR plus 2 of other 5 criteria		Insulin in top 25% plus 2 of other 4 criteria		Any 3 of 5 criteria listed below		Increased waist plus any of 2 of other 4 criteria		Any 3 of 5 criteria listed below	
Abdominal obesity (men/women)	Waist-to-hip ratio >0.9/0.85 BMI > 30 (kg/m^2)		Waist $\geqq$ 94/80		Waist > 90/80		Men ≥94 cm (European) ≥90 cm (Chinese) ≥90 cm (South Asian) ≥85 cm (Japanese)	Women ≥80 cm (European) ≥80 cm (Chinese) ≥80 cm (South Asian) ≥90 cm (Japanese)	Waist $\geqq$ 90/80	
Triglycerides (nmol/L)	$\geqq$1.7 or drug treatment for this lipid abnormality		>2.0 or drug treatment for this lipid abnormality		$\geqq$1.7 or drug treatment for this lipid abnormality		$\geqq$1.7 or drug treatment for this lipid abnormality		$\geqq$1.7 or drug treatment for this lipid abnormality	
HDL cholesterol (nmol/L) (men/women)	<0.9/1.0 or drug treatment for this lipid abnormality		<1.0 or drug treatment for this lipid abnormality		<1.0/1.3 or drug treatment for this lipid abnormality		<1.0/1.3 or drug treatment for this lipid abnormality		<1.0/1.3 or drug treatment for this lipid abnormality	
Blood pressure (mmHg)	More than 140/90 or drug treatment for hypertension		More than 140/90 or drug treatment for hypertension		More than 130/85 or drug treatment for hypertension		More than 130/85 or drug treatment for hypertension		More than 130/85 or drug treatment for hypertension	
Fasting glucose (nmol/L)	More than 6.1 HOMA-IR >2.53		More than 6.1		More than 6.1		More than 5.6		More than 5.6	
Urinary albumin excretion	More than 30 mg/g creatinine		—		—		—		—	
Adjusted ORs (95% CI) of microalbuminuria [41]	Men 4.44*** (2.85–6.91)	Women 4.16*** (2.57–6.73)	Men 2.62*** (1.49–4.60)	Women 1.80 (0.99–3.29)	Men 1.99 (1.31–3.03)	Women 2.21*** (1.47–3.32)	Men 1.51 (0.97–2.35)	Women 2.29*** (1.51–3.48)	Men 1.64* (1.08–2.50)	Women 2.26*** (1.52–3.38)

World Health Organization (WHO), European Group for the Study of Insulin Resistance (EGIR), National Cholesterol Education Program (NCEP), Adult Treatment Panel III (ATP-III), International Diabetes Federation (IDF), American Heart Association and National Heart Lung and Blood Institute (AHA/NHLBI), Metabolic Syndrome (MetS); Body mass index (BMI); high-density lipoprotein (HDL); homeostasis model assessment of insulin resistance (HOMA-IR); insulin resistance (IR). Adjusted OR (95% CI) of microalbuminuria: a cross-sectional epidemiological study based on data from the Taichung Community Health Study [41]. *$P < .05$; **$P < .01$; ***$P < .001$.

many of the same risk factors as CVD, namely obesity [9, 57], high blood pressure [58–60], diabetes mellitus [51, 58], hypertriglyceridemia [61], low HDL level [18, 20, 51], and smoking [51]. These factors overlap with components of MetS [51]. Direct measurement of GFR value may be the most reliable measure of renal function. However, the obesity-related renal injury is also associated with glomerular hyperperfusion, hyperfiltration and causes slightly increases of GFR [9, 55].

3.2.2. Urine Albumin. Albuminuria is generally conceived as an attractive marker of MetS-related renal injury [6, 50]. According to the previous study, it is a better risk marker than low estimated GFR to identify individuals at risk for accelerated GFR loss [62] and even a target to improve cardiovascular and renal outcomes [63]. But some limitations should be noted in evaluation about the urinary albumin excretion for it would be affected by infection, stress condition and needed to be repeatedly measured. In addition, while end-stage renal disease causes the reduction of urine volume, albuminuria may no longer be increased with renal function progression.

3.2.3. Cystatin C. Cystatin C is suggested to be a new biomarker for the early detection of acute renal injury, MetS, and cardiovascular risk [52–55, 64–66]. According to the results of the Chennai Urban Rural Epidemiology Study (CURES) (MetS was defined using National Cholesterol Education Program criteria for adults modified for waist measured using the World Health Organization Asia Pacific guidelines. Serum cystin-C was estimated by a high-sensitivity particle-enhancing nephelometry assay),

it showed that subjects with four or five metabolic abnormalities had the highest cystatin C level. With decreasing number of metabolic abnormalities, the cystatin C levels decreased linearly (P for trend $< .001$), and it concluded that Cystatin C levels are highly correlated with the number of metabolic abnormalities in Asian Indians [67]. Previous evidence suggested that the measurement of serum cystatin C may be useful for evaluating cardiovascular risk profile [54]. A study reported that the association of cystatin C level with all-cause and CVD mortality is even stronger than that of GFR with these outcomes in stage 3 or 4 CKD [66]. Furthermore, cystatin C is considered to be a marker of inflammation as well as renal function [64]. Among elderly persons without CKD, cystatin C is a prognostic biomarker of risk for death, CVD and CKD, and seems to identify a preclinical state of kidney dysfunction that cannot be completely detected by measurement of serum creatinine or eGFR [65]. However, more clinical studies will be required to evaluate the clinical usefulness and cost effectiveness as compared with traditional markers.

4. Plausible Biologic Links between MetS and CKD

4.1. Hyperinsulinemia, Central Obesity, Hypertension, Dyslipidemia (Figure 1)

4.1.1. Hyperinsulinemia. Hyperinsulinemia-related insulin resistance is suspected to be the most important link between obesity and other metabolic complications leading to renal injury [9]. Insulin resistance and associated hyperinsulinemia may lead to renal involvement and injury through several different pathways. For example, activation of the renin-angiotensin system (RAS) with elevated angiotensin II and aldosterone, which subsequently affect insulin/insulin-like growth factor-1 signaling pathways, reactive oxygen species formation to destroy endothelial function, would cause the development of CVD [68]. Hyperinsulinemia causes atherosclerosis through hyperglycemia and dyslipidemia and endothelial dysfunction by inducing oxidative stress and attenuating peroxisome proliferator-activated receptor (PPAR) gamma, and the downregulation of peroxisome proliferator-activated receptors (PPARs) was proved by several studies in vivo [69, 70]. Adipokines and proinflammatory cytokines play an important role in the regulation of endovascular atherosclerosis [71].

4.1.2. Central Obesity. It is well known that patients with atherosclerotic complications are at a higher risk of CKD. Abdominal obesity is especially related to incident CKD and mortality. Inflammatory genes and genes implicated in insulin resistance are overly expressed in glomeruli of patients with obesity-related nephropathy [34, 35, 72]. Adipose tissue is the source of a novel group of hormonally active substances known as adipokines. Adipokines including IL-6, TNF-α, and plasminogen activator inhibitor-1 (PAI-1) may cause tissue damage by a direct proinflammatory mechanism or insulin resistance (some adipokines improve insulin resistance, for example, leptin, adiponectin, and Visfatin) (Table 3) [4, 73, 74] and can be translated into inflammatory changes in the kidney [48, 71].

4.1.3. Hypertension. Hypertension cause, nephrosclerosis by blood pressure-dependent and -independent mechanisms. In addition, adipokines is implicated in hypertension and sodium retention secondary to obesity because it potently activates the sympathetic system, including sympathetic activity in the kidney [21]. Because of the interference with glomerular hemodynamics and with inflammatory mechanisms, the RAS is of paramount importance in CKD generation, and the angiotensin-II blockade significantly reduces cytokines and oxidative stress [75]. Reduced GFR has been found in prehypertensive patients with high blood pressure load as well as increased proteinuria, suggesting that even mild elevated blood pressure puts patients at risk of developing renal injury [19, 76–78]. Evidence of relationship between hypertension and CKD is further supported by several clinical studies. Hypertension seems to be an important risk factor of CKD (detected by eGFR and albuminuria) for the elders [78]. A recent study, using NHANES 1999–2004 data (n = 15,332; age $\geq$ 20 years), indicated that the effects of CVD are less dramatic when hypertension and diabetes are considered [79].

4.1.4. Dyslipidemia. Dyslipidemia is related to the incidence and prognosis of CKD through the following mechanisms, such as inflammation and increased oxidative stress, which would cause endothelial damage and atherosclerosis diseases [80–82]. The mechanisms discussed above are congruent with some clinical evidences, for example, hypertriglyceridemia is an independent risk factor for CKD [61], and low HDL cholesterol predicts CKD progression [21].

4.2. Impact of Treating the MetS on the Risk of Kidney Injury or CKD Progress. The effects of MetS treatments in improving renal outcomes remain largely unexplored. We try to discuss the effects of the interventions in controlling MetS components based on limited evidence (Figure 1).

The adjusted ORs of renal injury associated with individual or multiple components of the MetS had ever been investigated. A cross-sectional survey conducted in a nationally representative sample of 15160 Chinese adults showed that the adjusted ORs of CKD with hypertension, impaired fasting glucose, waist >102 cm in men or >88 cm in women, high triglyceride, low HDL cholesterol were 1.17 (CI, 0.88 to 1.56), 1.93 (CI, 1.40 to 2.76), 1.95 (CI, 1.21 to 3.14), 0.92 (CI, 0.68 to 1.24), and 1.34 (CI, 0.98 to 1.83), and the ORs of renal injury increased with increasing the number of metabolic abnormalities [26].

4.2.1. Hyperglycemia. It is widely recognized that intensive treatment of hyperglycemia can significantly delay the onset of albuminuria and decrease the risk of diabetic CKD [83–85]. Some evidences about using insulin sensitizer (e.g., Thiazolidinedione and Metformin) suggested that

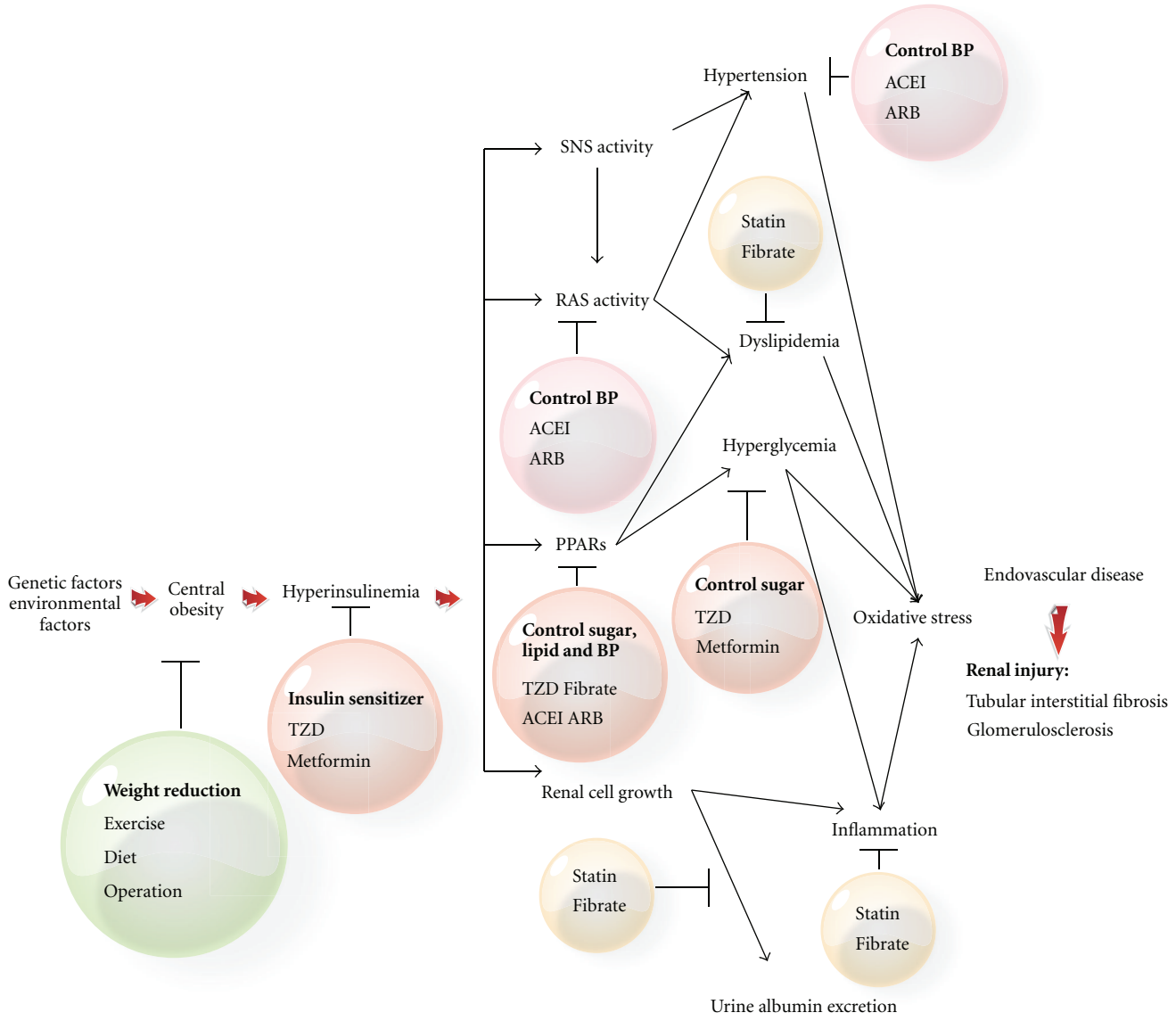


Figure 1: Mechanisms of insulin resistance with the consequent development of renal injury and the target of treatments. SNS: sympathetic nervous system, RAS: renin-angiotensin system, PPAR: peroxisome proliferator-activated receptors, ACEI: angiotensin-converting enzyme inhibitor, ARB: angiotensin II receptor blocker, TZD: thiazolidinediones.

improving endothelial function may be beneficial to renal injury [86, 87].

4.2.2. Obesity. Exercise improves insulin resistance, values of TG, HDL cholesterol, and blood pressure in patients with the MetS. A cross-sectional analysis showed that reduced renal function correlated with lower physical activity [88], and previous evidence reported the improvement of microalbuminuria after intense exercise in patients with MetS [89]. *Dietary changes* are as follows: a low-calorie diet can improve CKD while high protein intake may worsen proteinuria and induce renal injury [90]. *Antiobesity drugs.* Orlistat blocks intestinal lipase and produces modest weight loss; it did not show obvious improvment on serum creatinine in 3 months of continuous study [91]. Sibutramine is a serotonin-norepinephrine reuptake inhibitor; it may improve insulin sensitivity [92], but a previous study reported that sibutramine exhibited weight loss and reductions of cystatin C levels at 6 months, while serum creatinine levels were not reduced [93]. It has a warning on its label from the US Food and Drug Administration because of cardiovascular risk. *Surgical treatment* includes a variety of procedures performed on people who are obese,

Table 3: The Adipokines effect on insulin sensitivity.

Adipokines (Adipose-derived protein)	Effect on insulin sensitivity [73]	Clinical significance in CKD [4, 74]
Resistin	Decline	Elevated serum levels Similar levels in both HD and PD Associated to heart disease in dialysis [4]
TNF-α	Decline	Elevated serum level Enhance gene expression of TNF-α in circulating blood cells in uraemia Elevated TNF-α associated to increased mortality in HD Anorexia and a poor nutritional status in PD [4]
IL-6	Decline	Elevated serum levels Reliable predictor of mortality Better mortality predictor than TNF-α in CKD and HD [4]
PAI-1	Decline	Elevated serum level Plasma PAI-1 levels increase in several chronic inflammatory states that are associated with CKD It may contribute to the pathogenesis of the accelerated vascular disease in this patient population [74]
Leptin	Improvement	Markedly elevated serum level Clinical marker of body fat content in dialysis Associated to inflammation, atherogenic lipid profile, and insulin resistance in CKD Low leptin is an independent risk factor for mortality in HD [4]
Adiponectin	Improvement	Elevated serum level Inversely associated with metabolic risk factors in uremia Inversely associated with CV events in HD Improved survival and better outcome in dialysis patients [4]
Visfatin	Improvement	Elevated serum level Anorexigenic Decreased circulating levels of amino acids and triacylglycerols Mortality predictor in CKD [4]

IL-6: interleukin-6, PAI-1: plasminogen activator inhibitor-1, TNF-α: tumor necrosis factor-alpha, HD: hemodialysis, PD: peritoneal dialysis.

reducing the size of the stomach with an implanted gastric banding or sleeve gastrectomy or biliopancreatic diversion with duodenal switch or gastric bypass surgery. Bariatric surgery may achieve long-term weight loss in patients with morbid obesity, improve the MetS, and reduce mortality, but the prevalence of microalbuminuria after surgery was only reduced in the diabetic group [91]. Reduction in albuminuria associated with improvement in glomerular hyperfiltration after gastroplasty has been reported [94]. However, we should notice the serious complications, such as oxalate nephropathy and nephrolithiasis, following bariatric surgery. Therefore, both surgical and nonsurgical approaches appear to be effective at reducing blood pressure and proteinuria [95]. A meta-analysis including thirteen studies reported that in smaller, short-duration studies in patients with CKD, nonsurgical weight loss interventions reduce proteinuria and blood pressure and prevent further decline in renal function; while in morbidly obese patients with glomerular hyperfiltration, surgical interventions normalize GFR and reduce blood pressure and microalbuminuria [96].

4.2.3. Hypertension. Blood pressure control helps in reducing CVD risk and CKD progression [97–101]. A continuous study of 8.8 to 12.2 years stint in evaluating the progression of CKD, which was defined as a doubling of the serum creatinine level, a diagnosis of end-stage renal disease, or death, and showed that intensive blood-pressure control (the mean blood pressure was 130/78 mmHg in the intensive-control group and 141/86 mmHg in the standard-control group) had no effect on kidney disease progression but may lead to differential effects on intensive blood-pressure control in patients with and those without baseline proteinuria [100]. Different antihypertensive drugs may have different effects on the protection of CKD [101]. Angiotension II signaling and subsequent oxidative stress in adipose tissue may be potential targets for the prevention of atherosclerotic cardiovascular disease in MetS and also in metabolic syndrome-based CKD [75], and a previous study reported that the Angiotensin-converting enzyme inhibitors (ACEIs) appear to be more effective than beta blockers or dihydropyridine calcium channel blockers in slowing GFR decline [101]. ACEI is recommended for the treatment of hypertension in patients with CKD and is considered a prognostic factor of CKD [102]. Previous evidences suggested that angiotensin-receptor blockers (ARBs) could reduce proteinuria, but the results are variable. A study provided that ARB inhibits albumin-elicited proximal tubular cell apoptosis and injury in vitro [103]. A meta-analysis from January 1990 to September 2006 also reported that the ARBs reduce proteinuria, and

the reduction in proteinuria from ARB and ACEI is similar [104].

4.2.4. Dyslipidemia. Fibrate therapy can decrease TG, increase HDL cholesterol, improve insulin sensitivity, and reduce the mesangium-induced glumerular matrix deposition [105]. Statin therapy can decrease LDL, TG, reduce inflammation, and improve endothelial function [106–109]. The current data are based on effects of proteinuria [110].

5. Relationship between MetS, Renal Injury, and CVD

It is known that CKD is associated with decreased cardiac function, ventricular hypertrophy, diastolic dysfunction, and increased risk of adverse cardiovascular events [111]. The components of MetS may contribute to the pathophysiological interactions between heart and kidney in type 4 cardiorenal syndrome and cause subsequent cardiac damage (traditional risk factors are diabetes, hypertension, low HDL cholesterol, and physical inactivity; nontraditional risk factors are albuminuria, oxidative stress, or high sympathetic tone) [111, 112]. A recent study reported the association between MetS, CKD, and left ventricular hypertrophy (LVH) and suspected that the combination of MetS and CKD is a strong risk for LVH as well as a strong and independent predictor of subsequent CVD [113]. Furthermore, a previous study indicated that the coexistence of early CKD with MetS could increase the accuracy of risk prediction for CVD mortality [114].

6. Conclusions

In addition to the effect of diabetes and hypertension, MetS is related to the incidence and prognosis of renal injury and CKD. MetS-associated renal injury may predict the subsequent CVD and even the mortality. Further studies about the MetS components that are implicated in renal damage can help to establish the targets in intervention of MetS in order to prevent CKD and CVD.

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Review Article

Cardiovascular Complications in CKD Patients: Role of Oxidative Stress

Elvira O. Gosmanova[1] and Ngoc-Anh Le[2,3]

[1] *Nephrology Division, Department of Medicine, The University of Tennessee Health Science Center, Memphis, TN 38103, USA*
[2] *Lipid Research Laboratory, Emory University School of Medicine, Atlanta, GA 30322, USA*
[3] *Atlanta Veterans Affairs Medical Center, Decatur, GA 30033, USA*

Correspondence should be addressed to Ngoc-Anh Le, ale@emory.edu

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Starting with the early stages, patients with chronic kidney disease (CKD) experience higher burden of cardiovascular disease (CVD). Moreover, CVD complications are the major cause of mortality in CKD patients as compared with complications from chronic kidney failure. While traditional CVD risk factors, including diabetes, hypertension, hyperlipidemia, obesity, physical inactivity, may be more prevalent among CKD patients, these factors seem to underestimate the accelerated cardiovascular disease in the CKD population. Search for additional biomarkers that could explain the enhanced CVD risk in CKD patients has gained increasing importance. Although it is unlikely that any single nontraditional risk factor would fully account for the increased CVD risk in individuals with CKD, oxidative stress appears to play a central role in the development and progression of CVD and its complications. We will review the data that support the contribution of oxidative stress in the pathogenesis of CVD in patients with chronic kidney failure.

1. Introduction

Cardiovascular disease (CVD) is a major cause of morbidity and mortality in patients with chronic kidney disease (CKD) [1, 2]. Even early stages of CKD that are characterized by relatively preserved or minimally decreased overall renal function are associated with increasing incidence of *de novo* and recurrent CVD events [3, 4]. As glomerular filtration rate (GFR) diminishes, the prevalence and severity of CVD abnormalities have been reported to be increasing [5, 6]. Among patients with stages III-IV CKD, the prevalence of CVD is 4- to 5-fold higher than that observed for the general population. CKD patients are known to be affected by diabetes, hypertension, and obesity—which are known traditional CVD risk factors in general population [7, 8]. However, cross-sectional studies demonstrated that the Framingham Risk Score which is based on the traditional CVD risk factors failed to determine the extent of CVD risk in subjects with CKD and those with end-stage renal disease (ESRD) [9–11], and other factors must be involved in the increased CVD prevalence in this high-risk population [12, 13]. Before a new biochemical marker could be considered as CVD risk factor, it must meet the following conditions: (a) evidence of the biological plausibility as to why the factor may promote CVD risk; (b) demonstration that the risk factor level increases with severity of kidney disease; (c) evidence of an association between the risk factor and cardiovascular disease in CKD patients; (d) demonstration in double-blind, randomized placebo-controlled clinical trials that treatment of the risk factor decreases CVD outcomes. Available data on the importance of oxidative stress as one of the contributing factors in the prevalence and severity of CVD abnormalities in patients with chronic kidney disease will be summarized in the following sections.

2. Role of Oxidative Stress in CVD

Oxidative stress (OxStress) is recognized as a critical factor in the development of atherosclerotic cardiovascular disease

(ACVD) [14, 15]. According to the oxidation hypothesis of atherosclerosis, low-density lipoprotein (LDL) in its native state is not atherogenic [16, 17]. LDL must undergo oxidative modification before it can contribute to the initiation and progression of atherosclerosis [16, 17]. Data from animal models of atherosclerosis, both diet-induced and genetically altered models, have demonstrated the presence of oxidized LDL (oxLDL) in plasma as well as in atherosclerotic lesions [18, 19]. Presence of oxLDL, autoantibodies against malondialdehyde-modified LDL, and of LDL-IgG immune complexes has also been reported in human plasma and human atherosclerotic lesions [18, 19]. The pathways involved in the formation of these oxidative markers and the relationship between these markers and disease progression remain to be elucidated.

In case-control studies, some reports have suggested a positive relationship between autoantibodies against MDA-LDL (one form of oxLDL) and disease severity [20, 21], while others have noted no relationship [22] or inverse relationship [23] between autoantibody levels to oxLDL and the extent of atherosclerosis. In the Watanabe rabbit, animals with high autoantibody levels following immunization with oxLDL were found to have less severe lesions than animals with low antibody levels [24]. We have reported that independent of fasting levels of autoantibodies, patients with diseased endothelium demonstrated a characteristic acute and transient reduction in autoantibody levels following meal consumption [25]. Such a reduction in autoantibody levels was not observed in young healthy controls with one or less than one risk factor. We also reported that this meal-induced reduction in autoantibody levels is unique to meal challenges that are enriched in polyunsaturated fatty acids. Isocaloric meal challenges containing primarily saturated or monounsaturated fatty acids failed to induce the transient reduction in autoantibody levels in these same individuals [26, 27].

A large body of evidence suggests that oxidized low-density lipoprotein (oxLDL) is the leading candidate in the pathogenesis of atherosclerosis [28] and may serve as a unique mediator of oxidative status in the vascular environment [28]. While the emphasis is on the oxidative modification of LDL, all plasma lipoproteins are subjected to oxidative modification [29]. Case-control studies as well as a limited number of prospective studies have linked the level of oxLDL to disease severity. Due to the heterogeneity of oxLDL and the available epitopes that are recognized by the various antibodies, a number of different immunoassays are available for oxLDL, and the correlation among these measurements is quite poor [30]. Several studies have reported strong and independent relationship between measures of oxLDL and CVD [31–33], including metabolic syndrome [34]. Data from progression/regression studies with nonhuman primates actually complicated the relationship between indices of LDL oxidation and disease status. Using antibodies that recognized the oxidative epitopes of phospholipids moiety of LDL (oxPL), diet-induced atherosclerosis is associated with increased levels of oxLDL and increased levels of total oxPL as well as oxPL/apoB [35]. With regression, as LDL-cholesterol is reduced, there was a modest reduction in total oxPL but a statistically significant increase in oxPL/apoB [35]. In humans, data from clinical trials (REVERSAL, MIRACL) with aggressive LDL-cholesterol reduction also reported and unexpected increase in oxPL/apoB [36, 37].

Oxidative modification of LDL resulted in the formation of a lipid-rich particle with specific characteristics that contribute to the development of early atherosclerosis [38]. By inducing adhesion molecules (VCAM-1) and specific receptors, oxLDL stimulates the adhesion of circulating monocytes to endothelial cells [39]. oxLDL can also stimulate the production and release of monocyte chemotactic protein-1 (MCP-1) by endothelial cells and smooth muscle cells resulting in the enhanced migration of monocytes into the arterial intima [40]. oxLDL has also been reported to inhibit in vitro proliferation and survival of vascular cells [41] as well as alterations in the normal function of endothelial cells [42]. Additionally, oxLDL has prothrombotic activity and increases platelet activation and expression of tissue factor and PAI-1 (plasminogen activator inhibitor 1) by endothelial cells [43].

3. Oxidative Stress in CKD

Oxidative stress is a state of imbalance between free radicals production and their degradation by antioxidant systems with increased accumulation of the radicals. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are examples of free radicals. Over 90% of ROS formation occurs "accidentally" in mitochondria during metabolism of oxygen when some of electrons passing "down" the electron transport chain leak away from the main path and go directly to reduce oxygen molecules to the superoxide anion [44]. In addition, ROS could be "deliberately" synthesized in phagocytic cells, as well as in vascular wall and various other tissues by enzymes such as NAD(P)H oxidase, myeloperoxidase, xanthine oxidase, cyclooxygenase, and lipoxygenase [45]. At low concentrations, ROS (superoxide anion, hydrogen peroxide, hydroxyl radical, hypochlorite ion, and hydroperoxyl radical) involved the vast array of physiologic functions. For example, ROS are known regulators of nitric oxide synthesis, intracellular signaling cascades, including cytokines, growth factors, MAPK, and NF-κB, and also involved in the modulation of immune responses, apoptosis, and mutagenesis [46–48]. Additionally, ROS produced during phagocytic burst is a key defense mechanism against environmental pathogens. However, when ROS are made in excess, they can react with various molecules such as lipids, carbohydrates, proteins, and DNA altering their structure and function, resulting in cellular damage that leads to pathologic processes including, but not limited to, atherosclerosis development. These potentially deleterious reactions are controlled by a system of enzymatic and nonenzymatic antioxidants which eliminate pro-oxidants and scavenge-free radicals. Superoxide dismutase (SOD), glutathione peroxidase, glutathione reductase, and catalase are among the main enzymatic antioxidants. Glutathione, thiols, ascorbic acid, alpha-tocopherol (vitamin E), mixed carotinoids, and bioflavonoids are among the nonenzymatic antioxidant defense processes.

Direct measurement of free radicals in vivo is difficult due to the highly reactive nature of these compounds and minute concentrations in biological fluids. Instead, we rely on measurement of stable end products of oxidation of different molecules. Numerous biomarkers of oxidative stress have been shown to be elevated in patients with CKD. These include products of lipid oxidation (lipid peroxides, malondialdehyde, and thiobarbituric acid reactive substances) and oxidized LDL [49, 50], advanced oxidation protein products (AOPPs) [51], F2 isoprostanes and isolevuglandins (a family of reactive γ-ketoaldehydes generated by free radical oxidation of arachidonate-containing lipids through the isoprostane pathway) [52, 53], and 8-hydroxyl 2′-deoxyguanosine—marker of oxidative DNA damage [54]. Furthermore, indices of OxStress are increased with severity of kidney disease. For example, glomerular filtration rate has been reported to be inversely associated with levels of AOPP [51], malondialdehyde (MDA) [55], and F2 isoprostanes [56, 57], suggesting that decline in renal function may have direct effect on worsening of oxidative stress.

The nature of oxidative stress in chronic kidney disease remains to be elucidated. Impaired oxidative balance in CKD is likely to come from a combination of increased ROS production and reduced clearance as well as an ineffective antioxidant defense mechanism. Several important antioxidant pathways have been reported to be altered in patients with CKD, including reduced erythrocyte SOD activity [55], reduced plasma thiol groups [58], diminished plasma glutathione, and glutathione peroxidase function [59]. However, total antioxidant capacity (TAC) of plasma remains normal or even becomes elevated as CKD progresses [57]. Elevated concentrations of uric acid in CKD patients have been suggested to account for the high capacity for peroxyl radicals that constitute the substrate for the in vitro TAC assay [60].

CKD patients are typically affected by multiple concomitant diseases such as diabetes and hypertension (HTN) which are also associated with oxidative stress [61, 62]. Increased activity of baseline and stimulated NAD(P)H oxidase are responsible for overproduction of superoxide anion, in circulating peripheral mononuclear (PMN) cells isolated from patients with stage I-II CKD [63]. The presence of CKD appears to further enhance the oxidative stress independently from underlying conditions. Agarwal [64] reported that urinary MDA excretion and protein carbonylation were increased in hypertensive patients with concomitant CKD as compared with patients with HTN and no CKD. The renin-angiotensin-aldosterone system (RAAS) plays an important role in activation of NAD(P)H oxidase in vascular smooth muscle cells and the kidney [65, 66]. Additionally, NAD(P)H oxidase could be activated by cytokines (*TNF*α), hyperglycemia, and mechanical stress [65]. Therefore, rigorous studies examining the relation between oxidative stress, CKD, and underline diabetes and HTN are needed in humans to clearly establish if oxidative stress is a marker of severity of underline condition leading to CKD or that CKD independently further promotes OxStress.

Hemodialysis—a procedure utilized as part of usual care in the management of terminal chronic kidney disease, has also been demonstrated to contribute to OxStress. Contact of blood with dialysis membrane during extracorporeal blood purification can lead to PMN cell activation and generation of ROS [67, 68]. Presence of inadequately removed endotoxin in water used for dialysate preparation also influences PMN activation and ROS production in hemodialysis patients [69]. Myeloperoxidase (MPO) activity has been found to be increased during hemodialysis, especially with the use of bioincompatible dialysis membranes [70]. Moreover, heparin that is routinely used for anticoagulation during hemodialysis is known to activate MPO leading to increased ROS production [71]. Intravenous administered heparin can also displace extracellular-superoxide dismutase (EC-SOD) from vascular endothelium [72] by interfering with the binding of the antioxidant enzyme to type C heparin sulfate proteoglycans. It has been suggested that EC-SOD is the major determinant of nitric oxide bioavailability in blood vessels, and loss of EC-SOD from vascular wall may contribute to endothelial dysfunction [73]. Additionally, plasma ascorbic acid and lipid-soluble alpha-tocopherol, both potent components of an antioxidant defense system, were significantly reduced after single hemodialysis session [74–76]. However, the hemodialysis procedure was also reported to have beneficial effects on total antioxidant capacity by increasing plasma thiol content [76, 77].

4. Association between Oxidative Stress Biomarkers and CVD in CKD Patients

Strong correlation between oxidative markers and the presence and extent of cardiovascular diseases was found in the general population as outlined in the recent paper [78]. Moreover, oxidative markers were shown to be important predictors of cardiovascular outcomes in prospective analyses [79–83]. Unfortunately, the limited number of studies examined the relationship between oxidative stress markers and cardiovascular disease in patients with kidney failure. Drüeke et al. [84] found that levels of AOPP strongly correlated with carotid artery intima-medial thickness (IMT) in 79 patients with ESRD. Similar finding was reported by Yang et al. in 109 patients with CKD [85]. Additionally, significant positive correlation between carotid artery IMT and TBARS [86] and MPO [87] and negative correlation between carotid artery IMT and reduced SOD and plasma sulfhydryl were reported in patients with ESRD [86]. Shoji et al. [88] observed a statistical trend in correlation between carotid artery IMT and autoantibodies against oxidized LDL. A stronger correlation was observed between femoral artery IMT and autoantibodies against oxidatively modified LDL in ESRD [88].

Prospective studies that examine the association between oxidative stress markers and clinical outcomes in hemodialysis patients are scarce. MPO levels have been shown to predict all-cause mortality in 356 chronic hemodialysis patients [89] with a hazard ratio of 1.14 (95% confidence interval 1.03–1.26) for each 1,000 pmol/L increase in MPO level. Interestingly, MPO gene polymorphism was also demonstrated to be associated with presence of CVD and higher CVD-related

mortality in ESRD patients [90]. Levels of autoantibodies against oxLDL were found to strongly predict cardiovascular mortality during 4 years of follow up in 94 hemodialysis patients [91].

5. Antioxidant Interventions and Cardiovascular Outcomes in Patients with CKD

Several small studies have examined the impact of antioxidant interventions on oxidative stress markers in patients with CKD [92–94]. Unfortunately, randomized controlled clinical trials addressing the impact of antioxidant interventions on CVD outcomes in patients with CKD are scarce. The SPACE (Secondary Prevention with Antioxidants of Cardiovascular Disease in End-Stage Renal Disease) was a clinical trial involving 196 patients with ESRD who were randomized to either 800 IU of alpha-tocopherol per day or placebo [95]. During a median followup period of 519 days, statistically significant reduction in the primary composite outcome, consisting of myocardial infarction (fatal and nonfatal), ischemic stroke, peripheral vascular disease, and unstable angina, was observed in patients receiving vitamin E supplementation [95]. The relative risk (RR) was 0.46 (95% confidence interval (CI) 0.27–0.78) in the vitamin E group as compared to the placebo.

In the second randomized controlled trial, N-acetylcysteine at oral dose 600 mg twice daily over a period of approximately 15 months also significantly reduced primary composite variable consisting of cardiac events including fatal and nonfatal myocardial infarction, cardiovascular disease death, need for coronary angioplasty or coronary bypass surgery, ischemic stroke, peripheral vascular disease with amputation, or need for angioplasty [96]. The relative risk was 0.6 (95% CI 0.38–0.95). However, no beneficial effects of vitamin E or N-acetylcysteine administration were observed on all-cause mortality, suggesting that exploration of additional strategies is needed to improve overall survival in dialysis patients. Subgroup analysis of some lipid-lowering studies which have included CKD patients has suggested that statin therapy may also reduce inflammatory and oxidative markers [97]. Additionally, subgroup of patients with CKD taking atorvastatin for a median period of 3.3 years had a statistically significant decrease in cumulative incidence for fatal and nonfatal stroke, total coronary events, total cardiovascular events, and all-cause mortality as compared to placebo in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA) [98]. However, it should also be noted that two large randomized clinical trials using atorvastatin [99] and rosuvastatin [100] failed to demonstrate any reduction of CVD events or all-cause mortality in patients with ESRD. Results from the Study of Heart and Renal Protection (SHARP) might shed more light on cardiovascular benefits of statin use in CKD patients [101]. Additional studies that address the efficacy of novel antioxidants including endogenous antioxidants such as hemeoxygenase-1 and bilirubin [102, 103] in reducing oxidative stress CKD patients are needed.

In summary, cardiovascular disease is an important cause of morbidity and mortality in patients with impaired kidney function. Increasing evidence strongly supports oxidative stress as plausible independent cardiovascular risk factor in patients with CKD. Nevertheless, several important questions remain unanswered. The exact processes underlying increased oxidative stress in CKD remain to be elucidated. Furthermore, identification of biochemical and/or functional biomarkers that could be used to monitor oxidative imbalance in CKD may allow the development of optimal intervention strategy to reduce oxidative stress in CKD.

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Review Article

Metabolic Syndrome, Chronic Kidney Disease, and Cardiovascular Disease: A Dynamic and Life-Threatening Triad

Mário Raimundo and José António Lopes

Department of Nephrology and Renal Transplantation, Centro Hospitalar Lisboa Norte, EPE, Hospital de Santa Maria, Avenida Professor Egas Moniz, 1649-035 Lisboa, Portugal

Correspondence should be addressed to José António Lopes, jalopes93@hotmail.com

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The metabolic syndrome (MS) and chronic kidney disease (CKD) have both become global public health problems, with increasing social and economic impact due to their high prevalence and remarkable impact on morbidity and mortality. The causality between MS and CKD, and its clinical implications, still does remain not completely understood. Moreover, prophylactic and therapeutic interventions do need to be properly investigated in this field. Herein, we critically review the existing clinical evidence that associates MS with renal disease and cardiovascular disease, as well as the associated pathophysiologic mechanisms and actual treatment options.

1. Introduction

During the last decades, we have witnessed a global epidemic of obesity [1]. A sedentary lifestyle and an atherogenic diet, along with genetic predisposition, are probably the driving forces of this problem. According to the last National Health and Nutrition Examination Survey (NHANES), more than one third of adult Americans are obese. The prevalence in children and adolescents is also rising at an alarmingly rate [2].

Obesity, particularly abdominal obesity, is associated with resistance to the effects of insulin on peripheral glucose and fatty acid utilization. The resulting hiperinsulinemia and hyperglycemia, as the release of adipocyte cytokines, have been shown to induce vascular endothelial dysfunction, an abnormal lipid profile, hypertension, and vascular inflammation, all of which are atherogenic [3–6]. The clustering of metabolic cardiovascular risk factors, under a common pathogenic process (insulin resistance), was described for the first time in 1988 by Reaven [3], leading to the concept of Metabolic Syndrome (MS). Since then, multiple definitions have been made, all of them considering some combination of insulin resistance, dyslipidemia (hypertriglyceridemia, low HDL cholesterol), elevated fasting serum glucose, abdominal obesity, and hypertension (Table 1) [7–11].

The MS affects over 20% of adults in Western populations [12], and is becoming increasingly common [13–15], inclusively in adolescents [16]. However, the prevalence of MS varies widely according to geographic location, race, gender, and urbanization. Since it was first described, an overwhelming body of evidence associated the MS with subsequent development of type II diabetes mellitus and cardiovascular disease (CVD) [17–25]. Recently, the evidence associating MS with CVD has been synthesized in three meta-analyses that showed an increased risk for incident CVD (ranging from 53% to 118%) and all-cause mortality (ranging from 27% to 60%) in subjects with MS [23–25]. This increased risk appears related to the risk factor clustering, rather than to obesity alone, as normal weight people from the Framingham population meeting the criteria for MS had a threefold increased risk for CVD, while obese individuals without MS did not have a significantly increased risk [26].

Additionally, especially in the last decade, a number of other obesity-related disorders have been associated with the MS, including: fatty liver disease, polycystic ovary syndrome,

Table 1: Current definitions of the metabolic syndrome.

Parameters	NCEP ATP3 (2005) [9]	IDF (2005) [11]	EGIR (1999) [8]	WHO (1999) [7]	NHLBI/AHA (2005) [10]
Required		Waist ≥ 94 cm (men) or ≥80 cm (women)[(a)]	IR or fasting hyperinsuline-mia in top 25%	IR in top 25%[(b)]; glucose ≥ 110 mg/dL (≥6.1 mmol/L); 2-hr glucose ≥140 mg/dL (≥7.8 mmol/L)	
No. of abnormalities	≥3 of:	And ≥2 of:	And ≥2 of:	And ≥2 of:	≥3 of:
Obesity	Waist ≥102 cm (men) or ≥88 cm (women)[(c)]		Waist ≥94 cm (men) or ≥80 cm (women)	Waist/hip ratio >0.9 (men) or 0.85 (women) or BMI ≥30 kg/m^2	Waist ≥102 cm (men) or ≥88cm (women)
Hypertension	≥130/85 mm Hg or drug treatment	≥130/85 mm Hg or drug treatment	≥140/90 mm Hg or drug treatment	≥140/90 mm Hg	≥135/85 mm Hg or drug treatment
Glucose	≥100 mg/dL (≥5.6 mmol/L) or drug treatment	≥100 mg/dL (≥5.6 mmol/L) or diagnosed diabetes	110–125 mg/dL (6.1–6.9 mmol/L)		≥100 mg/dL (≥5.6 mmol/L) or drug treatment
HDL cholesterol	<40 mg/dL (<1.0 mmol/L) (men); <50 mg/dL (<1.3 mmol/L) (women) or drug treatment	<40 mg/dL (<1.0 mmol/L) (men); <50 mg/dL (<1.3 mmol/L) (women) or drug treatment	<40 mg/dL (<1.0 mmol/L)	<35 mg/dL (<0.9 mmol/L) (men); <40 mg/dL (<1.0 mmol/L) (women)	<40 mg/dL (<1.0 mmol/L) (men); <50 mg/dL (<1.3 mmol/L) (women) or drug treatment
Triglycerides	≥150 mg/dL (≥1.7 mmol/L) or drug treatment	≥150 mg/dL (≥1.7 mmol/L) or drug treatment	≥180 mg/dL (≥2.0 mmol/L) or drug treatment	≥150 mg/dL (≥1.7 mmol/L)	≥150 mg/dL (≥1.7 mmol/L) or drug treatment

BMI: body mass index; EGIR: group for the study of insulin resistance; HDL: high-density lipoprotein; IDF: International Diabetes Federation; IR: insulin resistance; NCEP: National Cholesterol Education Program; NHLBI/AHA: National Heart, Lung and Blood Institute/American Heart Association; WHO: World Health Organization.

(a) South Asia and Chinese patients, waist ≥90 cm (men) or ≥80 cm (women); Japanese patients, waist ≥90 cm (men) or ≥80 cm (women).

(b) Insulin resistance measured using insulin clamp.

(c) Asian patients, waist ≥90 cm (men) or ≥80 cm (women).

obstructive sleep apnea, hyperuricemia, and, in particular, chronic kidney disease (CKD).

Chronic kidney disease is an important risk factor for End-Stage Renal Disease (ESRD), CVD, and premature death [27–31] and has become a global public health problem, with increasing social and economic impact due to its high prevalence [32, 33]. Indeed, almost 5% of adult Americans have CKD but only a minority reach ESRD, suggesting that most of these patients die of other causes, such as CVD [26, 33, 34]. The possible association between MS and CKD, in light of the growing epidemic of obesity, could represent a window of opportunity to identify individuals at risk of CKD (and, evidently, CVD) and to improve the burden of these diseases through early detection and prevention.

Herein, we aim to critically review the existing clinical evidence that associates MS with renal disease and CVD, as well as the possible pathophysiologic mechanisms involved and actual treatment options.

2. Chronic Kidney Disease and Cardiovascular Disease

Chronic kidney disease is an independent risk factor for CVD and all cause-mortality and is considered a coronary heart disease risk equivalent [35–37]. In patients with CKD stage 2 or higher, there is a direct relationship between the degree of renal function impairment and cardiovascular risk, independent of other known risk factors (age, blood pressure, diabetes, and smoking), history of CVD, and presence of proteinuria [36]. Even subtle reductions in renal function, in apparently healthy persons, increase the risk of cardiovascular morbidity and mortality [37, 38].

The main factors pointed out as responsible for this increased risk include volume overload and anemia leading to left ventricular hypertrophy, bone mineral disease causing valvular and vascular calcification, inflammation, oxidative stress, endothelial dysfunction, and sympathetic nervous

system hyperactivity [39]. Additionally, several epidemiologic studies point to a high prevalence of traditional and non-traditional risk factors for CVD in patients with CKD [35, 40–42]. Moreover, the prevalence and magnitude of major risk factors for coronary heart disease increase as renal failure progresses (e.g., hypertension, insulin resistance, and hyperhomocysteinemia) [43].

The prevalence of left ventricular hypertrophy and congestive heart failure is strikingly elevated in patients with CKD stages 2 through 5 [44, 45]. Morbidity and mortality for congestive heart failure and coronary heart disease are also excessive in CKD [45–48]. For example, in the large Study of Left Ventricular Dysfunction (SOLVD) Trial, moderate renal impairment was associated with a 41% increased risk for all-cause mortality, explained largely by heart failure, death and hospitalization [49]. Even in acute coronary syndromes, an estimated creatinine clearance less than 70 mL/min was associated with a 20% increase in mortality in both ST and non-ST elevation myocardial infarction [50].

The close relationship between CVD and CKD may be a manifestation of similar disease processes involved. Indeed, cardiovascular and renal diseases have many types of markers in common, including: clinical, pathophysiologic (e.g., increased angiotensin II activity, upregulation of inflammatory and fibrosis producing cytokines), histopathologic (e.g., inflammatory infiltrates, vascular remodeling), biochemical (e.g., c-reactive protein, homocysteine, lipoprotein (a) and fibrinogen), acute and chronic inflammation and subclinical signs of atherosclerosis (e.g., increased common carotid artery intima-media thickness) [51–59].

It is not surprising, then, that the MS, a constellation of cardiovascular risk factors with well established impact in the incidence of CVD and type II diabetes mellitus, might be associated with the development and progression of CKD.

3. Metabolic Syndrome and Chronic Kidney Disease

3.1. Metabolic Syndrome as Risk Factor for Renal Disease. All the components of the MS have individually been associated with the incidence and progression of CKD. The mechanisms and impact of hypertensive and diabetic injuries, the two major etiologies of CKD in the world, have been well studied and described [60–62]. Obesity has also been associated with increased risk for ESRD in several epidemiological studies [63, 64]. Dyslipidemia, in particular atherogenic dyslipidemia (low HDL cholesterol, high triglycerides), has also been shown to be an independent risk factor for the development and progression of CKD in observational studies and meta-analysis [42, 65–67].

The clustering of all these risk factors should identify individuals at high risk for CKD. Over the last decade a growing body of clinical evidence addressed this issue.

Several observational studies found that individuals with the MS are at increased risk for presenting renal manifestations, namely, microalbuminuria and decreased glomerular filtration rate (GFR). In fact, epidemiologic studies have linked the MS with an increased risk for microalbuminuria, an early marker of glomerular injury and endothelial dysfunction [68–73]. A cross-sectional survey of nondiabetic native Americans that was conducted by Hoehner et al. [70] found that, after controlling for social, demographic, and comorbidity factors, the patients with one to two and those with three or more traits of the MS were 80% and 130% more likely to have microalbuminuria than those without MS, respectively. Chen et al. [68] corroborated these findings in another cross-sectional analysis with data from 6125 individuals extracted from the National Health and Nutrition Examination Survey (NHANES) III database-the multivariate-adjusted odds ratio for microalbuminuria in participants with the MS compared with participants without MS was 1.89 (1.34–2.67), and the risk increased with the number of components of the MS.

Similarly, a number of observational studies evaluated the association of MS and CKD (Table 2) [68, 73–81]. Almost all of them found a significant association between MS and CKD and consistently demonstrated an increased risk parallel to the number of MS traits [68, 74, 77, 79]. However, the majority of the studies were cross-sectional and, as so, unable to establish a cause-and-effect relationship, remaining unclear if the MS is a cause or a consequence of the reduced kidney function. In fact, some reports suggest that renal dysfunction *per se*, even in early stages, is a cause of insulin resistance and MS which increases as the nephropathy progresses [82, 83]. Additionally, experimental work indicates that uremia is a cause of insulin resistance rapidly reversible by peritoneal dialysis or hemodialysis, further suggesting the presence of a low-molecular-weight substance that functions as an insulin desensitizer in uremia [84]. On the other hand, most of these studies included patients with diabetes and hypertension, two known risk factors for the development and progression of CKD, further impairing the analysis.

In order to address the issues of causality and impact of MS in the development of CKD, two relatively large longitudinal studies, that excluded diabetic patients at baseline, were published to date [74, 76]. Rashidi et al. showed an 88% (OR 1.88; 1.26–2.8) increased risk for CKD in patients with MS compared to those without, after a 3-year followup period [76]. However, when hypertensive patients at baseline were excluded from the analysis the increased risk was wiped out (OR 0.92; 0.446–1.917). Probably, the most significant study to date was published by Kurella et al., given its large database and long followup period [74]. In this study, the significant association between the MS and subsequent development of CKD was confirmed (OR 1.43; 1.18–1.73). Moreover, this association remained true after excluding patients with hypertension at baseline (OR 1.46; 1.08–1.97) and patients with incident hypertension or diabetes during the followup (OR 1.24; 1.01–1.51), although with marginal statistical significance. However, even when hypertensive patients were excluded at baseline, the patients with MS had statistically significant higher blood pressure within the normal range (at baseline and at the end of followup) than the ones without MS, making it impossible to exclude the effect of hypertension. Additionally, in this and other studies [68, 73, 76] hypertension was the individual MS trait with

Table 2: Studies that evaluated the association between the metabolic syndrome and chronic kidney disease.

Study	Design	Results
Chen et al.; *Ann Intern Med* 2004 [68]	Observational, cross-sectional $N = 6217$ American adults (database: NHANES III)	OR for CKD 2.60 (CI: 1.68–4.03) OR for 2, 3, 4 or 5 traits of MS: 2.21 (CI: 1.16–4.24), 3.38 (C: 1.48–7.69), 4.23 (CI: 2.06–8.63), and 5.85 (CI: 3.11–11.0), respectively.
Kurella et al., *J Am Soc Nephrol* 2005 [74]	Observational, longitudinal (followup 9 yrs) $N = 10\,096$ nondiabetic, American adults (database: ARIC Study)	OR for CKD 1.43 (CI: 1.18–1.73) OR for CKD associated with 1, 2, 3, 4 or 5 traits of MS: 1.13 (CI: 0.89–1.45), 1.53 (CI: 1.18–1.98), 1.75 (CI: 1.32–2.33), 1.84 (95% CI, 1.27–2.67), and 2.45 (CI: 1.32–4.54), respectively. OR for CKD (excluded pts with DM or HT during followup) 1.24 (CI: 1.01–1.51)
Tanaka et al., *Kidney Int* 2006 [75]	Observational, cross-sectional $N = 6980$ Japanese adults	OR for CKD 1.54 (CI: 1.28–1.85) Association only significant for participants younger than 60 y/o.
Rashidi et al., *Clin J Am Soc Nephrol* 2007 [76]	Observational, longitudinal (followup 3 yrs) $N = 4\,607$ non-diabetic (database: TLGS Study)	OR for CKD 1.88 (CI: 1.26–2.8) OR for CKD (excluded pts with HT) 0.92 (CI: 0.446–1.917)
Chen et al., *Nephrol Dial Transplant* 2007 [77]	Observational, cross-sectional $N = 15\,160$ chinese adults (database: inter-Asia study)	OR for CKD 1.64 (CI: 1.16–2.732) OR for CKD associated with 1, 2, 3 and 4 + 5 traits of MS: 1.51 (CI: 1.02–2.23), 1.50 (CI: 0.97–2.32), 2.13 (CI: 1.30–3.50), and 2.72 (CI: 1.50–4.93), respectively. OR for CKD (excluded pts with HT) 1.74 (CI: 1.00–3.02) OR for CKD (excluded pts with DM) 1.46 (CI: 1.02–2.07)
Zhang et al., *Mayo Clin Proc* 2007 [73]	Observational, cross-sectional $N = 2\,310$ chinese adults	OR for CKD 1.74 (CI: 1.32–2.30) OR for CKD (excluded pts with HTor DM) 2.03 (CI: 1.05–3.94)
Kitiyakara et al., *Kidney Int* 2007 [78]	Observational, cross-sectional with a longitudinal subgroup (followup 12 yrs) $N = 3\,195$ Southeastern Asians (subgroup 2067)	OR for CKD 2.48 (CI: 1.33–4.62)-cross-sectional OR for CKD 1.62 (CI: 1.00–2.61)-longitudinal Association only significant with the NCEP ATP III criteria, not the IDF criteria
Luk et al., *Diabetes Care* 2008 [79]	Observational, longitudinal (Mean followup 4.6 yrs) $N = 5\,829$ diabetic type II pts (database: Hong Kong Diabetes Registry)	OR for CKD 1.31 (CI: 1.12–1.54) OR for CKD associated with 2, 3, 4 or 5 traits of MS: 1.15 (0.83–1.60), 1.32 (0.94–1.86), 1.64 (1.17–2.32), and 2.34 (1.54 –3.54), respectively.
Jang et al., *J Public Health* 2010 [80]	Observational, cross-sectional $N = 5136$ Korean adults (Database: KNHANES III)	OR for CKD 1.77 ($P < .05$)
Yu et al., *Nephrol Dial Transplant* 2010 [81]	Observational, cross-sectional $N = 5911$ Korean adults (Database: KNHANES III)	OR for CKD: NS Association only significant in men younger than 60 y/o and postmenopausal women.

ARIC: Atherosclerosis Risk in Communities; CI: Confidence Interval; CKD: Chronic Kidney Disease; DM: Diabetes Mellitus; HT: Hypertension; IDF: International Diabetes Federation; KNHANES: Korean National Health and Nutrition Examination Survey; MS: Metabolic Syndrome; NCEP ATP: National Cholesterol Education Program Adult Treatment Panel; NHANES: National Health and Nutrition Examination Survey; NS: no significance; OR: Odds Ratio; TLGS: Tehran Lipid and Glucose Study.

the strongest association to CKD, even stronger than the MS itself. The same consideration is valid for hyperglycemia in some studies [68, 73, 77]. As Bakker et al. elegantly demonstrated the problem with the concept of MS, as a way to predict renal (and CVD) risk, is the dichotomization of continuous variables and clustering correlated risk factors, resulting in a significant loss of predictive power [85]. A study of Kitiyakara et al. has even suggested that the risk of CKD associated with the MS was different accordingly to the definition of MS used [78].

Although the results of these studies suggest there is a close association between MS and renal disease, two questions still do persist Does the MS add any relevant additional information in terms of renal risk? Are there specific pathophysiologic mechanisms of renal injury in the MS? Kurella et al. also found that there were graded relations among the number of MS traits, the Homeostasis Model Assessment (HOMA)-insulin resistance, fasting insulin levels and the risk for CKD, suggesting a pathophysiologic basis for their findings [74]. Similar associations were previously

reported by Chen et al. [86]. These findings indicate that that the MS directly contributes to the development of CKD and the claimed pathophysiologic link is obesity, a hallmark of the MS. Part of the explanation is, in fact, the link between obesity, diabetes and hypertension [85]. However, obesity (in particular visceral obesity) has independently been associated with the risk of CKD and ESRD [63, 64, 68, 76, 87], even when corrected for these two indirect mechanisms and proteinuria, suggesting the existence of additional direct pathomechanisms.

3.2. Pathophysiology and Pathology of Renal Disease in Metabolic Syndrome. Many studies evaluated the mechanisms by which the factors in MS mediate pathological and pathophysiological changes in the kidney. The underlying mechanisms are still not completely understood but include insulin resistance itself, inflammation, renal endothelial dysfunction, oxidative stress, altered renal heamodynamics, activation of the reninangiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS), and dietary factors.

3.2.1. Inflammation and Insulin Resistance. Inflammation has been implicated in MS pathogenesis, especially as a mechanism of insulin resistance and endothelial dysfunction [88]. As mentioned, genetic and environmental factors lead to central obesity. This enlarged mass of adipocytes plays a vital role in the pathophysiology of MS. There is increased flux of free fatty acids into the liver leading to excessive hepatic production of triglycerides and resultant hypertriglyceridemia. Moreover, the adipocytes also secrete inflammatory cytokines (e.g., MCP-1, TNF-α, IL-6, leptin and C reactive protein), while there is relative deficiency of the anti-inflammatory and antiatherogenic cytokine adiponectin, resulting in a low-grade inflammatory state thought to be responsible for insulin resistance and endothelial dysfunction [89]. At the molecular level, the link between inflammation and insulin resistance has already started to be elucidated [90–92], but is over the scope of this article.

The role of chronic inflammation in renal pathophysiological changes in the setting of MS, driven both by proinflammatory cytokines and adipocytokines, is not clear. As stated, in obesity, the adipocyte-derived adiponectin, an insulin-sensitizing anti-inflammatory protein, is decreased along with an increase in the plasma levels of leptin. Increased adipokines have been shown to directly contribute to insulin resistance but their effects on CKD have not been examined. However, adipokines such as leptin can cause renal vascular remodeling and disruption of renal function. Some evidence indicates that leptin may represent a link between obesity and increased sympathetic activity, through its action on the hypothalamus, to increase blood pressure [93]. It has also been shown that increased levels of TNF-α promote generation of reactive oxygen species (ROS) in glomerular cells and proximal tubular cells. These ROS contribute to renal injury in several ways like inducing renal endothelial dysfunction and microalbuminuria, matrix accumulation, mesangial expansion, and fibrosis [94, 95].

Within the kidney, insulin resistance and hyperinsulinemia associated with MS seem to induce local inflammation, an important pathophysiological pathway for CKD. Insulin may induce renal fibrosis through stimulation of mesangial cells and proximal tubule cells to produce TGF-b [96, 97]. Moreover, insulin stimulates the production of IGF-1 by vascular smooth muscle cells and other cell types, which has been implicated in the development of diabetic kidney disease [98]. IGF-1 increases the activity of connective tissue growth factor, a cytokine that has profibrogenic actions on renal tubular cells and interstitial fibroblasts. In addition, IGF-1 decreases the activity of matrix metalloproteinase-2, an enzyme responsible for extracellular matrix degradation, thereby promoting extracellular matrix expansion and renal fibrosis [99, 100]. Additionally, insulin resistance promotes sodium and uric acid reabsorption, resulting in salt-sensitive hypertension and hyperuricemia [88]. In the end, at the glomerular level, insulin resistance and the release of inflammatory cytokines induce mesangial expansion, basement membrane thickening, podocytopathy and loss of slit pore diaphragm integrity, leading to the so-called "obesity-related glomerulopathy" [89, 101]. This condition is characterized by a specific histopathologic pattern of glomerulomegaly (100% of cases), frequently accompanied by focal segmental glomerulosclerosis (80% of cases), and has been repeatedly described in obese patients without any other defined primary or secondary glomerular diseases (including diabetic nephropathy, hypertensive nephrosclerosis, and secondary focal segmental glomerulosclerosis). This glomerulopathy has pathologic features strikingly resembling the ones induced by diabetes and/or hypertension and, similarly, has a progressive clinical course. Of particular concern, the biopsy incidence of this condition had a 10-fold increase over a period of 15 years [101] and has been observed in children as young as 3 years of age [101, 102].

3.2.2. Renal Haemodynamics. The consistent observation of glomerulomegaly raised the hypothesis that glomerular hyperfiltration was a major mechanism in the pathogenesis of obesity-related glomerulopathy. This was first elucidated in an animal model, the obese Zucker rat, which has hyperphagia due to a defect in the brain leptin receptor, resulting in obesity and associated hyperglycemia, hyperinsulinaemia, insulin resistance, dyslipidaemia and hypertension, thus closely mimicking MS in humans. This model has glomerular hyperfiltration and develops albuminuria, which progress to renal failure with histological characteristics of glomerulomegaly and focal and segmental glomerulosclerosis [103]. These findings have elegantly been confirmed in humans by Chagnac et al. [104, 105]. These authors demonstrated that obese patients, with clinical characteristics consistent with the diagnosis of MS, had a 50% and 30% increase in GFR and renal plasma flow (RPF), respectively, as compared to lean controls, resulting in increased filtration fraction, an indirect indicator of glomerular hypertension [104]. Moreover, when 17 morbidly obese patients who lost an average of 48 kg

at 1 year after bariatric surgery, postprandial GFR and RPF were significantly decreased and approached normal levels, even though the patients were still obese [105]. In a relatively recent study with young (mean age 18 years) healthy males, MS was associated with a 6.9-fold increase in the OR of glomerular hyperfiltration [106]. The authors concluded that glomerular hyperfiltration has an early-onset in life, before any manifestations of CVD, and so may be a marker of metabolic risk. It is well known that hyperfiltration (even in nondiabetic patients) leads to albuminuria (a well established cardiovascular and renal risk factor), which is consistent with the aforementioned epidemiologic studies that showed a graded prevalence of microalbuminuria according to the number of MS traits [68–73]. Besides the known effect of hyperglycemia, these renal haemodynamic changes have been attributed in experimental studies to a higher intake of dietary protein in these individuals [107–109]. The amino acid excess induces a profibrotic and proliferative mesangial injury response, mediated by increased formation of advanced glycation end-products, presumably the result of greater availability of free amino groups for glycation reactions [110, 111].

3.2.3. Oxidative Stress. The presence of renal oxidative stress has been documented in animal models of insulin resistance, diabetic patients, and patients with CKD of various etiologies [112, 113].

High glucose and free fatty acid increase mitochondrial ROS in renal endothelial cells, which may contribute to tissue dysfunction by dysregulation of redox-sensitive signaling pathways or by oxidative damage to biological structures (DNA, proteins, lipids, etc.) [114].

Lipid peroxidation, a well-known consequence of excessive ROS, is the first step in the generation of oxidized LDL, which accumulates in renal mesangial cells and form foam cells [115]. Lipid peroxidation also induces endothelial damage and inflammatory response, impairs vasodilatation and activates macrophages [116, 117]. Lipid peroxidation itself generates more free radicals and ROS thereby increasing the potential for renal injury.

Additionally, the aforementioned glomerular hyperfiltration may also be caused by mitochondrial ROS, through the activation of cyclooxygenase-2 gene transcription followed by prostaglandin E2 overproduction and preglomerular vasodilation [114]. Furthermore, excessive oxidative stress stimulates the synthesis of angiotensin II (via the nuclear factor-kB pathway), which further increases glomerular hypertension and hyperfiltration by causing efferent arteriole vasoconstriction. Angiotensin II also stimulates the synthesis of TGF-b, thereby promoting glomerular fibrosis [118].

Moreover, ROS-dependent b-cell damage is thought to be involved in the progression from MS to type II diabetes mellitus [119] and ROSs enhance the formation of advanced glycation end products [120], which have a major pathophysiologic role in the development of diabetic nephropathy.

3.2.4. Endothelial Dysfunction. Dysfunction of the vascular endothelium is an important factor in the pathogenesis of diabetic nephropathy and has its clinical counterpart in microalbuminuria [121, 122].

Available evidence indicates that the insulin-receptor signaling pathway mediating glucose uptake in vascular endothelium requires stimulation of endothelial nitric oxide (NO) synthase and subsequent NO production [123], a potent vasodilatory and antithrombotic substance. Comparable endothelial responses—enhanced NO production with vasodilation—are induced by adiponectin [124]. These actions mediate a hemodynamic component of energy distribution, enhancing tissue blood flow to optimize nutrient delivery. In insulin-resistant states, such as obesity, MS and type 2 diabetes mellitus, insulin- (and adiponectin-) induced NO production and endothelium-dependent vasodilatation are impaired, representing one of several mechanisms linking abdominal obesity/insulin resistance and hypertension [125–127]. Additionally, excessive oxidative stress further decreases NO production and availability thereby contributing to endothelial dysfunction in diabetic and MS patients [120].

Another product of endothelial cells, endothelin-1, has been implicated in CVD, hypertension and several kidney diseases. Insulin stimulates the secretion of endothelin 1 from glomerular endothelial, mesangial and vascular smooth muscle cells through the insulin receptor. Endothelin-1 is associated with severe intrarenal vasoconstriction, reduced GFR, mesangial cell contraction and proliferation and sodium and water retention [128–130]. Patients with the MS are hyperinsulinemic, suggesting that endothelin-1 may be involved in the development of nephropathy in these patients.

3.2.5. Fructose. Recently, another dietary factor-fructose-has been implicated in the pathophysiology of MS, and could establish the link between modern dietary patterns, systemic inflammation, MS and cardiovascular and renal disease progression [131]. Fructose is a simple sugar that is a component of table sugar as well as of high fructose corn syrup, which is a universally used sweetener. Fructose consumption has increased markedly worldwide during the last several decades, which correlates closely with the increasing incidence of obesity and MS [132]. The administration of fructose to both animals and humans has been showed to induce most of the features of MS [133, 134]. This is clinically relevant as some studies have reported that adolescents can easily ingest 15%–20% of their energy intake as fructose [135]. In recent years, experimental evidence associating fructose and systemic inflammation has accumulated, pointing out an increased expression of leukocyte adhesion proteins (ICAM-1) and chemokines (MCP-1) in various cell types (endothelial, proximal tubular, and vascular smooth muscle cells) [131]. The underlying mechanism appears to be related to increased uric acid generation and resulting hyperuricemia. Uric acid has been shown to induce oxidative stress, reduce nitric oxide generation, stimulate the local renin-angiotensin system and induce expression of proinflammatory chemokines, resulting in a significant increase in renal injury and inflammation [136–139]. These recent insights into the pathophysiology

may represent new treatment opportunities (e.g., reduction of dietary fructose, uric acid lowering agents or, in the future, blocking the signaling pathways driving the response), as there is increasing evidence that systemic inflammation may increase the risk of cardiovascular outcomes and progression of renal disease [140–142].

3.2.6. Sympathetic Nervous System and Renin-Angiotensin-Aldosterone System. Finally, the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS) are considered important pathophysiologic factors in the development of MS, which can also contribute to the high cardiovascular risk associated with it. Some studies have associated plasma aldosterone levels with insulin resistance and MS, in both normotensive and hypertensive patients [143–145]. Angiotensin II is thought to have a role in the development of insulin resistance by inducing oxidative stress and also in the development of salt-sensitive hypertension by promoting sodium reabsorption, which could explain the benefits of blocking the RAAS on prevention of new cases of diabetes [146].

In summary, apart from the effect of hypertension and diabetes, there are other contributing factors for development of kidney injury in MS. These include oxidative stress and systemic inflammation (probably induced by dietary factors like fructose and adipose tissue-derived cytokines), endothelial dysfunction, altered renal hemodynamics (partially as the result of high dietary protein intake), excessive renal sodium reabsorption, activation of the RAAS and SNS, atherogenic lipid profile, and even physical compression of the kidneys by adipose tissue. Complex interactions between all these factors ultimately lead to glomerular hyperfiltration, glomerular cell proliferation, matrix accumulation, and, finally, glomerulosclerosis and progressive loss of nephrons.

3.3. Prevention of Renal Disease in Metabolic Syndrome. The association between MS and renal disease raises the question whether treating the components of the syndrome could prevent renal injury. Interventional randomized controlled trials addressing renal endpoints in the specific setting of MS have not been published to date. However, each diagnostic criterion of MS identifies a risk factor for CVD that requires intervention independently of its contribution to CKD incidence or progression. Although the value of a multifactorial intervention for preventing cardiovascular events and CKD in the setting of MS has not been examined, it has already been proposed [147]. According to this strategy, upon the diagnosis of MS, clinicians should implement a multitargeted intervention with treatment goals based on global CVD risk assessment (using, e.g., the 10-year Framingham risk score or the European risk SCORE chart and the estimated GFR). This multidimensional intervention should focus simultaneously on life-style changes, glycemic and blood pressure control, lipid lowering, and other proven beneficial treatments, like antiplatelet therapy (Figure 1).

The value of simultaneous management of multiple risk factors has been tested in type II diabetic patients (a group for which MS is intended to be a high risk factor), resulting in a lower risk of CVD and nephropathy in the intensive treatment group (stepwise implementation of behavior modification and pharmacologic therapy with strict treatment targets for hyperglycemia, hypertension, dyslipidemia, and microalbuminuria, plus secondary prevention of cardiovascular disease with aspirin; treatment overseen by a project team) compared to conventional treatment (treatment for multiple risk factors from their general practitioner, according to current recommendations, with the possibility of being referred to specialists) [148]. Moreover, it has been shown in this group of patients that intensive blood pressure (<130/80 mm Hg) and blood glucose control (aiming at glycated hemoglobin level 6.5%) effectively prevent cardiovascular events, the development of microalbuminuria, and overt nephropathy [149, 150]. Despite that, the Action to Control Cardiovascular Risk in Diabetes Study Group (ACCORD) trials alert us that treating diabetic patients to normal values (systolic blood pressure <120 and glycated hemoglobin level 6.0%) may not be beneficial and increase the risk of adverse events [151, 152]. These studies reinforce the notion that aggressive, although cautious, multitargeted management of the MS may confer protection for CVD and CKD [147]. In fact, several lines of evidence indicate that interventions directed at each component of the MS can protect the kidney.

3.3.1. Therapeutic Lifestyle Changes. Lifestyle modifications, including physical activity and dietary interventions, with the objective of weight loss are a cornerstone of therapy [1]. Physical activity and weight reduction improve insulin resistance even in people with renal impairment and ESRD [153]. Small weight reductions have been shown to have significant beneficial effects. A weight loss of 5%–10% of initial body weight has lowered the risk for diabetes and CVD, as well as significant ($P = .001$) improvements in related modifiable risk factors, including HbA1c, HDL cholesterol, triglycerides, and systolic and diastolic blood pressure [154].

Beneficial renal effects, like reduction of glomerular hyperfiltration and albuminuria, have been demonstrated after weight loss (either through diet or bariatric surgery) [105, 155], although these results still need to be demonstrated by properly designed clinical trials. Additionally, the impact on renal outcomes resulting from improved insulin resistance through pharmacologic weight loss [156] or the Mediterranean diet [157] has not been studied. Moreover, in light of what is known about renal hemodynamics (see above), the safety of the so popular "high-protein low-carbohydrate" weight reduction diet should also be analyzed. Finally, the potential effects of dietary fructose reduction in the incidence of MS and its renal and cardiovascular consequences represent an exciting field of research in the near future.

We strongly believe that a reasonable goal for obese patients with the MS would be a weight loss of 5–10% of body weight, through an effective ongoing program that includes an increase in physical activity to at least 150 min/week of moderate exercise, similar to the recommendations for prevention of type II diabetes mellitus in

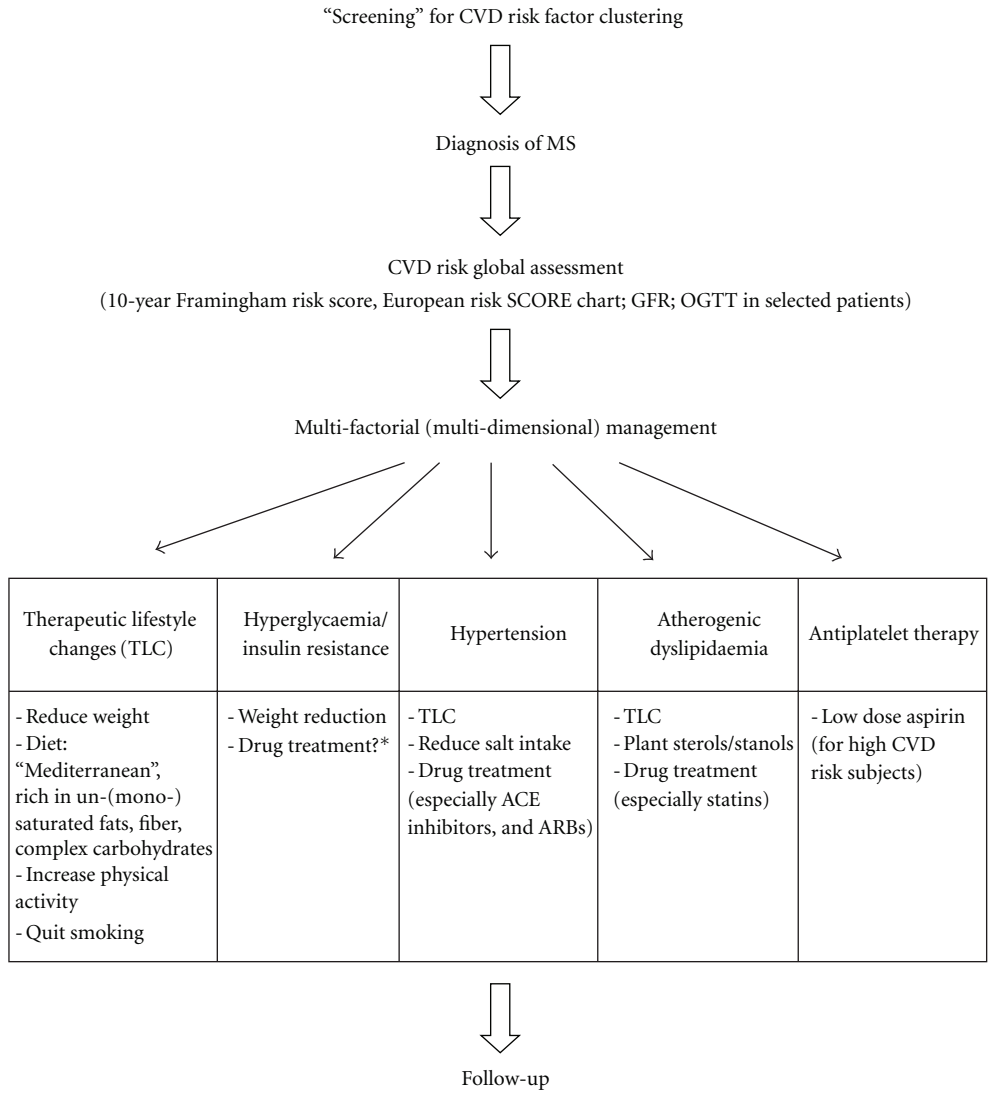

Figure 1: Management of the metabolic syndrome [147] (reproduced with permission). ACE: angiotensin converting enzyme; ARBs: angiotensin II receptor antagonists; CVD: cardiovascular disease; GFR: glomerular filtration rate; MS: metabolic syndrome; OGTT: oral glucose tolerance test.

patients with impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) [158].

3.3.2. Blood Pressure Control. As mentioned, intensive treatment of diabetes and hypertension has been shown to improve renal outcomes in diabetic patients. Moreover, blocking the RAAS is extensively recommended as first-line anti-hypertensive therapy for renal and cardiovascular protection, especially in diabetic and/or proteinuric patients [159, 160]. Given the aforementioned role of RAAS activation in the pathophysiology of the MS and the importance of hypertension on CKD risk in the setting of MS, we should expect great impact of RAAS blockers on the development of kidney injury. This, however, has never been studied. Nevertheless, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers should be the preferred antihypertensive drugs in patients with MS as in diabetics [161]. On the other hand, the use of thyazide diuretics and b-blockers should be avoided (or restricted to treatment of resistant hypertension) in patients with MS due to the risk of new-onset diabetes [162].

The therapeutic goal should be established according to the global cardiovascular risk, as recommended by the latest guidelines [162]. In general, given that the MS is a constellation of CVD risk factors (implying the presence of at least two traits) and often with subclinical organ damage, a blood pressure lower than 130/80 mm Hg should be attained in most patients [162]. Probably, for renal protection, a lower target (<120/75 mm Hg) is beneficial in highly proteinuric patients (>1 gr/day) [163]. However,

as mentioned before, bringing systolic blood pressure to normal values (<120 mm Hg) may increase treatment side-effects without additional benefit, especially in patients with advanced atherosclerotic disease [152].

3.3.3. Glycemic Control. Given the known impact of diabetes in the development and progression of CKD, glycemic control in diabetic patients or preventing/delaying new-onset type II diabetes mellitus is a main goal of therapy in patients with MS. The use of agents that improve insulin sensitivity, like metformin or thiazolidenidiones, is of great interest but also raises some concerns. Metformin has been shown to reduce the incidence of both type II diabetes mellitus and MS in subjects with IGT. However, metformin was less effective than intensive lifestyle modification (regular physical activity and low-fat diet) [164, 165]. Despite its beneficial effects, metformin is contraindicated in CKD patients with creatinine clearance lower than 60 mL/min due to the risk of severe lactic acidosis. Thiazolidenidiones (peroxisome proliferator activator receptor-γ agonists), another class of antidiabetic agents with insulin sensitizing properties, have multiple pleotropic effects that, in theory, are of great interest in the setting of MS. They reduce blood pressure and modulate dyslipidaemia, inflammation, oxidative stress, endothelial dysfunction, fibrosis and remodelling, and glomerular cell proliferation, and reduce urine albumin excretion [166]. Moreover, thiazolidenidiones also reduce the incidence of type II diabetes mellitus in prediabetic subjects [167]. However, their use causes weight gain and fluid retention, an undesirable effect especially for obese subjects and some drugs of this class have been associated with an increased incidence of myocardial infarction [168].

Other classes of antidiabetic drugs have been shown to improve cardiovascular risk profile in diabetic and prediabetic patients, beyond glycemic control [169]. Drugs that promote weight loss, improve control of other cardiovascular risk factors (like blood pressure and lipid profile) or that produce beneficial effects in surrogate markers of subclinical atherosclerosis, are very attractive in the setting of MS. For example, in a systematic review, the old alpha-glucosidase inhibitors have been shown to produce a modest weight reduction (-1.2 Kg) as well as improvements in total cholesterol, LDL cholesterol, triglycerides, systolic and diastolic blood pressure in patients with IGT and/or IFG [170]. Additionally, in the same group of patients, acarbose was associated with a significant reduction in the progression of carotid intima-media tickness (IMT) compared to placebo-the annual progression of IMT was reduced by 50%, with a mean followup of 3.9 years [171]. More importantly, in the Study to Prevent Non-Insulin-Dependent Mellitus (STOP-NIDDM), also in patients with IGT, acarbose was found to reduce the risk of developing any cardiovascular event by 49% with an absolute risk reduction of 2.5% [172].

On the opposite time-line end, also the new incretin mimetics—Glucagon-like peptide-1 (GLP-1) receptor agonists and Dipeptidyl peptidase-4 (DPP-4) inhibitors-have beneficial pleotropic effects on various MS traits. GLP-1 receptor agonists are associated with progressive, dose-dependent weight loss in patients with type 2 diabetes [173] while the DPP-4 inhibitors are generally considered weight neutral [169]. Exenatide, a GLP-1 receptor agonist, has been shown to produce significant reductions in total cholesterol, triglycerides, systolic and diastolic blood pressure in patients with type II diabetes mellitus with the MS [174]. The effect on blood pressure, a major determinant of renal and cardiovascular risk in patients with MS, is very significant and is greater in patients with systolic blood pressure >130 mmHg (-11.4 mm Hg and -3.6 mm Hg for systolic and diastolic blood pressure, resp.; $P < .05$) [175]. Similarly, DPP-4 inhibitors also produced favorable trends on lipid levels and systolic and diastolic blood pressure, even in patients without diabetes [173, 176]. Moreover, GLP-1 receptor agonists were recently associated with improvements in inflammatory state, insulin resistance and beta-cell function as compared to sulfonylureas in patients with type II diabetes [177].

At the present time, there are no data on glycemic control goals in patients with MS who are not diabetic. Both for renal and CVD prevention the obvious treatment goal is to prevent the onset of overt type II diabetes in this group of patients. Current recommendations are to treat patients with IFG, IGT or glycated hemoglobin of 5.7%–6.4% though weight loss and physical activity [158]. Despite their beneficial effects, the use of antidiabetic drugs is actually not recommended in prediabetic subjects [178], maybe with the exception of metformin for patients at very highrisk of developing diabetes (combined IFG and IGT plus other risk factors such as glycated hemoglobin >6%, hypertension, low HDL cholesterol, elevated triglycerides, or family history of diabetes in a first-degree relative) who are obese and under 60 years of age [158].

For patients with overt type II diabetes mellitus, both for prevention of nephropathy and CVD risk reduction, the recommended goal is to achieve a glycated hemoglobin <7%, although the available evidence is more compelling for microvascular disease prevention [158]. Moreover, data from large diabetes trials suggest a small but incremental benefit in microvascular outcomes with glycated hemoglobin closer to normal [150, 158, 179]. Therefore, despite the results of the aforementioned ACCORD trial, for renal disease prevention a lower glycated hemoglobin might be pursued in selected patients (those with short duration of diabetes, long life expectancy, and no significant CVD), with close monitoring for hypoglycemia and other adverse effects of treatment [158]. In the setting of MS, the antidiabetic drugs with insulin sensitizing properties and/or with beneficial effects on other cardiovascular risk factors/markers should be considered for first-line therapy.

3.3.4. Dyslipidaemia Correction. Statins are the most widely used agents for dyslipidemia, but their role in the MS has not been well evaluated. Nevertheless, for example, in the Scandinavian Simvastatin Survival Study (4S), among patients with elevated serum LDL-cholesterol and established coronary disease, those with characteristics of the MS

had both the highest risk of major coronary events and the greatest benefit from statin therapy [180]. Additionally, treatment of patients with known coronary disease and the MS with atorvastatin (80 mg/day), compared to atorvastatin (10 mg/day), decreased the rate of major cardiovascular events [181]. The effect of statins on kidney function has been addressed in several clinical studies and meta-analysis. It was demonstrated that statins reduce kidney function loss in CKD patients and reduce albuminuria in microalbuminuric and macroalbuminuric patients [182, 183]. Moreover, statins have been shown to slow down GFR decline in high cardiovascular risk patients with normal or near normal renal function at baseline and the patients with MS were the ones with the greatest benefit [184]. The role of statins for renal protection is attributed to their presumed pleiotropic effects including anti-inflammatory, antifibrotic, antihypertensive, and antioxidant properties.

Fibrates are hypolipidaemic drugs very effective in reducing triglycerides, a major feature of MS. Some studies have suggested an improvement in proteinuria progression on diabetic patients treated with fibrates [185], but their role in preventing CKD in MS patients is still unknown.

For CVD prevention (and probably also for renal disease prevention and/or progression), the goal of therapy for MS patients, as for diabetic patients, should focus primarily in LDL cholesterol. In most cases, patients with MS represent a group with very high added risk for CVD (Framingham 10 year risk >20%), even if they are not diabetic. As so, most patients with MS and all patients with type II diabetes mellitus (a coronary heart disease equivalent) should be treated to a primary treatment goal of LDL cholesterol <100 mg/dL. In patients with overt CVD, a lower target of <70 mg/dL may be considered [158]. For patients with lower CVD risk (Framingham 10 year risk 10%–20%), a target of <130 mg/dL is considered adequate [9]. Secondary treatment goals, in this population are triglycerides <150 mg/dL and HDL cholesterol >40 mg/dL in men and >50 mg/dL in women. To achieve these goals therapeutic lifestyle changes (with emphasis on weight loss and physical activity) should be implemented, but statin therapy will almost always be necessary and should be started simultaneously with lifestyle changes in high risk patients [9, 158].

4. Conclusions

The existence of MS as a unique pathophysiologic process and whether it confers risk beyond its individual components have been questioned and are still under debate. Moreover, other clinical variables and risk scores have been proven superior to MS in indentifying individuals at risk for type II diabetes mellitus or CVD [186, 187].

Despite that, in the last decade, a growing body of epidemiologic evidence has associated the MS with the risk for developing renal damage, clinically expressed in the form of microalbuminuria and/or CKD. Given the additional association between MS and CVD risk, which can be further aggravated if renal impairment is superimposed, MS represents, at least, a powerful awareness tool for the need to aggressively prevent and manage risk factors. This need is underscored by the epidemic of obesity in the developed world, particularly affecting adolescents and young adults, which can pose in the future a huge burden on the health care system including dialysis facilities [85].

The association between MS and renal damage is, in part, explained by hypertension and impaired glucose metabolism. However, experimental and epidemiologic data suggest that other aspects of the MS are associated with the development of renal abnormalities and should also deserve close attention as they are modifiable risk factors. In particular, prevention of obesity and promotion of healthy lifestyles are likely to be the most effective approaches and should be a public health priority.

An increasing body of evidence suggests that treating each component included in the MS definition can improve renal outcomes. However, it has never been investigated whether treating patients with MS will prevent the development and progression of CKD. Clinical trials, in the setting of MS, to verify whether treating its components may effectively prevent renal impairment should be a priority. These should include trials of weight loss and nutritional strategies (e.g., low protein and low fructose diets) and multitargeted treatment of risk factors (blood pressure and glycemic control, renin-angiotensin system inhibition, lipid lowering and insulin resistance). Finally, the new insights into the pathophysiology of systemic inflammation in the MS can provide, in the future, new treatment targets.

Conflict of Interests

There is no conflict of interests to declare.

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Review Article

Local Bone Marrow Renin-Angiotensin System and Atherosclerosis

Yavuz Beyazit,[1] Tugrul Purnak,[2] Gulay Sain Guven,[3] and Ibrahim C. Haznedaroglu[1]

[1] *Department of Gastroenterology, Turkiye Yuksek Ihtisas Teaching and Research Hospital, 06100 Ankara, Turkey*
[2] *Department of Gastroenterology, Ankara Numune Education and Research Hospital, 06100 Ankara, Turkey*
[3] *Department of Internal Medicine, Faculty of Medicine, Hacettepe University, 06100 Ankara, Turkey*

Correspondence should be addressed to Yavuz Beyazit, yavuzbeyaz@yahoo.com

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Local hematopoietic bone marrow (BM) renin-angiotensin system (RAS) affects the growth, production, proliferation differentiation, and function of hematopoietic cells. Angiotensin II (Ang II), the dominant effector peptide of the RAS, regulates cellular growth in a wide variety of tissues in pathobiological states. RAS, especially Ang II and Ang II type 1 receptor (AT1R), has considerable proinflammatory and proatherogenic effects on the vessel wall, causing progression of atherosclerosis. Recent investigations, by analyzing several BM chimeric mice whose BM cells were positive or negative for AT1R, disclosed that AT1R in BM cells participates in the pathogenesis of atherosclerosis. Therefore, AT1R blocking not only in vascular cells but also in the BM could be an important therapeutic approach to prevent atherosclerosis. The aim of this paper is to review the function of local BM RAS in the pathogenesis of atherosclerosis.

1. Introduction

The renin-angiotensin system (RAS) plays a crucial role in the control of blood pressure, blood flow, fluid volume, and electrolyte balance, and overactivity of this system contributes to the pathogenesis of a variety of clinical conditions, including onset, progression, and outcome of atherosclerosis [1–3]. Angiotensinogen (AGT) produced in the liver is the precursor of angiotensin I (Ang I), an inactive decapeptide that is converted into Ang II, the main effector of the RAS. Its only role known is as a substrate for renin, a highly specific aspartyl protease. Renin that is secreted from juxtaglomerular apparatus of the kidney cleaves the N-terminal end of AGT to generate Ang I. Ang I is then activated to the Ang II by angiotensin converting enzyme (ACE), which is predominantly expressed in high concentrations on the surface of endothelial cells in the pulmonary circulation [4].

Ang II plays a main role in the RAS mediated mainly by two seven transmembrane domain receptors termed Ang II type 1 receptor (AT1R) and Ang II type 2 receptor (AT2R) showing a complex pattern of regulation and function [5]. Most of the well-known actions of Ang II-AT1R interaction causes vasoconstriction and aldosterone release from the adrenal gland. This classical description of the RAS has been expanded by recent findings that RAS is activated locally, particularly in the vessel wall, heart, the kidney, and the brain [6–14]. Ang II was also described to be produced by other enzymes such as chymase, an efficient Ang II-forming serine protease [15]. It is not affected by ACE inhibition and has been suggested as relevant for alternative pathways of Ang II generation [16–18]. Although several other alternative enzymes involved in Ang II formation such as tonin and cathepsins, chymase deserves special attention due to its high substrate specificity. The enzyme is also expressed in the vascular wall, where it has been suggested as a possible player in Ang II-mediated arteriosclerosis [15].

Inflammatory cells detected in atherosclerotic lesions are mainly originated from bone marrow (BM). The presence of a locally activated bone marrow (BM) RAS affecting the growth, production, proliferation, and differentiation of hematopoietic cells was suggested in 1996 [19]. Other than a wide variety of evidences disclosed the existence of a functional local BM RAS. Angiotensin II, through interacting

with AT1 receptor enhances erythroid differentiation in the BM [20]. Ang II-stimulated erythroid progenitors formed significantly higher numbers of burst forming unit-erythroid (BFU-E) colonies in normal human erythropoiesis. Recently, Fukuda and Sata [21] proposed a hypothesis that the local RAS in BM plays crucial roles in atherosclerosis. They have demonstrated that Ang II-AT1R pathway in BM contributes to atherosclerotic development in the hypercholesterolemic mice. The aim of this paper is to outline the function of local BM RAS during the course of progression and destabilization of atherosclerosis.

2. RAS Activation in Atherosclerotic Lesions

2.1. Potential Effects of Activated RAS on Vascular Structure. Atherosclerosis is a chronic inflammatory disease involving accumulation of lipoproteins and mononuclear cells in the subendothelial space with a result of a cascade of events in blood vessels leading to a remodeling of the arterial wall and a consecutive reduction in lumen size. Novel advances in biotechnology and molecular methods have enabled us to understand the molecular pathways that induce and promote inflammatory responses in the formation of atherosclerotic lesions. Although RAS plays a central role in the control of blood pressure, fluid volume, and sodium balance, overactivity of this system contributes to the pathogenesis of atherosclerosis by simulating a series of coordinated cellular and molecular events observed in the lesions [22–25].

In the past Ang II was believed to affect atherosclerosis through its hemodynamic effects, but in the last two decade it has been shown that, direct cellular effects of Ang II affect the structural changes in the vessel wall seen in atherosclerosis [26]. All components of the RAS are expressed in the vessel wall and mostly the effects of Ang II are mediated by the G-protein-coupled receptors AT1 and AT2 [27]. Both AT1R and AT2R have been well identified in the vessel wall; AT1R is believed to mediate most of the atherogenic actions of Ang II [28, 29]. Yang et al. [30] demonstrated that in hypercholesterolemic atherosclerosis in rabbits, the density of AT1 receptors in the media of diseased blood vessels is increased fivefold compared to healthy animals. They also found a significant AT1R binding in the neointima of the diseased arteries. The highest receptor density in the vessel wall is on vascular smooth muscle cells (VSMCs), but cell culture studies also established a significant AT1R-mediated responses in endothelial cells and macrophages and AT2Rs comprise only about 10% of total angiotensin receptors in healthy blood vessels [30, 31]. Those results suggested that not only systemic but also local Ang II-AT1R pathway could contribute to initiation and progression of atherosclerosis in blood vessels.

2.2. Effects of Activated RAS on Vascular Endothelial Cells. Ang II, produced locally by endothelial ACE, is one of the key substances that affects endothelial function (or dysfunction). To better understand the effect of Ang II on vascular pathobiology, one must need to examine the pivotal role of the endothelium in maintaining normal vascular function and structure. Ang II is synthesized by and has a key action on the endothelium: it exerts direct influence on endothelial function [7, 32]. Vascular endothelium is known as a metabolically active secretory tissue, presents a thromboresistant surface to blood, and acts as a selective macromolecular barrier. It is now believed that structural abnormalities and function of endothelial cells is the cause of not only vascular diseases including atherosclerosis but also certain visceral disorders [33]. Endothelial cells produce factors that regulate vessel tone, coagulation, cell growth and death, and leukocyte migration. Under the control of the endothelium and other factors, VSMCs are also able to release cytokines and growth-regulatory factors that can influence vascular cellular phenotype and growth [7, 34]. Cytokines can exert both pro- and antiatherogenic actions because they are multipotent mediators of inflammation and immunity that can affect key functions of vascular wall cells. The functions of vascular wall cells regulated by cytokines may influence lesion initiation, progression, or complication. The cytokines also adjust endothelial functions that control the development and stability of blood thrombi. Thus, cytokines can influence multiple aspects of atherogenesis and provide new and interesting targets for therapeutic management [35]. Endothelial cells also regulate vascular tone in a strict balance between vasodilators-like nitric oxide (NO), and vasoconstrictors-like Ang II. This balance is crucial to a healthy endothelium. When Ang II is elevated, endothelial dysfunction begins. The imbalance toward Ang II by itself can cause many of the changes in the endothelium that set the atherosclerotic process in motion [36].

Ang-II upregulates expression of adhesion molecules, cytokines, and chemokines and exerts a proinflammatory effect on leucocytes, endothelial cells, and VSMCs [22, 24, 26, 37–39]. And also Ang II upregulates expression of vascular endothelial growth factor (VEGF) which contributes to adventitial angiogenesis [40–42]. Acting via the type 1 receptor, Ang II initiates an inflammatory cascade of reduced nicotinamide-adenine dinucleotide phosphate oxidase, reactive oxygen species (ROS), and nuclear factor-kappa B, which mediates transcription and gene expression and increases chemokines and adhesion molecules [43]. The Ang II type 1a (AT1a) receptor is expressed on multiple cell types in atherosclerotic lesions, including bone-marrow-derived cells and vascular wall cells, and mediates inflammatory and proliferative responses. Indeed, Ang II infusion accelerates atherogenesis in hyperlipidemic mice by recruiting monocytes and by activating vascular wall cells [44]. In advanced atherosclerotic lesions, Ang II stimulates matrix metalloproteinases (MMPs) and plasminogen activator inhibitor-1 expression, causing destabilization of atherosclerotic plaque and alteration of fibrinolytic balance [45–47].

Besides inducing oxidative stress, endothelial damage, and disease pathology including vasoconstriction, thrombosis, and inflammation, Ang II is also involved in vascular remodeling, acting as a bifunctional growth factor that stimulates production of growth factors and vasoactive agents (e.g., platelet-derived growth factor, insulin-like growth factor, and basic fibroblast growth factor) in VSMCs [48, 49].

Other mechanisms whereby Ang II may promote vascular remodeling and formation of vascular lesions are the modulation of vascular cell migration, decreased vascular smooth muscle apoptosis, and extracellular matrix deposition [50–52]. These multiple actions of Ang II are mediated via complex intracellular signaling pathways including stimulation of the PLC-IP3-DAG cascade, tyrosine kinases, MAP kinases, and RhoA/Rho kinase [53]. Intracellular signaling pathways that are stimulated after binding of the peptide to its cell-surface receptors, of which two major subtypes have been characterized, AT1R and AT2R [54, 55]. Although Ang IV receptor was identified recently, as insulin-regulated aminopeptidase, however, its roles in angiogenesis still remain unknown. In humans, AT1R is widely expressed in blood vessels, kidney, heart, liver, and adrenal glands, whereas AT2R is present largely in foetal tissue, decreasing quickly after birth, with relatively low amounts normally expressed in adult tissue [53]. AT1R mediates proangiogenic effect through enhancement of inflammation and leukocytes infiltration, while AT2R mediates antiangiogenic effect through regulation of apoptosis. AT2R expression is increased in pathological circumstances associated with cardiac and vascular remodeling or inflammation. Although they differ in their unique actions, both of the receptors play a crucial role in regulating VSMC function.

2.3. Reactive Oxygen Species and Inflammatory Cells in the Formation of Atherosclerosis. Experimental and clinical studies using Ang II, ACE inhibitors, and AT1 receptor blockers have provided indirect evidence supporting the role of oxidative stress in the pathogenesis of endothelial dysfunction and atherogenesis, independent of the hemodynamic stress of blood pressure [56, 57]. Growing evidence suggests that vascular reactive oxygen species (ROS) play a key role in atherogenesis. Besides its vasoconstrictive properties, Ang II, via the AT1 receptor, generates O_2-production in endothelial cells, adventitial fibroblasts, vascular smooth muscle cells (VSMCs), and mesangial cells through activation of nicotinamide adenine dinucleotide (reduced form)/NADH phosphate (reduced form) (NADH/NAD(P)H) oxidase leading to endothelial dysfunction, growth, and inflammation [58, 59]. Among many ROS generator, nicotinamide dinucleotide phosphate (NAD(P)H) oxidase dependent pathway is an important one in vascular system [60]. Recent researches demonstrated that in endothelial cells as well as in VSMCs, NAD(P)H-dependent oxidase represents the most significant O_2-source. Interestingly, this oxidase is activated upon stimulation with Ang II, suggesting that under all conditions of an activated circulating and/or local RAS endothelial dysfunction secondary to increased vascular O_2-production is expected. In a previous study by Barry-Lane et al. [61], it has been demonstrated that NAD(P)H oxidase is a crucial enzyme in the pathogenesis of atherosclerosis by analyzing the genetically altered mice that are lacking for both apolipoprotein E (ApoE) and p47phox, one subunit of NAD(P)H oxidase. In this interesting study, significant reduction in atherosclerotic lesion was shown in the double knockout mice, compared with that of ApoE-deficient mice. ROS takes actions not only as a regulator of vascular tonus but also as a second messenger to modify the vascular cell phenotypes. ROS stimulates janus kinase (JAK)/STAT (signal transducers and activators of transcription), Akt, and mitogen-activated protein kinase pathways [62–65]. Increased oxidative stress contributes to endothelial dysfunction and to vascular inflammation by stimulating the redox-sensitive transcription factors (NF-kappa B) and by upregulating adhesion molecules, cytokines, and chemokines.

In the cardiovascular system, the major catalytic subunits of NAD(P)H oxidase are, nox 1, gp91phox (nox 2), and nox 4, and the regulatory subunits are p22phox, p47phox, p67phox, and rac [59]. The four phox subunits are knownt to be upregulated in endothelial cells and VSMCs from vessels exposed to Ang II [59]. Ang II induces ROS production, one of the most significant mediators of the atherogenic actions of RAS. The ROS produced by Ang II contributes to the pathogenesis of vascular diseases by inactivating nitric oxide, impairing endothelial function, enhancing VSMC growth and proliferation, and stimulating proatherogenic, inflammatory, and adhesion molecule expression [66–68]. Importantly, the Ang II-induced elevation in O_2-generation in the vessel wall does not seem to be related to the hemodynamic effects of Ang II, because norepinephrine-induced hypertension did not have a similar effect [57].

Ang II is a key mediator of oxidative stress and decreased activity of NO. Ang II causes the activation of NADH/NADPH oxidase that results in the production of superoxide anion and, subsequently, hydrogen peroxide [69]. Moreover, it has been shown that Ang II plays a cruical role in neointimal monocyte infiltration through NF-kappa B activation and monocyte chemoattractant protein-1(MCP-1) expression an important effect that is blocked by angiotensin converting enzyme (ACE) inhibitors [22]. Although Ang II activates NF-kappa B and upregulates expression of cytokines such as interleukin-6 and tumor necrosis factor-α, pharmacological blockade of AT1R with angiotensin receptor blockers would not be so efficient to inhibit cytokine production entirely [38, 70, 71].

Ang II regulates not only adhesion molecule expressions like vascular cellular adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1) and *P*-selectin but also cytokine, chemokine, and growth factor secretion within the arterial wall [72]. Alternatively, RAS can adjust the activation of complement system in both atherosclerosis and renal injury [73, 74]. This inflammatory cascade accelerate the vascular inflammatory response by elevating inflammatory cell recruitment to vessel walls. After migrating into the vessel wall, monocytes transform into macrophages and contribute to lipid deposition in the plaque [75, 76]. Chemokines and MMPs secreted from monocytes/macrophages cause acceleration of atherosclerotic lesions [77]. Furthermore, angiotensin II favors the intraplaque recruitment of monocytes and lymphocytes and directly enhances TNF-α, IL-6 and cyclooxygenase-2 expression in atherosclerotic arteries [1, 78–80]. Moreover recruited leukocytes themselves have NAD(P)H oxidase subunits and serve as a source of ROS [81]. In addition, Ang II triggered activation of transcription factor nuclear

factor-kappa B through redox-sensitive pathways, induces cell adhesion molecules as well as the chemokines MCP-1 and interleukin-8. These molecules promote monocyte and T-lymphocyte adherence, invasion, and accumulation in atherosclerotic lesions [22, 24, 37, 82]. Taken together, these data support a local activated RAS in vessel walls that promotes infiltration of inflammatory cells into the vessel walls, which is an important feature of atherosclerosis.

3. The Function of Local Bone Marrow RAS

We have recently reviewed the pathobiological aspects of local hematopoietic BM RAS [83]. The local haematopoietic bone marrow (BM) renin-angiotensin system (RAS) mediates pathobiological alterations of haematopoiesis in an autocrine/paracrine/intracrine fashion [84]. Recent data further indicated the existence of angiotensin-converting enzyme (ACE) in human primitive lympho-haematopoietic cells, embryonic, foetal, and adult haematopoietic tissues [85, 86]. Human umbilical cord blood cells also express renin, angiotensinogen, and ACE mRNAs [87, 88]. As ACE and other angiotensin peptides function in human haematopoietic stem cells (HSCs) throughout haematopoietic ontogeny and adulthood [85, 86], local RAS could also have a function in HSC plasticity, and the development of haematological neoplastic disorders [83, 89, 90]. The presence of ACE on leukaemic blast cells within leukaemic BM [91, 92], on erythroleukaemic cells [93], ACE-expressing macrophages in lymph nodes of Hodgkin disease [94], renin activity in leukaemic blasts [95, 96], Ang II as an autocrine growth factor for AML [97], increased renin gene activity during NUP98-HOXA9-enhanced blast formation [98], higher levels of BB9/ACE (+) AML isoforms [85], and altered JAK-STAT pathway as a link between RAS and leukaemia [83, 99] indicated the wide pathobiological aspects of local BM RAS. Local hematopoietic BM RAS particularly mediates pathogenesis of myeloproliferative disorders (MPDs) [83]. JAK-STAT pathway represents the point of crosstalk between the upstream local BM RAS and neoplastic hematopoiesis [83, 99]. Abnormally enhanced expressions of the main RAS components in MPD are downregulated by the targeted therapy, imatinib mesylate [100]. JAK1 and JAK2 inhibitor, INCB018424, decreased clonal neoplastic cells and downregulated inflammatory responses in MPD [101]. Since neoplasia and inflammation are the main pivotal actions of hematopoietic BM RAS, which is the upstream controlling pathway of JAK-STAT signaling [83, 102]; direct effects of INCB018424 on RAS shall be further searched to understand its clinically translated pleiotropic molecular engagements. The comparable biological actions of local RASs throughout the human body (including myocardium, pancreas, pituitary gland, ovary, and kidney) represent the true basis for the search of their prominence in tissue functions [83].

Interestingly a previous study provided by Savary et al. [103] demonstrated the presence of a locally active RAS in the yolk sac and possible RAS-dependent participation of ACE in the modulation of early yolk sac erythropoiesis. Moreover the discovery that ACE/CD143 marks primitive embryonic hemangioblasts raised the probability that the versatile RAS plays a crucial role in regulating the earliest stages of human hematoendothelial differentiation, as it does in avian embryos. Zambidis et al. [104] successfully demonstrated a dramatic upregulation of AT2R during expansion of human embryoid body (hEB)-derived ACE+ hemangioblasts, which proposes an exclusive role for the RAS in guiding the early developmental phases of human angio-hematopoiesis [105–107]. Furthermore they found that hEB-derived blast-colony-forming cell could be targeted to differentiate into either hematopoietic or endothelial progeny by manipulating signaling pathways normally mediated by the RAS. And also manipulation of angiotensin II signaling with either AT1R or AT2R specific inhibitors toward either endothelium, or multipotent hematopoietic progenitors, resulted in obvious deviations of hEB differentiation [105].

4. Local Haematopoietic Bone Marrow RAS in the Pathogenesis of Atherosclerosis

There is a close interrelationship between hematopoietic bone marrow RAS and the cardiac RAS [105, 106]. Myocardial tissue repair via hematopoietic stem cell plasticity may represent a point of crosstalk between local cardiac RAS and hematopoietic RAS (Figure 1) [89, 108]. Inflammatory mediators particularly macrophages/monocytes, neutrophils and T-lymphocytes play a central role in all phases of atherosclerosis. Atherosclerotic lesions are initiated by endothelial cell damage, followed by monocyte/macrophage adhesion and invasion as well as smooth muscle cell migration and proliferation [109, 110]. In this perspective, restenosis after angioplasty shares a common pathophysiological process with atherosclerosis, where endothelial injury followed by impaired endothelialization [111, 112]. Previously it has been believed that only migration and proliferation of adjacent endothelial cells in the vessel wall causes re-endothelialization, but afterwards it has been proved that endothelial progenitor cells derived from bone marrow (BM) also participate in this course [113–115]. A local RAS in BM has a possible role in endothelial progenitor cell biology causing neovascularization. Recently it has been demonstrated that RAS activation stimulates endothelial progenitor cell proliferation and neovascularization [26, 116].

Strawn et al. was the first to propose a lipid-angiotensin system connection within the BM that accounts for the predisposition of immune cells to home to coronary arteries and initiate atherosclerosis [117, 118]. Their data supported a positive regulatory role of plasma LDL on AT1R-mediated haematopoetic stem cell differentiation and the production of proatherogenic monocytes which may explain in part hypercholesterolemia-induced inflammation as well as the anti-inflammatory and antiatherosclerotic effects of AT1R blockers. This innovative theory combines the former lipid hypotheses and allows for an immunological activation concept that begins as early as changes in the BM that result in the generation of activated circulating monocytic phenotypes that participate in atherogenesis. The "bone marrow response-to-lipid" hypothesis incorporates

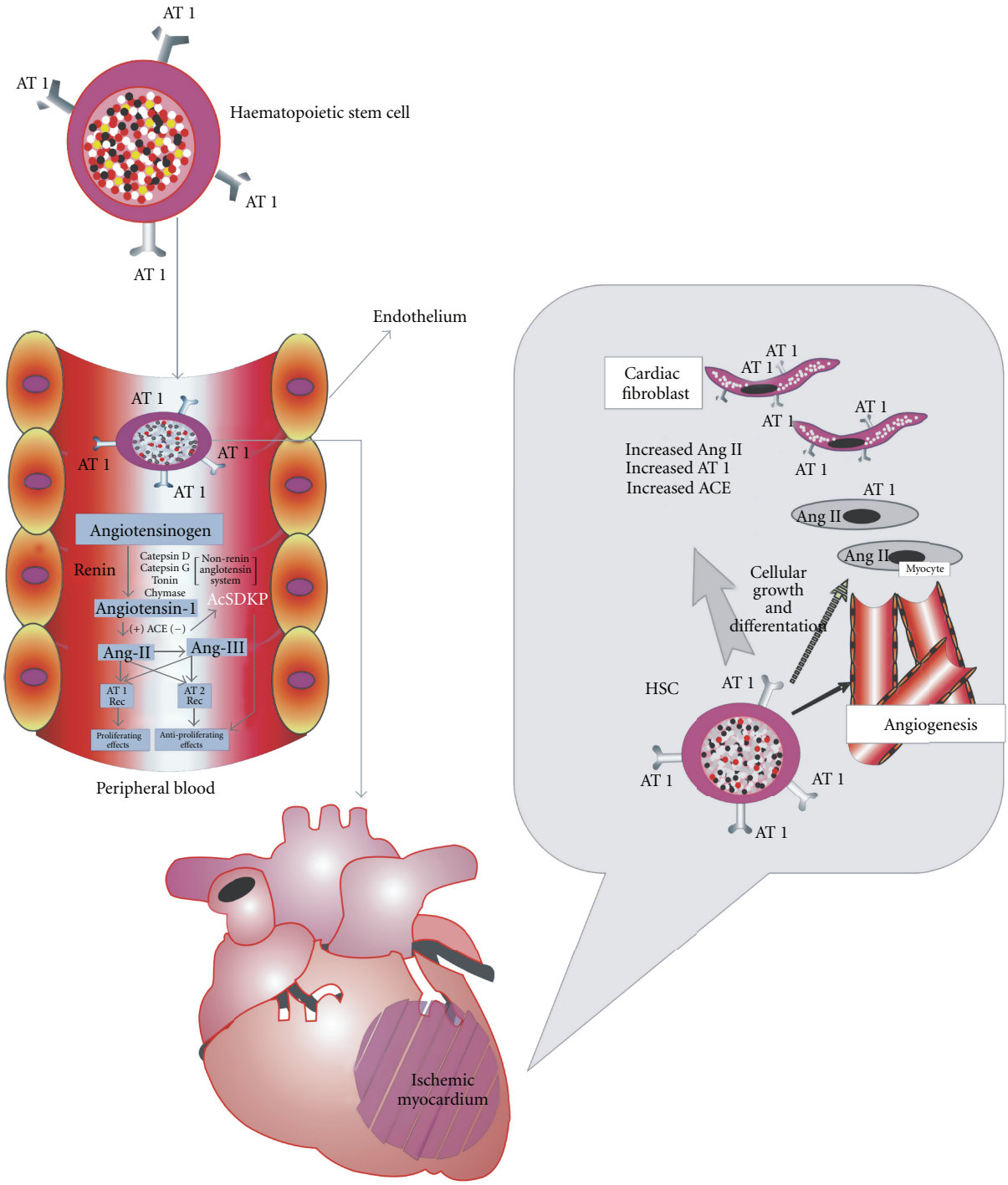

Figure 1: Possible functions of hematopoietic stem cells in the vasculature and cardiac microenvironment, suggesting the interrelationships of local bone marrow renin-angiotensin system (RAS), circulating RAS, and local myocardial RAS.

the idea that proatherogenic properties of hematopoietic and nonhematopoietic progenitors are determined by the local actions of modified LDL on the expression of local RAS genes [117].

Fukuda and Sata successfully demonstrated that BM-derived cells significantly contribute to the development of atherosclerotic lesions [21, 26, 119]. Although Ang II is supposed to promote contribution of BM-derived cells to atherosclerosis by enhancing their mobilization, recruitment, differentiation, and proliferation, Fukuda and Sata performed an experiment for to evaluate the potential participation of AT1aR in BM in the pathogenesis of atherosclerosis. They generated several combinations of BM chimeric mice in a murine model of hyperlipidemia and

atherosclerosis by analyzing several BM chimeric mice whose BM cells were positive or negative for AT1aR. They also mentioned that Ang II infusion increased the number of smooth muscle progenitor cells, which are peripheral blood cells that turn to α-smooth muscle actin-positive cells after culture in the presence of PDGF-BB. These smooth muscle-like cells expressed abundant matrix metalloproteinase-9 (MMP-9), which substantially contribute to destabilization of atherosclerotic plaques [21]. Their results suggested that blockade of AT1R not only in vascular cells but also in BM could be an important strategy to prevent atherosclerosis. In a previous study by Cassis et al. [120] it has been shown that, bone marrow recipient AT1a receptors are required to initiate Ang II-induced atherosclerosis in hypercholesterolemic mice in which bone marrow transplantation studies were performed. They have concluded that AT1a receptors expressed on infiltrating cells exert modest regulation of Ang II-induced atherosclerosis. Moreover the existence of this receptor in resident tissue is necessary for the initiation of Ang II-induced atherosclerosis and abdominal aortic aneurysms. An other study by Tsubakimoto et al. [121], the Ang II regulated differentiation/proliferation of monocyte-lineage cells to exert proatherogenic actions was clearly defined. In this study the authors generated BM chimeric apoE negative mice repopulated with AT1-deficient ($Agtr1^{-/-}$) or wild-type ($Agtr1^{+/+}$)) BM cells. The atherosclerotic development was significantly reduced in $apoE^{-/-}$/BM-$Agtr1^{-/-}$ mice compared with $apoE^{-/-}$/BM-$Agtr1^{+/+}$ mice, accompanied by decreased numbers of BM granulocyte/macrophage progenitors and peripheral blood monocytes. And finally they have been proposed that Ang II controls the expression of c-Fms in HSCs and monocyte-lineage cells through BM stromal cell derived TNF-alpha to promote M-CSF–induced differentiation/proliferation of monocyte-lineage cells and contributes to the proatherogenic action [121].

In contrary to the studies demonstrating that [21, 122] blockade of AT1 receptor in BM cells might have inhibitory effects on atherosclerosis, little or no changes of atherosclerosis in LDL receptor knockout mice by transplantation with BM from AT1a receptor knockout mice are also reported [120, 123]. These reports suggest the ameliorative function of AT1 receptor blockade in vascular cells for the AT1 receptor blocker- (ARB-) mediated atherosclerosis inhibition. In conjunction with the latter reports, the study by Kato et al. [124] also demonstrates that the beneficial effects of ARB in end-organ injuries are due to the blockade of AT1 receptor expressed in the end organs, but not in bone-marrow-derived cells. They proposed that distinct results observed in the kidney injury and atherosclerosis is possibly from the differences in the pathogenesis of mouse models. Moreover they have speculated that depending upon the tissues and model systems examined, AT1 receptor function in BMDCs may have differential action points.

Taken as a whole, the hematopoietic BM RAS, as well as local vasculature RAS, plays a crucial role in the initiation and progression of atherosclerosis, thereby contributing to development of cardiovascular diseases.

5. Future Therapeutic Perspectives

Endothelial dysfunction, cellular proliferation, and programmed inflammation triggered by RAS provide a clue to a novel understanding of the pathological hallmark of atherosclerosis, and may be important in developing new antiatherosclerotic strategies. AT1aR expressed on BM-derived cells plays a crucial role in the pathogenesis of atherosclerosis by accelerating BM-derived inflammatory cell infiltration in the vessel wall. For that reason, AT1R blockade not only in vascular cells but also in BM could help to prevent progression and destabilization of atherosclerotic plaques [21, 26, 117, 119, 125]. Pharmacological therapeutic strategies must focus on the distribution and the density of angiotensin receptors, gene expression, and proteomics along hematopoietic BM structures. Future therapeutic interventions would interfere with the pathobiological activation of the local hematopoietic BM in a variety of diseases, particularly atherosclerosis, to elucidate the importance of the system from an actual clinical point of view.

In summary, a large number of studies have shown that RAS has a central role in the initiation and progression of atherosclerosis, as outlined in this paper. Ang II may compromise the structural integrality of the endothelial barrier by induction of endothelial cell apoptosis. Inflammatory reaction in the vascular intimal layer involving macrophages and T lymphocytes by RAS-induced oxidative stress and hyperthrombotic state results in oxidative lipoprotein modification, smooth muscle cell migration from the media into the intima, proliferation, and transformation from a contractile to a synthetic phenotype. While the earlier stages may remain subclinical, this stage of the atherosclerotic process leads to a significant reduction in the vessel lumen. AT1aR expressed not only on vascular cells but also on BM-derived cells plays a role in the atherosclerotic plaque pathogenesis, at least partially by accelerating infiltration of BM-derived inflammatory cells in the vessel wall. Understanding the diversity of intracellular Ang II synthesis pathways may help in developing therapeutic interventions, and blockade of AT1R not only in vascular cells but also in BM could be an important strategy to prevent progression and destabilization of atherosclerotic plaques.

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Review Article

Clinical Interaction between Brain and Kidney in Small Vessel Disease

Masaki Mogi and Masatsugu Horiuchi

Department of Molecular Cardiovascular Biology and Pharmacology, Graduate School of Medicine, Ehime University, Tohon, Ehime 791-0295, Japan

Correspondence should be addressed to Masaki Mogi, mmogi@m.ehime-u.ac.jp

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Patients with chronic kidney disease (CKD) are well known to have a higher prevalence of cardiovascular disease from epidemiological studies. Recently, CKD has also been shown to be related to neurological disorders, not only ischemic brain injury but also cognitive impairment. This cerebrorenal connection is considered to involve small vessel disease in both the kidney and brain, based on their hemodynamic similarities. Clinical studies suggest that markers for CKD such as estimated glomerular filtration rate (eGFR), proteinuria, and albuminuria may be helpful to predict brain small vessel disease, white matter lesions (WMLs), silent brain ischemia (SBI), and microhemorrhages. Recently, changes in the vascular system of the brain have been shown to contribute to the onset and progression of cognitive impairment, not only vascular dementia but also Alzheimer's disease. Patients with CKD are also reported to have higher risk of impaired cognitive function in the future compared with non-CKD subjects. These results indicate that CKD markers may be helpful to predict the future risk of neuronal disease.

1. Introduction

Recently, the relation between chronic kidney disease (CKD) and neurological disorders, not only cerebrovascular disease such as ischemic brain injury but also cognitive impairment such as Alzheimer's disease, has been highlighted. This cerebrorenal interaction is considered to be based on small vessel disease. Cerebral and glomerular small vessel disease might have a common soil of pathogenesis, as these organs are closely connected with each other through anatomic and vasoregulatory similarities. Because small vessel disease is a systemic disorder, information about small vessel disease in one organ may provide information on damage in another organ. For the kidney, damage markers are albuminuria/proteinuria and a reduction in estimated glomerular filtration rate (eGFR), which is also a marker of CKD. On the other hand, damage markers in the brain could be magnetic resonance imaging- (MRI-) documented small vessel alterations. Recently, clinical investigations have suggested a relation between these damage markers in the kidney and the brain. Here, we review the cerebrorenal interactions mainly from a clinical view.

2. Clinical Relation between CKD and Cerebrovascular Disease

2.1. Stroke. Recently, the relation between CKD and the onset of stroke has been highlighted. The Northern Manhattan Study (NOMAS), which followed 3298 stroke-free subjects for vascular outcomes with a mean follow-up time of 6.5 years, showed that CKD, which was estimated using serum creatinine and the Cockcroft-Gault formula, between 15 and 59 mL/min is a strong risk factor for stroke (hazard ratio (HR) = 2.65) [1]. In contrast, Bos et al. demonstrated that decreased eGFR (<60 mL/min/1.73 m^2) is a strong risk factor for hemorrhagic but not ischemic stroke (HR = 4.10 for hemorrhagic stroke versus 0.87 for ischemic stroke) in the Rotterdam Study [2]. The authors considered two hypotheses for this relation. The first, decreased GFR indicates small vessel disease not only in the kidney but also in the brain. Small vessel disease seems to be the main pathophysiological mechanism in hemorrhage rather than brain infarction; therefore, the authors suggested that GFR may be a marker of cerebral small vessel disease, especially hemorrhage. The second, the authors considered platelet dysfunction to be

an inducible factor by CKD. Severe CKD patients show prolonged bleeding time and mucosal oozing [3], indicating that platelet dysfunction may be involved in the relation between eGFR and hemorrhagic stroke. In the relation between microalbuminuria and incident stroke, prospective cohort studies using meta-analysis with 12 prospective cohort studies including 48,596 individuals with more than 1200 stroke events have been very recently published [4]. The presence of microalbuminuria was greatly associated with stroke onset even after adjustment for cardiovascular risk factors (overall HR 1.92), indicating that albuminuria contribute to be a strong predictor for the incidence of stroke. Recently, asymptomatic cerebral small vessel disease has been investigated as a predictor of the risk of future stroke. Oksala et al. demonstrated that cerebral small vessel disease is closely associated with kidney function in patients with acute stroke. Patients with cerebral small vessel disease and impaired kidney function (eGFR $< 60\,\text{mL/min/1.73}\,\text{m}^2$) exhibit poor poststroke survival [5]. These results indicate that Representative cerebral small vessel diseases include white matter lesions (WMLs), silent brain infarction (SBI), and microhemorrhages as well as lacunar infarcts and subcortical atrophy.

2.2. White Matter Lesions. WMLs are detected as hyperintense areas on T2-weighted MRI in areas that are bilaterally and symmetrically sited in the hemispheric white matter. The prevalence of WMLs is significantly related to the risk of stroke, cognitive decline, and dementia [6–8]. The NOMAS demonstrated that white matter hyperintensity volume is associated with moderate-to-severe CKD, which was estimated using serum creatinine and the Cockcroft-Gault formula, between 15 and 59 mL/min [9]. Wada et al. demonstrated that subjects with lower eGFR (less than $60\,\text{mL/min/1.73}\,\text{m}^2$) tended to have more lacunar infarcts and higher grade of WMLs; moreover, mean grade of WMLs and the mean number of lacunar infarcts in subjects with albuminuria were greater than those in subjects without albuminuria [10]. Furthermore, they also reported that urinary albumin level was associated with cerebral small vessel disease, independently of traditional cerebrovascular risk factors, in community-based elderly [11]. Similarly, Ikram et al. investigated the relation between kidney function evaluated by eGFR and cerebral small vessel disease via MRI analysis. They clearly showed that decreased eGFR was related to subclinical markers of cerebral small vessel disease such as deep white matter volume and WNLs independent of cardiovascular risk factors such as age, sex, blood pressure, and diabetes [12]. Interestingly, they also demonstrated that persons with lower eGFR had a smaller brain volume, indicating that CKD may relate to brain atrophy.

2.3. Silent Brain Infarction. On the other hand, SBI is defined as a cerebral infarction detected by brain imaging without clinical symptoms. Kobayashi et al. also reported that there is an independent association between SBI and eGFR [13]. The prevalence of SBI and the number of SBIs increased markedly as eGFR decreased. The presence of SBI is reported to predict clinical overt stroke [14, 15] or cognitive impairment. Therefore, patients with CKD should be assessed for SBI by MRI during the follow-up period. In contrast, Uzu et al. followed 608 patients with type 2 diabetes for 7.5 years and very recently reported that SBI may predict the progression of kidney disease in these patients [16]. The risk of end-stage renal disease (ESRD) or death was significantly higher in patients with SBI than in those without (HR 2.44). The estimated eGFR declined more in patients with SBI than in those without; however, the presence of SBI did not increase the risk of progression of albuminuria.

2.4. Microhemorrhages. Microhemorrhages are discrete or isolated punctate hypointense lesions smaller than 5 mm on T2*-weighted MRI. They are considered to be clinically silent but are strongly associated with advanced small vessel or microvascular ischemic disease [17, 18] and to be a marker for increased risk of future intracranial hemorrhage [19, 20]. Interestingly, Cho et al. showed that lower eGFR is associated with the presence of cerebral microhemorrhages [21]. Moreover, proteinuria is also strongly associated with both the frequency and number of cerebral microhemorrhages in patients with recent cerebral ischemia [22]. Therefore, CKD may increase the risk of hemorrhagic microangiopathy in the brain.

2.5. Hypertensive Nephroangiosclerosis. Hypertensive nephroangiosclerosis was observed in 25% of patients with ESRD in the United States [23]. Because nephroangiosclerosis is also mostly clinically silent, its prevalence in stroke patients is not well known. A recent autopsy data bank clearly demonstrated that nephroangiosclerosis is common in patients with fatal stroke. Indeed, nephroangiosclerosis is independently associated with the prevalence or history of hypertension in stroke patients (39.8% of patients with stroke versus 9.0% of patients with other neurologic diseases) [24]. These results suggest that senile kidney change is also commonly observed in patients with cerebrovascular disease and a true relation between kidney dysfunction and cerebral small vessel disease; however, the factors connecting kidney dysfunction and cerebrovascular disease remain under discussion.

3. Clinical Relation between CKD and Cognitive Impairment

Dementia and cognitive decline impair the quality of life and are associated with a profound disease burden, morbidity, and mortality, not only in patients but also in caregivers. Although an earlier approach to prevent cognitive dysfunction has been expected, there are few markers for evaluating the future risk of cognitive decline in subjects. Recently, impaired kidney function was reported to be associated with dementia and cognitive impairment. The REasons for Geographic and Racial Differences in Stroke (REGARDS) Study with 23,405 participants showed that reduced kidney function is associated with a higher prevalence of cognitive impairment [25]. In patients with CKD, each $10\,\text{mL/min/1.73}\,\text{m}^2$ decrease in eGFR below $60\,\text{mL/min/1.73}\,\text{m}^2$ was associated with an 11% increased

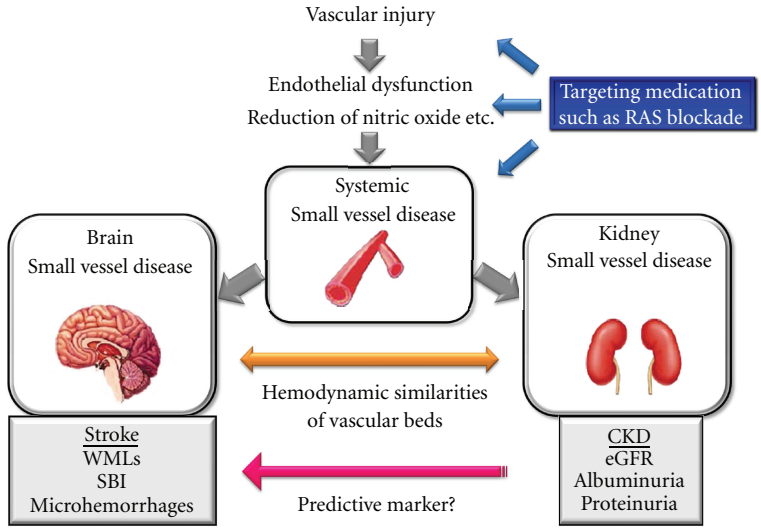

Figure 1: Schematic representation of cerebrorenal connection. RAS: renin-angiotensin system, CKD: chronic kidney disease, eGFR: estimated glomerular filtration rate, WMLs: white matter lesions, and SBI: silent brain infarction.

prevalence of cognitive impairment (HR = 1.11). Yaffe et al. conducted a chronic renal insufficiency cohort cognitive study in 825 adults aged 55 and older with CKD [26]. Participants with advanced CKD (eGFR < 30 mL/min/1.73 m^2) were more likely to have clinically significant impairment of global cognition than those with mild-to-moderate CKD (eGFR 45–59 mL/min/1.73 m^2) (HR = 2.0). Moreover, Buchman et al. reported a prospective, observational cohort study in 886 elderly without dementia [27]. Impaired kidney function (eGFR < 60 mL/min/1.73 m^2) at baseline was associated with a more rapidly decline in cognitive, especially in semantic memory, episodic memory, and working memory. In contrast, Jassal et al. very recently demonstrated that baseline albuminuria, but not eGFR, was associated with reduced cognitive function only in men [28]. They indicated that albuminuria was a simple predictor of future cognitive decline. Although there is sex difference in the relation between albuminuria and cognitive impairment, kidney function may provide an important window on future cognitive impairment. Recently, changes in the vascular system in the brain have been shown to contribute to the onset and progression of dementia [29]. The so-called "central nervous system (CNS) neurovascular unit" is linked to many common human CNS pathological conditions including dementia. Although multiple mechanisms are involved in cognitive impairment and dementia associated with CKD, small vessel disease in the kidney and brain is also considered to have a key role in this connection.

4. Hemodynamic Similarities of Vascular Beds between Kidney and Brain

Unlike most organs, both the kidney and brain are low resistance end-organs that are exposed to high-volume blood flow throughout the cardiac cycle. These hemodynamic similarities are observed in the vascular beds in the kidney and the brain [30]; therefore, small vessel disease in the kidney may let us know of the presence of small vessel disease in the brain. Ito et al. proposed the very interesting "strain vessel hypothesis" as a possible mechanism for cerebro-cardio-renal connections [31]. Based on the similarity of the juxtamedullary afferent arterioles in the kidney to the perforating arteries in the brain, they are thought to be evolutionally developed to maintain the perfusion of vital tissues such as nephrons and the brainstem directly from large arteries to deliver blood to the tissue. These "strain vessels" are exposed to very high pressure and maintain a high vascular tone. Vascular damage induced by high arterial blood pressure and diabetes mellitus occurs in these similar strain vessels; therefore, microalbuminuria may be an indicator of vascular damage not only in the kidney but also in the brain. One of the common molecular components of small-vessel physiology that may also mediate microvascular dysfunction or injury is nitric oxide. Many papers have reported that nitric oxide deficiency could occur in renal disease, and this subject was been well reviewed by Baylis [32]. Nitric oxide regulates the microcirculation and the blood brain barrier [33], both of which are implicated in the development of WMLs and other manifestations of small vessel disease in the brain. Moreover, patients with impaired cognitive function show increased levels of endogenous inhibitors of nitric oxide synthesis and decreased nitric oxide metabolites [34]. Therefore, decreased nitric oxide may be one of the key factors in the cerebrorenal connection.

5. Prevention and Future Perspectives

These reports above strongly suggest that a brain and kidney connection exists and that systematic treatment targeting small vessel disease is therapeutically effective on not only the apparent damaged organ but also on the silently damaged organs (Figure 1). According to their unique shared susceptibility to vascular injury from central aortic pressure as

a strain vessel, a logical preventive approach to cerebrorenal-related dysfunction is to achieve a reduction of central pulse pressure. A reduction of the central pulse pressure involves a reduction of the wave reflection by dilation of conduit arteries, since drugs do not directly affect the aorta and large arteries. Therefore, antihypertensive drugs should be selected to reduce the central pulse pressure, such as renin-angiotensin system (RAS) blockers and calcium-channel antagonists (CCB). For the kidney, there is good evidence from large clinical studies that blockade of RAS is highly effective to prevent renal damage compared with other antihypertensive drugs. In the brain, recent large clinical trials indicate that RAS blockade with angiotensin receptor blockers (ARBs) is effective to prevent a first or recurrent stroke beyond their blood pressure-lowering effect [35–37]. Moreover, a very recent paper clearly demonstrated that patients treated with ARBs have less severe deficit after stroke [38]. These results suggest that treatment with ARBs may be effective not only to reduce blood pressure but also to protect both the kidney and brain via preventing small vessel disease. However, the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) demonstrates that all of the blood pressure-lowering regimens have broadly similar protection against stroke [39]. Moreover, there are not any large clinical studies that demonstrate the effect of ARBs on dementia or cognitive impairment. Therefore, there is few evidence of the preventive effect of RAS blockade in the brain compared with that in the kidney. On the other hand, CCBs are proved to have preventive effect on dementia in the Systolic Hypertension in Europe (Syst-Eur) study [40]. CCB, nitrendipine was found to be effective to reduce the incidence of dementia. This is the only large clinical study that shows the effect of anti-hypertensive drug on dementia. Although several CCBs are reported to have renoprotective effects, generally CCBs do not have a remarkable effect on CKD prevention compared with RAS blockade due to the preferentially dilate afferent arteriole. Therefore, preventive effect of CCBs on cerebrorenal connection is also still under investigation. Furthermore, although hypertension may be involved in each pathological change in brain and kidney, it can be result of high blood pressure "in parallel," indicating that direct evidence of common mechanistic factors in hypertension-induced cerebrorenal damage is still under investigation.

6. Conclusion

A cerebro-renal connection exists clinically. CKD markers may be helpful to evaluate the future risk of neuronal disease (Figure 1). Further investigation of the brain-kidney connection may contribute to prevention of impaired quality of life from multiple organ dysfunction due to small vessel disease. Furthermore, protection of the damaged organ will shift to protection of multiple hidden damaged organs, focusing on systemic small vessel disease.

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Review Article

Transforming Growth Factor-β1 as a Common Target Molecule for Development of Cardiovascular Diseases, Renal Insufficiency and Metabolic Syndrome

Ken-ichi Aihara,[1] Yasumasa Ikeda,[2] Shusuke Yagi,[3] Masashi Akaike,[3] and Toshio Matsumoto[1]

[1] *Department of Medicine and Bioregulatory Sciences, The University of Tokushima, Graduate School of Health Biosciences, 3-18-15 Kuramoto-cho, Tokushima 770-8503, Japan*
[2] *Department of Pharmacology, The University of Tokushima, Graduate School of Health Biosciences, 3-18-15 Kuramoto-cho, Tokushima 770-8503, Japan*
[3] *Department of Cardiovascular Medicine, The University of Tokushima, Graduate School of Health Biosciences, 3-18-15 Kuramoto-cho, Tokushima 770-8503, Japan*

Correspondence should be addressed to Ken-ichi Aihara, aihara@clin.med.tokushima-u.ac.jp

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Transforming growth factor-β1 (TGF-β1) is a polypeptide member of the transforming growth factor β superfamily of cytokines. It is a secreted protein that performs many cellular functions including control of cell growth, cell proliferation, cell differentiation and apoptosis. In the cardiovascular system, TGF-β1 plays pivotal roles in the pathogenesis of hypertension, restenosis after percutaneous coronary intervention, atherosclerosis, cardiac hypertrophy and heart failure. In addition, TGF-β1 has been shown to be increased in adipose tissue of obese subjects with insulin resistance. Furthermore, TGF-β1 is a potent initiator of proliferation of renal mesangial cells leading to chronic kidney disease. Some currently available agents can manipulate TGF-β1 expression leading to amelioration of cardiovascular diseases. Thus, an understanding of interactions between chronic kidney disease and metabolic syndrome and the development of cardiovascular diseases is an important issue, and attention should be given to TGF-β1 as a crucial factor for regulation and modulation of those pathological conditions.

1. Introduction

Transforming growth factor-β (TGF-β) is a polypeptide member of the TGF-β superfamily of cytokines. The TGF-β superfamily consists of TGF-β, activins, inhibins, growth differentiation factors, and bone morphogenetic proteins (BMPs). The TGF-β superfamily proteins share common sequences and motifs to exert their various biological actions, including cell growth, differentiation, proliferation, migration, adhesion, apoptosis, and extracellular matrix (ECM) production (Figure 1) [1–4]. Experimental studies on TGF-β signaling pathway manipulation have confirmed crucial roles of TGF-β in the process of development and/or regression of malignant tumors, autoimmune diseases, organ fibrotic changes, kidney diseases, and cardiovascular diseases (CVD) [4]. TGF-β exists in three known subtypes in humans, TGF-β1, TGF-β2, and TGF-β3. Since TGF-β1 is present in endothelial cells, vascular smooth muscle cells (VSMCs), myofibroblasts, macrophages, and other hematopoietic cells, it is recognized as the most pivotal TGF-β isoform for the cardiovascular system [5]. TGF-β1 is synthesized and secreted into the extracellular matrix as an inactive precursor protein consisting of a signal peptide, latency-associated peptide (LAP) domain, and mature TGF-β1. Activation of TGF-β1 is involved in proteolytic cleavage of LAP, and TGF-β1 is activated by thrombospondin-1, plasmin, acidic microenvironments, matrix metalloproteinases (MMPs) such as MMP-2 and -9, and β6 integrin [5–7]. In VSMCs, angiotensin II (Ang II) enhances TGF-β1 mRNA expression by transcriptional and posttranscriptional actions and accelerates its conversion to the biologically active form [8].

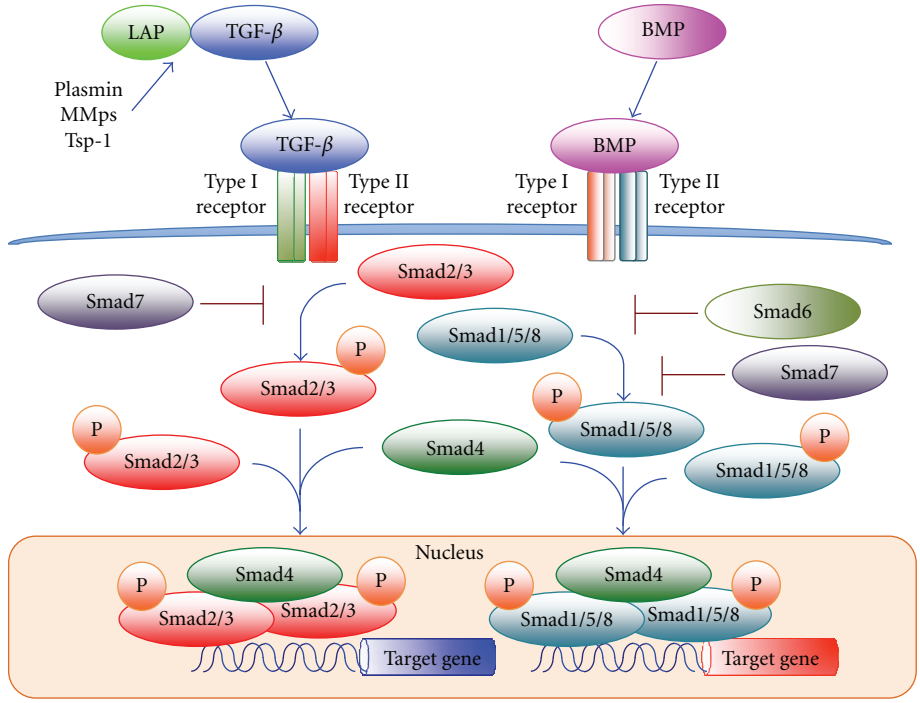

Figure 1: Schematic diagram of TGF-β superfamily signaling pathway. TGF-β is produced as a latent protein that is activated by various factors including plasmin, MMPs, and Tsp-1. Active form of TGF-β binds to its receptors and induces Smad2/3 phosphorylation, and BMPs induce Smad1/5/8 phosporylation. Activated R-Smads, form heteromeric complexes with Smad4 and regulate the expression of target genes of TGF-β such as fibronectin, collagen type I, PAI-1 and MMP-2 in the nucleus. TGF-β: transforming growth factor-β, LAP: latency-associated peptide, MMPs: metalloproteinases, Tsp-1: thrombospondin-1 and BMP: bone morphogenetic protein.

Previous studies has shown that TGF-β1 activation is closely associated with the development of cardiovascular diseases, including hypertension [9], cardiac hypertrophy [10] and cardiac fibrosis [11] leading to heart failure as well as restenosis after coronary intervention [12] and atherosclerosis [13, 14]. Moreover, TGF-β1 is known to induce progression of experimental renal disorders, and it has been shown that there are associations between serum level of TGF-β1 and risk factors for progression of clinically relevant renal disorders in humans [15]. Visceral fat obesity with insulin resistance has been considered to play a central role in the development of metabolic syndrome (MetS) leading to an increase in the incidence of cardiovascular events, and recent studies have shown a possible interaction between TGF-β1 and visceral fat obesity [16].

There are some elaborate review articles concerning associations between TGF-β1 and CVD [4, 17–20]; however, in this review, we focus on the importance of TGF-β1 for, linking the pathologic processes of CVD, renal insufficiency, and MetS.

2. Mechanism of TGF-β Superfamily Signaling Pathway

TGF-β superfamily ligands exert their biological effects via binding to high-affinity cell surface receptors, including type I and type II TGF-β superfamily receptors. Seven type I receptors (activin-like kinase (ALK) 1–7) and five type II receptors are known to be present in mammals [21–23]. Type II receptors are constitutively active serine/threonine kinases, with ligand binding resulting in conformational changes that induce recruitment and complex formation with an appropriate type I receptor (ALK1-7) [24], and the type II receptor then phosphorylates the type I receptor in the glycine/serine-rich domain. The activated type I receptors mediate their cellular actions through interaction and phosphorylation of Smad proteins, which are often in complex with other Smads, and act as transcription factors to regulate the expression of various target genes [1, 25]. Based on their function, Smads proteins have been classified into three groups: receptor-activated Smads (R-Smads), including Smad1, Smad2, Smad3, Smad5, and Smad8, the comediator Smad Smad4, and inhibitory Smads, Smad6, and Smad7. Smad2 and Smad3 are specific mediators of TGF-β/activin pathways, whereas Smad1, Smad5, and Smad8 are involved in BMP signaling (Figure 1) [1, 2].

3. TGF-β1 and Cardiovascular Diseases

Since clinical and experimental studies have shown that TGF-β1 is involved in the development of CVD, it is absolutely imperative to understand the biological actions of TGF-β1 in the cardiovascular system.

3.1. Role of TGF-β1 in the Development of Vascular Diseases. In experimental models, targeting disruption of the TGF-β1 gene prevents neointima hyperplasia and constrictive remodeling after vascular injury such as angioplasty [12, 26, 27]. In diseased vessels such as arteries in patients with atherosclerosis, type I receptor expression is enhanced and TGF-β1 stimulates extracellular matrix (ECM) production and can promote early fatty streak lesion formation [28, 29]. In addition, it has been reported that TGF-β1 reduces collagenase production and accelerates the expression of tissue inhibitors of MMPs, resulting in overall inhibition of ECM degradation and leading to excessive matrix accumulation [6, 30]. In addition, TGF-β1 can stimulate VSMCs to produce collagen synthesis; however, TGF-β1 has been shown to be involved in both positive and negative plaque stabilization [31–33]. TGF-β1 also acts as a mediator of vascular fibrosis induced by several cardiovascular stress factors that are involved in CVD, including mechanical stress, angiotensin II (Ang II), high glucose, and advanced glycation products [34–36].

3.2. Role of TGF-β1 in the Development of Cardiac Diseases. Tissue levels of TGF-β1 are markedly increased in the hypertrophic myocardium after cardiac stress loading such as Ang II excess [37, 38]. Furthermore, it has been reported that TGF-β1 stimulation alters the program of differentiation-related gene expression in isolated cardiac myocytes, promoting the synthesis of fetal contractile proteins, characteristic of pressure-overload hypertrophy [39]. Overexpression of TGF-β1 in transgenic mice results in cardiac hypertrophy that is characterized by both interstitial fibrosis and hypertrophic growth of cardiomyocytes [40]. Local production of TGF-β1 in the hypertrophic myocardium and the link between the renin-angiotensin-aldosterone system and TGF-β1 signaling pathway are involved in the hypertrophic response. Since it is well known that Ang II enhances TGF-β1 expression and TGF-β1-Smad signaling pathways, cardiac remodeling, including cardiac hypertrophy, and cardiac fibrosis, through activation of TGF-β1 is closely associated with excess of Ang II [4].

On the other hand, Shultz et al. showed that the cardiomyocyte cross sectional area was markedly increased in Ang II-treated wild-type (WT) mice but was unchanged in Ang II-treated TGF-β1-deficient mice [10]. We have found that Ang II stimulated cardiac remodeling, including cardiac hypertrophy and left ventricular dysfunction, along with increased expression of TGF-β1 in WT mice. We have also found that not only WT mice but also gene-engineered mice such as mice with gene disruption of endothelial nitric oxide synthase (eNOS), androgen receptor, and heparin cofactor II manifested acceleration of Ang II-induced cardiac remodeling with increased expression of TGF-β1 [37, 38, 41, 42] (Figure 2).

3.3. Possible Link between TGF-β1 and Hypertension. Hypertension is a major cause of the development of cardiovascular events and causes crucial organ damage such as renal sclerosis, stroke, and coronary heart disease. While environmental and lifestyle-related problems including lack of exercise, obesity, and excessive salt intake contribute to the increased incidence of hypertension, approximately 50% of causes of hypertension are thought to have a genetic background [18]. Recent studies have been suggested that there is a link between increased levels of circulating TGF-β1 and hypertension [9]. It has been shown that emilin-1, an extracellular matrix protein that is associated with microfibrils of the elastic matrix in the aortic media, modulates TGF-β1 availability and is involved in regulation of arterial diameter [43]. Gene disruption of emilin-1 results in increased conversion of pro-TGF-β1 to the mature form and a subsequent increase in TGF-β1 signaling. The accelerated TGF-β1 signaling pathway results in a reduction in arterial lumen diameter with a resultant increase in vascular resistance and hypertension [43]. A possible mechanism is that excessive levels of active TGF-β1 cause premature cytostasis of VSMCs and subsequently suppress arterial wall expansion. On the other hand, a study using mice has indicated the possibility that reduced arterial diameter is a secondary consequence of vascular remodeling [44]. These accelerated TGF-β1 activation-induced aberrant phenotypes concerning arterial remodeling and elevated blood pressure were abolished by disruption of the TGF-β1 gene in mice [10].

3.4. TGF-β as a Predictive Biomarker for Cardiovascular Diseases. Previous studies have shown that several components of TGF-β superfamily signaling pathways have significance as prognostic markers for CVD. For instance, in patients with coronary artery disease, increased serum levels of TGF-β1 are significantly associated with extended survival with reduced incidence of coronary events and interventions [45]. In contrast, after angioplasty, there is a greater risk of development of restenosis in patients that have higher levels of TGF-β1 in their blood 15 min, 24 h, and 2 weeks after the procedure has been performed [46], suggesting that these patients would benefit from additional interventions to prevent restenosis. Further examinations are needed to clarify the significance of serum level of TGF-β1 as a biomarker of cardiovascular diseases.

4. TGF-β1 and Progression of Renal Diseases

TGF-β1 is known to induce progression of experimental renal disease [47]. Suthanthiran et al. demonstrated that serum TGF-β1 protein levels were positively and significantly associated with plasma renin activity along with elevated systolic and diastolic blood pressure and were predictive of microalbuminuria in African Americans [15]. Connective tissue growth factor (CTGF) expression is stimulated by all TGF-β isoforms and is abundant in glomerulosclerosis and other fibrotic disorders [48]. CTGF has been suggested to mediate profibrotic effects of TGF-β1 and to facilitate interaction of TGF-β1 with its receptor [48]. In addition, TGF-β1 is a cytokine known to participate in several processes related to the development of chronic kidney disease (CKD), including tubular degeneration [49]. The major pathogenesis has

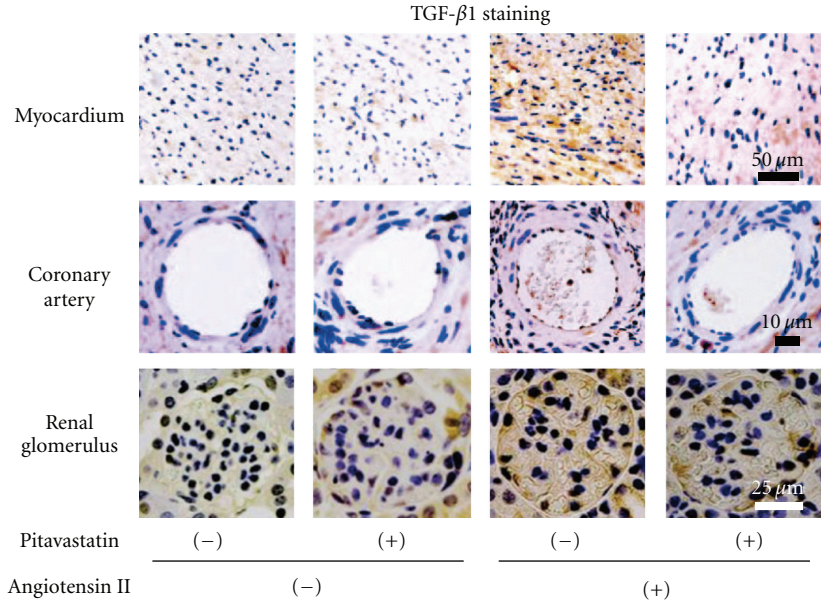

Figure 2: Cardiorenal immunohistochemistry of TGF-β1. TGF-β1-stained spots are observed in the myocardium (upper panels) and coronary artery (middle panels) in Ang II-infused wild-type mice (upper and middle panels). Macroscopic renal injury and TGF-β1-stained renal glomerulus are found in Ang II-infused mice, especially eNOS$^{-/-}$ mice (lower panels). Pitavastatin treatment attenuates cardiorenal TGF-β1 expression in Ang II-infused mice. Modified from the article by Yagi et al. [37].

been thought to be apoptosis and epithelial-to-mesenchymal transition of tubule epithelial cells, which is involved in the fibrotic healing process of the interstitial compartment [49]. On the other hand, *in vivo* blockade of TGF-β action has been shown to reduce CKD-associated tubular damage. Proliferation of injured and hyperplastic podocytes with increased TGF-β1 expression has been found in several types of glomerulonephritis [50]; however, pathophysiological roles of TGF-β1 in podocyte growth and development of glomerulosclerosis have not been fully elucidated. Since TGF-β activates Smads, Ras/extracellular signal-regulated kinase (ERK) and phosphatidyl inositol-3-kinase (PI3K) pathways in podocytes [50], enhancement of the TGF-β/Smad signaling pathway by hyperplastic podocytes has been thought to lead to mesangial cell matrix overproduction and eventually to podocyte apoptosis and/or detachment, culminating in the development of glomerulosclerosis.

In addition to glomerulonephritis, autosomal dominant polycystic kidney disease (ADPKD), a common inherited renal disease with multiple cysts and interstitial fibrosis in the kidneys, has been noted as an important cause of chronic renal failure. Interestingly, Hassane showed that activation of the TGF-β-Smad signaling pathway is involved in the progression of ADPKD with increased mRNA levels of TGF-β target genes, such as fibronectin, collagen type I, plasminogen activator inhibitor 1 (PAI-1), and MMP-2 [51].

In experimental animal studies, we have found accelerated cardiac remodeling with activation of the TGF-β1-Smad 2/3 signaling pathway in Ang II-induced eNOS$^{+/+}$ and eNOS$^{-/-}$ mice [37]. High-dose Ang II stimulation also markedly increased mortality rate with oliguria in eNOS$^{-/-}$ mice but not in eNOS$^{+/+}$ mice. In pathological studies, we have found that pitavastatin treatment attenuates the enhanced TGF-β1 expression in glomeruli and reduced the high mortality rate in Ang II-treated eNOS$^{-/-}$ mice (Figure 2) [37]. Taken together, these results indicate that activation of the TGF-β1-Smad 2/3 signaling pathway is closely involved in the development of cardiorenal disorders.

5. TGF-β1 and Metabolic Syndrome

Metabolic syndrome is mostly characterized as visceral fat obesity with multiple cardiovascular risk factors, including elevated blood pressure, hyperglycemia, and dyslipidemia. Therefore, an understanding of the molecular mechanism by which visceral obesity is promoted is essential for preventing cardiovascular events in individuals with MetS. In humans, there is a variant of TGF-β1, commonly known as Pro 10, that results from substitution of leucine at codon 10 with proline. This variant has been found in Swedish men and has been found to cause a 4% increase in BMI, 6% increase in waist circumference, and a 24% increase in fasting insulin [52]. Although it has not been determined how the Pro 10 variant form of the TGF-β1 protein is linked to visceral adiposity and elevated levels of circulating insulin, there is a possibility that TGF-β1 is involved in the insulin resistance with obesity. Since macrophage infiltration into adipose tissue causes insulin resistance [53, 54] and since coculture experiments with human adipocytes and macrophages have shown that downstream effectors of TGF-β such as PAI-1, collagen VI, and phosphorylated Smad were increased

in both macrophages and adipocytes [55], TGF-β has the potential for increasing insulin resistance. In experimental animal studies, Samad et al. reported enhancement of gene and protein expression of TGF-β1 in two strains of genetically obese mice (*ob/ob* and *db/db*) compared with that in lean mice [56] and Raju et al. showed that an obese state increases levels of TGF-β1 but not TGF-β2 in platelets of Zucker rats, recognized as an experimental model of MetS [57]. Moreover, Sciarretta et al. showed that serum levels of inflammatory markers, including C-reactive protein, tumor necrosis factor-alpha and TGF-β, in hypertensive patients with MetS were significantly higher than those in patients without MetS [16]. Interestingly, Herder et al. showed that elevated serum concentrations of TGF-β1 are associated with incident type 2 diabetes and that the association remained stable in multivariate analyses taking into account demographic, anthropometric, metabolic, and lifestyle factors [58]. However, the molecular pathogenesis between increased serum levels of TGF-β1 and MetS or type 2 diabetes has not been fully elucidated, and further investigations are needed to clarify this issue.

Since hypertriglycemia is one of the criteria for diagnosis of MetS, treatment with fibrates for dyslipidemia is thought to reduce the development of MetS leading to an increase in cardiovascular events. Nakano et al. demonstrated that bezafibrate directly inhibits hepatic fibrogenic response induced by TGF-β1 *in vitro*. Therefore, the use of bezafibrate has a possibility to be a new therapeutic strategy against nonalcoholic steatohepatitis, hepatic fibrosis, and CVD via attenuation of TGF-β1 production [59]. Although consideration should be given to monitoring serum creatinine levels, treatment with fenofibrate, bezafibrate, and gemfibrozil, but not treatment with clofibrate, in patients with elevated triglycerides and low HDL cholesterol resulted in a lower incidence of CV events without unfavorable effects on atherogenic mortality [60–63].

6. Pharmacological Manipulation of TGF-β1

Possible links between the TGF-β1 signaling pathway and CVD, CKD, and MetS have been noted as mentioned above. Therefore, modulation of the TGF-β1 pathway by target-designed molecules or existing pharmacological agents might be available therapeutic approach in aberrant expression or signaling activities of TGF-β1-related disorders.

6.1. Manipulation of the TGF-β1 Signaling Pathway by Specific Inhibitors. Several new properties have been proposed as specific modulators of the TGF-β signaling pathway. The secreted exoplasmic domain of the TGF-β type II receptor (TβRII) inhibits the biological effects of TGF-β1 *in vitro* [64]. Smith et al. demonstrated that TGF-β signaling accelerates negative remodeling with adventitial fibrosis and neointima formation in an arterial balloon injury model and that this TGF-β-mediated effect was inhibited by a soluble TGF-β receptor II (TβRII) after vascular injury [65]. Kingston et al. performed a randomized trial using a recombinant adenovirus expressing a secreted form of TβRII to test the hypothesis that localized inhibition of TGF-β1 inhibits luminal loss after angioplasty, and they demonstrated that adenovirus-mediated gene transfer of TβRII attenuates vessel stenosis after angioplasty through prevention of constrictive remodeling [66]. Furthermore, small-molecule-specific inhibitors of TGF-β1 receptor kinase have been targeted for cancer treatment and experimental investigations for the kidney [67], liver [68], and lung fibrosis [69].

6.2. Manipulation of the TGF-β1 Signaling Pathway by Currently Available Agents. Several currently available agents have been shown to act on the TGF-β1 signaling pathway. Redondo et al. demonstrated that TGF-β1 plays an important role in aspirin-mediated inhibition of cell proliferation via inhibition of VSMC proliferation [70]. They also reported that pioglitazone, a synthetic PPAR-γ agonist, subsequently increased the nuclear recruitment of phosphorylated Smad2 via TGF-β1 activation leading to VSMC apoptosis [71]. Statins, HMGCoA reductase inhibitors, have been established as efficient agents for reducing coronary plaque instability and cardiovascular death with pleiotropic effects as well as amelioration of aberrant lipid profiles. Moreover, statins have also been shown to be involved in expression of TGF-β1 signaling pathways [37, 41, 72, 73]. Porreca et al. showed that pravastatin administration was associated with increased plasma levels of TGF-β1 in atherosclerotic patients while increasing both protein synthesis and secretion of TGF-β1 in plaque monocytes, and they postulated that activated TGF-β1 signaling pathways lead to stabilization of coronary plaque through anti-inflammatory actions [72]. Interestingly, we and others have demonstrated that strong statins, including pitavastatin and atorvastatin, reduced tissue expression levels of cardiorenal TGF-β1 leading to attenuation of cell proliferation, hypertrophic changes, and fibrotic alterations [37, 41, 73]. Therefore, the detailed mechanism of TGF-β1 modulation by statins remains a matter of debate. In addition, inhibitory effects of ACE inhibitors and Rho kinase inhibitors on the TGF-β1 signaling pathway have been reported [74–76].

Taken together, the results indicate that an understanding of the organ-specific pathological role of TGF-β1 and appropriate manipulation of TGF-β1 expression and activation should be considered for prevention of cardiorenal diseases.

7. Conclusions

An understanding of the complexities of the interplay between the TGF-β1 signaling pathway and the development of CVD, CKD, and MetS with insulin resistance are matters of great importance (Figure 3). Based on accumulating evidence concerning TGF-β1 signaling pathway and human diseases, appropriate modulation of the biological actions of TGF-β1 might be a valuable therapeutic approach in patients with the above-described pathological conditions.

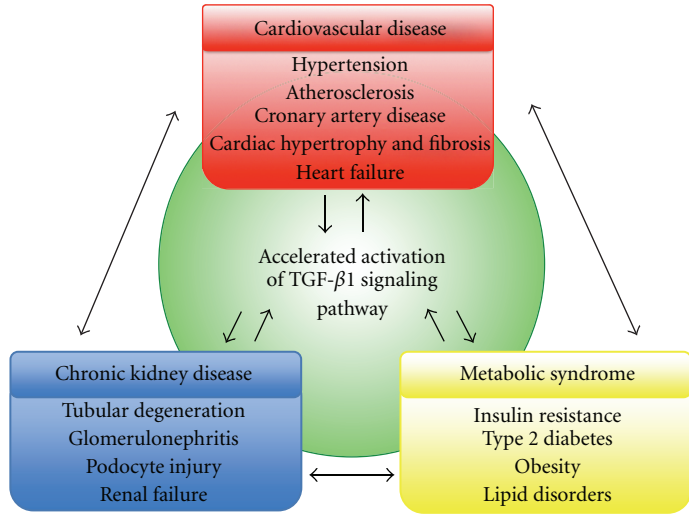

Figure 3: Accelerated activation of the TGF-β1 signaling pathway causes CKD, MetS, and CVD. Since TGF-β1 is a common target molecule and interactive regulator in those pathological conditions, manipulation of the TGF-β1 signaling pathway may be a useful approach for amelioration of mortality and morbidity in individuals with cardiovascular risk factors.

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Review Article

Adiponectin Provides Cardiovascular Protection in Metabolic Syndrome

Yoshihisa Okamoto

Department of Bioregulation, Nippon Medical School, 1-396 Kosugi-machi, Nakahara-ku, Kawasaki, Kanagawa 211-8533, Japan

Correspondence should be addressed to Yoshihisa Okamoto, yokamoto@nms.ac.jp

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Adipose tissue plays a central role in the pathogenesis of metabolic syndrome. Adiponectin (APN) is a bioactive adipocytokine secreted from adipocytes. Low plasma APN levels (hypoadiponectinemia) are observed among obese individuals and in those with related disorders such as diabetes, hypertension, and dyslipidemia. APN ameliorates such disorders. Hypoadiponectinemia is also associated with major cardiovascular diseases including atherosclerosis and cardiac hypertrophy. Accumulating evidence indicates that APN directly interacts with cardiovascular tissue and prevents cardiovascular pathology. Increasing plasma APN or enhancing APN signal transduction may be an ideal strategy to prevent and treat the cardiovascular diseases associated with metabolic syndrome. However, further studies are required to uncover the precise biological actions of APN.

1. Introduction

Obesity is one of the most common disorders in industrialized countries and is fast becoming a worldwide health problem. Metabolic disorders such as hypertension, dyslipidemia, and glucose intolerance frequently, but not incidentally, cluster in an individual with obesity, resulting in atherosclerotic cardiovascular diseases. This pathophysiology, based on excess visceral fat accumulation, has been conceptualized as "syndrome X," "deadly quartet," or "visceral fat syndrome," which are currently recognized as "metabolic syndrome [1]."

Adipose tissue plays a pivotal role in metabolic syndrome. Accumulating evidence indicates that adipose tissue secretes a variety of bioactive adipocytokines such as tumor necrosis factor (TNFα), plasminogen activator inhibitor type 1, retinol binding protein-4, monocyte chemotactic protein-1, and adiponectin (APN). Of these, APN has been cloned and is the most abundant. In the past decade, a large number of clinical and experimental studies have uncovered a variety of biological functions for APN. This paper updates the protective roles of APN in cardiovascular diseases and discusses the association of APN with metabolic syndrome.

2. Clinical Features of Low Plasma APN (Hypoadiponectinemia)

2.1. Obese Subjects and Patients with Coronary Risk Factors. The first clinical study of APN was conducted to observe plasma levels of APN among obese subjects. Although plasma levels of most other adipocytokines are higher in obese individuals, Arita et al. reported that plasma levels of APN are lower in obese individuals and are negatively correlated with body mass index (BMI) [2]. Subsequent studies demonstrated that plasma APN is lower (hypoadiponectinemia) in patients with diabetes, hypertension, and dyslipidemia than BMI-matched controls [3–5], indicating that hypoadiponectinemia is associated with an increased prevalence of coronary risk factors.

2.2. Coronary Artery Diseases. Subsequently, a series of clinical studies reported an association between hypoadiponectinemia and coronary artery diseases (CAD). Plasma APN is significantly lower in patients with CAD than control subjects, and male patients with hypoadiponectinemia have a twofold increase in CAD prevalence, independent of well-

known risk factors [6, 7]. Another prospective study revealed that high plasma APN concentrations are associated with a lower risk for myocardial infarction in men, independent of inflammation and glycemic status [8]. Moreover, Otsuka et al. reported that patients with acute coronary syndrome have lower APN levels than patients with stable CAD and that plasma APN levels are significantly associated with coronary lesion complexity in men with CAD [9]. Several studies of patients undergoing percutaneous coronary intervention (PCI) indicate that hypoadiponectinemia is an independent predictor for in-stent restenosis [10, 11]. Recently, a multiple regression analysis revealed that levels of high molecular weight (HMW) APN correlate negatively with glycated hemoglobin in nondiabetic patients but positively with high-density lipoprotein cholesterol in diabetic patients with CAD [12]. These results indicate that total or HMW hypoadiponectinemia is an independent risk factor for CAD and that APN may directly protect against abnormal vascular remodeling.

2.3. Cardiac Diseases. Obesity is strongly associated with pathological cardiac remodeling, and several studies have investigated the association between plasma APN levels and cardiac diseases. Hypoadiponectinemia is associated with the progression of left ventricular hypertrophy (LVH) with diastolic dysfunction among patients with essential hypertension [13]. Even among healthy subjects, APN concentration is inversely and independently associated with LVH diagnosed by electrocardiography in Japanese men [14]. Another study using echocardiography revealed that circulating total APN and HMW APN are related to left ventricular wall thickness and diastolic function independent of age and metabolic factors [15]. These data suggest that APN may regulate hypertrophic progression of cardiomyocytes.

However, the role of APN in heart failure is controversial. Several studies have shown that plasma APN levels are high in patients with chronic heart failure (CHF) and are associated with CHF severity or mortality despite the protective effect of APN on CHF in mice [16–19]. β-blocker therapy correlates with lower APN levels in patients with CHF, especially in nonobese patients, suggesting that this relationship should be considered when assessing plasma APN among patients with CHF [20]. Further careful studies may be required to clarify the relationship between APN and heart failure.

2.4. Chronic Kidney Disease (CKD). Increased albuminuria among patients with obesity and diabetes is a risk factor for cardiovascular and renal disease, and patients with CKD are at high risk for cardiovascular events. CKD patients show higher plasma APN levels than healthy subjects due to the low renal clearance rate of APN [21]. A prospective study of patients with renal failure demonstrated that patients who experience new cardiovascular events had lower plasma APN levels than event-free patients [22]. Several other studies have also indicated that increases in plasma APN in patients with CKD decrease their risk for cardiovascular disease and increase survival rate [23, 24]. In contrast, a high APN level is associated with mortality, independent of risk markers for CHF severity among patients with CKD [16, 25]. Therefore, the cardioprotective role of APN in CKD remains controversial. A recent report by Komura et al. revealed that the loss of the vascular protective function of APN in the presence of high cystatin C levels in patients with CKD indicates that cystatin C may mask the beneficial effect of APN in patients with CKD despite high plasma APN levels [21].

3. Biological Features of APN

3.1. Atherosclerosis

3.1.1. In Vitro. After initial clinical findings of the association between CAD and hypoadiponectinemia were reported, several experimental studies have been conducted to elucidate the biological effect of APN in atherosclerosis. APN has structural similarity with complimentary C1q or the collagen families [1]. APN specifically binds to collagen types I, III, and V, which are present in vascular intima and detected in the subendothelial space of rat balloon-injured arteries, implying an interaction between APN and vascular pathology [26].

When atherosclerosis commences, low-density lipoprotein (LDL) particles in the blood become oxidized (oxLDL) and induce the expression of adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1, in endothelial cells (ECs). Leukocytes in blood attach to the endothelial layer and induce proinflammatory chemokines that attract leukocytes into the subendothelial space [27]. APN inhibits the expression of these adhesion molecules in TNFα-activated endothelial cells by suppressing inflammatory transcriptional factors and activating nuclear factor (NF)-κB [6, 28]. Additionally, APN inhibits TNFα-inducible interleukin (IL)-8 synthesis in ECs by inactivating NF-κB and activating Akt [29]. An *in vivo* study in mice demonstrated that APN deficiency increases leukocyte-endothelium interactions with impaired endothelial nitric oxide signaling (eNOS) via upregulation of endothelial cell adhesion molecules [30].

The recruited inflammatory cells subsequently enhance the oxidization of LDL and various inflammatory reactions. Monocytes migrate to the subendothelial space in the atherosclerotic lesion and become lipid-laden macrophages. Monocytes change into macrophages in the subendothelial space by taking up oxLDL via scavenger receptors and form cells with accumulated cholesterol esters. APN suppresses scavenger receptor type A (SR-A) in macrophages and the internal cholesterol ester content. However, macrophages play an important role in reverse cholesterol transport (RCT), a protective system against atherosclerosis. APN increases apoA-I-mediated cholesterol efflux from macrophages through an ATP-binding cassette transporter A1-dependent pathway, indicating that APN may prevent atherosclerosis by accelerating RCT [31]. Macrophages sustain and amplify the inflammatory process by releasing several growth factors, cytokines, and chemokines that may further recruit immune cells, including monocyte/

macrophages, T lymphocytes, or vascular smooth muscle cells. Pretreatment with recombinant APN significantly suppresses the production of cytokines/chemokines, such as TNFα, and CXCR3 ligand chemokines, such as IFN-inducible protein of 10 kDa (IP-10), monokine induced by IFN-γ, and IFN-inducible T cells, which is a chemoattractant in lipopolysaccharide-stimulated macrophages [32, 33]. The inflammatory process includes enzymes that can destroy the arterial extracellular matrix such as metalloproteinases (MMPs). APN treatment also induces anti-inflammatory IL-10 and subsequent tissue inhibition of MMP-1 production, suggesting that APN may stabilize atherosclerotic plaques and prevent their rupture [34].

Aortic smooth muscle cells (AoSMCs) are another major player in atherosclerosis, and their pathological migration and proliferation in the intima relates to restenosis of coronary arteries after PCI. APN suppresses growth factor-stimulated AoSMC proliferation and migration by inhibiting the ERK signal [35].

3.1.2. In Vivo. Several experimental studies have demonstrated the effect of APN on atherogenesis. The increment of total APN or globular APN significantly attenuates the progression of atherosclerosis in apoE knockout mice [36, 37]. In atherosclerotic lesions, APN accumulates to form cells in fatty streaks and inhibits the expression of VCAM-1, SR-A, and TNFα [36]. In addition, APN/apoE double knockout mice show advanced atherosclerotic lesions with increased T-lymphocyte accumulation and higher plasma IP-10 levels compared with apoE single knockout mice (Figure 1) [33]. Moreover, APN deficiency worsens neointimal formation after endothelial injury in mice, while APN supplements reverse the abnormal vascular remodeling [38]. These data support the *in vitro* bioactivity of APN as an anti-inflammatory adipocytokine in the atherosclerotic process.

3.2. Cardiac Diseases. Clinical studies have demonstrated that APN is associated with myocardial pathophysiology. APN deficiency causes severe concentric cardiac hypertrophy in mice after pressure overload with increased extracellular signal-regulated kinase, diminishes AMP-activated protein kinase (AMPK) signaling in the myocardium, and increases mortality [39]. Supplementing APN with an adenovirus vector attenuates the pathological cardiac hypertrophy. In an ischemia/reperfusion myocardium injury model, APN knockout mice exhibit increases in myocardial infarct size, apoptosis, and TNFα expression compared with controls. In cultured cardiomyocytes, APN inhibits TNFα production by inducing cyclooxygenase-2-dependent synthesis of prostaglandin E 2 [40]. A similar experiment showed that globular APN protects myocardium from ischemia/reperfusion injury by inhibiting inducible NOS and nicotinamide adenine dinucleotide phosphate oxidase protein expression and resultant oxidative/nitrate stress [41]. Two recent reports demonstrated that APN knockout mice show enhanced cardiac fibrosis following permanent ligation of the left anterior descending artery or angiotensin II infusion. APN accumulates in the injured cardiomyocytes and protects it against fibrosis by reducing apoptosis and AMPK-dependent peroxisome proliferator-activated receptor (PPARα) activation [19, 42]. Despite the potential association between heart failure and high plasma APN shown by several clinical studies, other experimental studies have demonstrated a beneficial, protective effect of APN on myocardium. Elevated plasma levels of APN among patients with heart failure can be a reflection of accompanying renal dysfunction or "APN resistance" including impaired APN signal transduction in myocardium.

3.3. APN and Pulmonary Artery Remodeling. Pulmonary arterial hypertension (PAH) is an idiopathic disease characterized by an increase in the thickness of pulmonary artery wall. APN suppresses platelet-derived growth factor BB-mediated proliferation of pulmonary artery smooth muscle cells harvested from mice [43], indicating that APN may play a role in the prevention of PAH. In a mouse model of chronic airway inflammation, APN deficiency causes pathological pulmonary arterial wall thickness and elevates right ventricular systolic pressure, indicating PAH [44]. APN knockout mice also show thickening of pulmonary arterial wall under chronic hypoxic exposure, and APN overexpression significantly decreases the wall remodeling and right ventricular hypertrophy [45].

3.4. APN and Endothelial Function, Angiogenesis, and Hypertension. APN serves as an angiogenic factor. In a mouse hindlimb ischemia model, APN deficiency impairs revascularization, whereas adenovirus-mediated APN administration recovers angiogenesis [46]. APN stimulates blood vessel growth in the *in vivo* mouse Matrigel plug implantation and rabbit corneal models of angiogenesis by promoting cross-talk between AMP-activated protein kinase and Akt signaling within endothelial cells [47]. APN also dose dependently suppresses endothelial cell apoptosis and proliferation, migration, and premature diabetic senescence of endothelial progenitor cells [48–50].

Hypoadiponectinemia is associated with impaired endothelial dysfunction related to vasorelaxation. APN knockout mice show a significantly reduced endothelium-dependent vasodilation in response to acetylcholine compared with wild-type mice [51]. Another experiment demonstrated that APN knockout mice develop hypertension when maintained on a high-salt diet (8% NaCl) without insulin resistance [52]. Notably, all of these APNs protective effects on endothelial function are mediated through an increase in the production of eNOS [51, 53–55].

3.5. APN Strategies for Cardiovascular Protection in Metabolic Syndrome. Hypoadiponectinemia directly promotes the pathological reactions in cardiovascular system (Figure 2). Therefore, the increment of plasma APN is important to maximize the beneficial effects of APN. A reduction in body weight, especially visceral fat mass, with a combination of diet therapy and exercise is a safe and effective way to increase plasma APN levels.

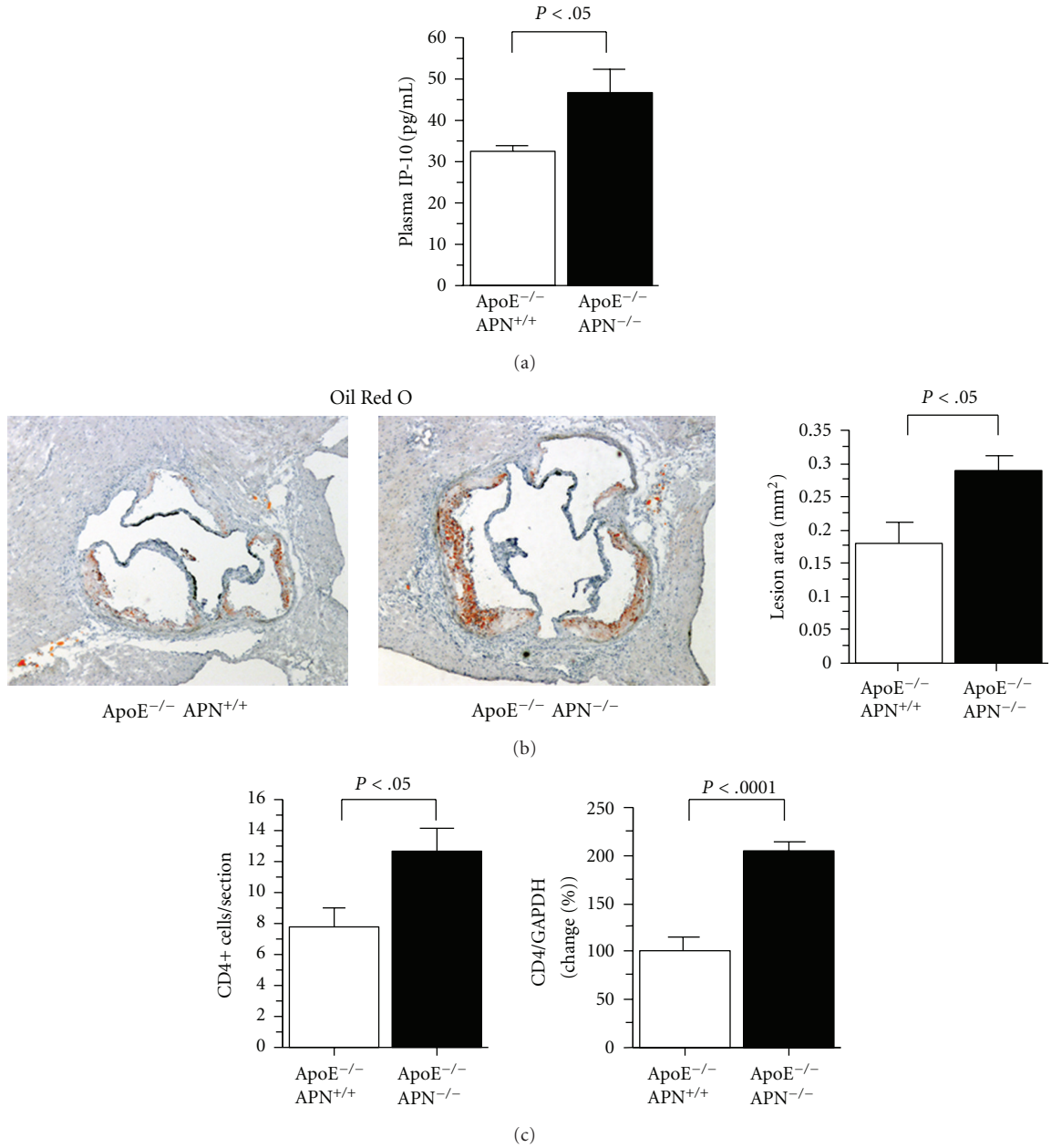

Figure 1: APN deficiency in apoE knockout mice. Compared with apoE single knockout mice, APN/apoE double knockout mice showed (a) higher plasma IP-10 levels, (b) advanced atherosclerosis, and (c) accelerated accumulation of T lymphocytes in atherosclerotic lesions (Adapted from [33]).

Another strategy to prevent cardiovascular disease using APN includes pharmacological changes in plasma APN levels. PPARγ agonists significantly increase plasma APN concentrations in insulin-resistant humans without affecting their body weight and in a mouse model of oxygen-induced retinopathy [56, 57]. Administering PPARα ligands and angiotensin receptor blockers also increases plasma APN levels [53, 58–60]. Furthermore, several statins are also effective for elevating plasma APN [61, 62]. Changes in HMW APN as well as total APN may also be an ideal target. The natriuretic peptides including atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) also increased the production of APN in adipocytes and plasma APN levels among patients with congestive heart failure [63]. Exogenous administration of adiponectin may be a therapeutic strategy as well. In a pig model, a single intracoronary administration of recombinant adiponectin protected myocardial ischemia/reperfusion injury by suppressing inflammation, apoptosis and oxidative stress [64].

APN receptors or candidate APN-receptor-binding proteins have been reported such as AdipoR1-R2, T-cadherin, and calreticulin [65–67]. Very recently, Denzel et al. reported that T-cadherin (glycosyl phosphatidylinositol-anchored cell surface glycoprotein) is critical for adiponectin-mediated cardioprotection by showing no effect of adenovirus-mediated adiponectin supplement in T-cadherin knockout

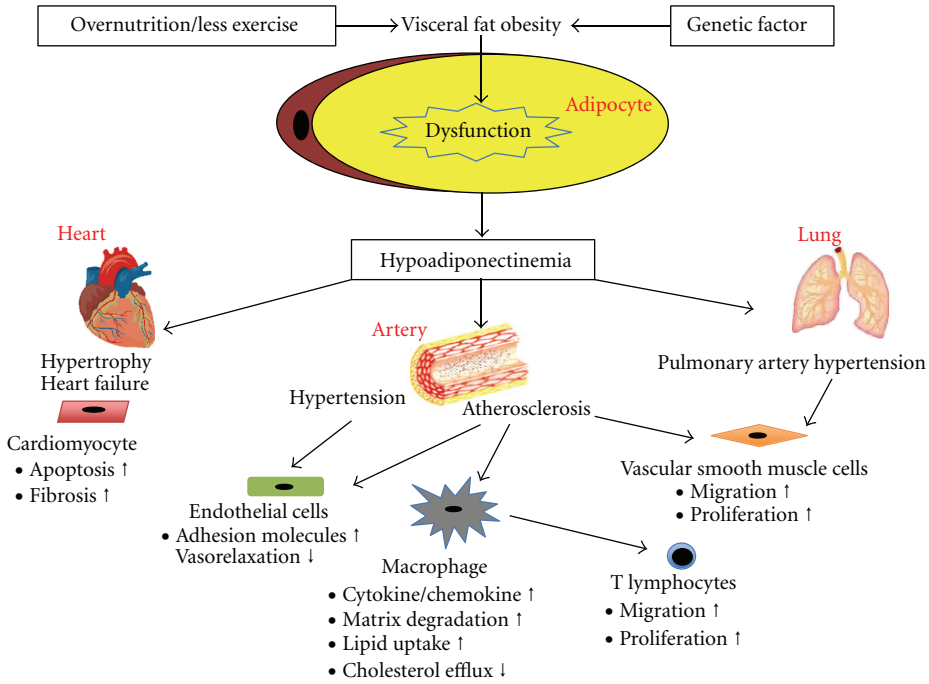

Figure 2: Hypoadiponectinemia directly promotes the pathological reactions in cardiovascular system.

mice [68]. Pharmacologically enhancing the expression of or activating APN receptors may be a good strategy for cardiovascular protection.

4. Conclusion

Adipose tissue stores not only excess body energy but also a variety of adipocytokines that regulate cardiovascular homeostasis directly and indirectly. Accumulating evidence has demonstrated that APN prevents diabetes, dyslipidemia, and hypertension, which are well-known risk factors for cardiovascular disease. Notably, APN directly interacts with cardiac and vascular tissues and mitigates pathological reactions. Generally, anti-inflammation is a key biological action of APN for cardiovascular protection. Further clinical and experimental studies will clarify the precise effects and mechanisms of APN action for future clinical use.

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Review Article

Metabolic Syndrome, Chronic Kidney, and Cardiovascular Diseases: Role of Adipokines

Manfredi Tesauro,[1,2] Maria Paola Canale,[1] Giuseppe Rodia,[1] Nicola Di Daniele,[1] Davide Lauro,[1] Angelo Scuteri,[3] and Carmine Cardillo[4]

[1] *Department of Medicina Interna, Università di Tor Vergata, Viale Oxford 81, 00133 Rome, Italy*
[2] *Laboratory of Molecular Medicine, Department of Internal Medicine, University of Rome Tor Vergata, Viale Oxford 81, 00133 Rome, Italy*
[3] *UOC Geriatria INRCA, POR Roma, 00189 Rome, Italy*
[4] *Università Cattolica del Sacro Cuore, 00168 Rome, Italy*

Correspondence should be addressed to Manfredi Tesauro, mtesauro@tiscali.it

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Obesity is a chronic disease, whose incidence is alarmingly growing. It is associated with metabolic abnormalities and cardiovascular complications. These complications are clustered in the metabolic syndrome (MetS) leading to high cardiovascular morbidity and mortality. Obesity predisposes to diabetic nephropathy, hypertensive nephrosclerosis, and focal and segmental glomerular sclerosis and represents an independent risk factor for the development and progression of chronic kidney disease (CKD). Albuminuria is a major risk factor for cardiovascular diseases (CVDs). Microalbuminuria has been described as early manifestation of MetS-associated kidney damage and diabetic nephropathy. Obesity and MetS affect renal physiology and metabolism through mechanisms which include altered levels of adipokines such as leptin and adiponectin, oxidative stress, and inflammation. Secretory products of adipose tissue also deeply and negatively influence endothelial function. A better understanding of these interactions will help in designing more effective treatments aimed to protect both renal and cardiovascular systems.

1. Introduction

The prevalence of obesity, among both adults and children, has worldwide increased over the past two decades; a phenomenon which is predominantly attributed to the change in dietary habits and lifestyle modifications [1, 2]. It is clearly knows that central obesity is an independent risk factor for CVD and is associated with Mets. Insulin resistance (IR) is a key feature of the Mets and consists in a decreased sensitivity or responsiveness of peripheral tissues to the metabolic action of insulin [3]. IR as well as all components of the Mets are associated with altered functions of endothelium which lead to CVD [4]. Hyperlipemia and coronary artery disease are also consequences of obesity which through a cascade of various reactions lead to kidney dysfunction. Moreover, obesity-induced sleep apnoea activates sympathetic nervous system increasing the tone of the glomerular efferent arterioles and the secretion of renin and angiotensin [5]. In the last decade, obesity has been suggested as a risk factor for chronic kidney disease, decline of renal function, and low-grade albuminuria, but conflicting results have been reported [6–10]. Yet obesity, per se, even in the absence of the above-mentioned medical complications alters renal physiology and metabolism. In this paper, we will examine the role of adipose tissue-secreted factors and the mechanisms of obesity-induced renal and vascular injury leading to chronic kidney and cardiovascular diseases.

2. Epidemiology of Mets, CKD, and CVD

CVD accounts for premature death in about 50% of dialysis patients [11]. As early as 1974, Lindner et al. demonstrated that dialysis patients have a higher prevalence of CVD compared to the general population [12]. The strong association between mild CKD and CVD has been shown, and recently Henry et al. reported that mild to moderate CKD is strongly

associated with an increase in cardiovascular mortality [13, 14].

Ninomiya et al. recently examined the relationship between Mets and CKD [15]. They performed a slope analysis of the association between the glomerular filtration rate (GFR) slope and Mets by using a multiple regression model. GFR decreased significantly faster in patients with 4 or more Mets components compared with those who had 1 or no components. Moreover the mean of the GFR slope was significantly lower in subjects with 3 Mets components in the 60 year and over group. In a large cohort of the NHANES III study with baseline normal renal function, Chen et al. examined the risk of developing CVD following patients for more than 20 years [16].

Interestingly, there also was a 2-fold increase in the risk of microalbuminuria that correlates with the number of components of Mets. Moreover, even low-grade albuminuria below the conventional cut-off point for albuminuria was associated with increased prevalence of CKD [17]. Data from the MESA [18] and LIFE studies [19] clearly demonstrated that albuminuria is one of the strongest risk factors for cardiovascular disease (CVD).

3. Adipose Tissue As an Active Endocrine Organ

There are multiple changes in adipose tissue in obesity including increase in numbers and size of adipocytes, infiltration of adipose by mononuclear cells, rarefaction of blood vessels, increases in adipocyte turnover rate, differentiation, and apoptosis [20]. The capillary diffusion capacity is reduced in patients with obesity and, in contrast with the response of lean subject, the adipose blood flow does not increase in response to food in obese patients [21]. Since the discovery of leptin as an adipocyte-derived satiety factor, adipose tissue is increasingly being considered as an endocrine organ. Adipose tissue secretes into the circulation a number of proteins and nonprotein factors that regulate glucose and lipid metabolism throughout the body. Among these bioactive adipokines, only adiponectin (ADN), leptin, adipsin, and visfatin are almost synthesized exclusively by adipocytes. In obese patients, the production of ADN is reduced [22–24]. ADN is a 30 kDa protein present as oligomers in the blood stream and has insulin-sensitizing, antiatherogenicity, and anti-inflammatory properties. Reduction of ADN levels is a consistent feature among obese patients who have evidence of IR and often develop diabetes mellitus. ADN plasma levels also negatively correlate with coronary artery disease and dyslipidemia in both mice and humans [25–28]. Overexpression or AND administration reduces oxidative stress, inflammation, IR, and vascular damage. Becker et al. found that low ADN levels in mild to moderate kidney disease were correlated with cardiovascular events [29]. The potential link between ADN levels and low-grade albuminuria was first observed in a clinical study where essential hypertensive patients had a negative correlation between ADN levels and low-grade albuminuria [30]. Later on, similar results were also obtained in obese patients from different ethnic groups [31, 32]. Despite some controversial observations [33, 34], clinical data strongly suggest the potential causative role of ADN in the development of albuminuria in obese patients. An important contribution in understanding the potential link between obesity and kidney damage comes from the work by Sharma [32]. In a recent study, he showed that ADN knockout mice had baseline increased albuminuria (twice normal values) with podocyte foot process effacement. Morphologically, the endothelium appeared to be normal under electron microscopy. Podocytes expressed the AdipoR1 receptor and ADN regulated an isoform of NAPDH oxidase through the AMPK pathway [32]. When treating ADN knockout mice with ADN, proteinuria was reversed and foot processes were normalized. In mice, Sharma et al. [32] also demonstrated that ADN deficiency was a susceptibility factor for early diabetic kidney disease. Consequently, the podocyte may play an important role in determining albuminuria associated with obesity [35]. The role of endothelial dysfunction may be important for albuminuria as well. At the present time, no data are available to document the presence of glomerular endothelial dysfunction in the presence of microalbuminuria. On the other hand, it has been established that podocyte dysfunction contributes to endothelial dysfunction [36, 37].

The increase of visceral fat promotes synthesis of proinflammatory adipokines which cause tissue-specific increase in reactive oxygen species derived from NADPH oxidase. Adipose tissue oxidative stress results in the development of systemic oxidative stress and inflammation, which further lead to the development of metabolic abnormalities. Leptin, a 167 amino acid polypeptide, is expressed mainly by adipocytes; leptin concentration positively correlates with adiposity [38], and hyperleptinemia is an independent risk factor for coronary artery disease [39] and a strong predictor of acute myocardial infarction [40]. Additionally, leptin has been implicated in many atherogenic processes, including platelet aggregation and thrombosis [41–43]; production of inflammatory cytokines, for example, TNF-α, IL-6, and IL-12 [44]; calcification of vascular smooth muscle cells [45]. Interestingly, recent reports have demonstrated that leptin possesses cytokine-like properties and that elevated plasma leptin levels occur concomitantly with elevated IL-6 and C-reactive protein in human obesity, the Mets, and noninsulin-dependent diabetes mellitus [46–48]. Animal testing showed that leptin induces proliferation of glomerular endothelial cells, enhances glomerular TGF-β1 beta expression, and increases collagen type IV mRNA production [49]. These factors result in focal glomerulosclerosis, glomerular and mesangial glucose uptake, and proteinuria [49]. Additionally, leptin is also associated with adrenergic activation, increased blood pressure and tachicardia, contributing to obesity-related hypertension and kidney damage [50–53].

In recent years, a great deal of attention has been focused on the orexigenic peptide ghrelin which is predominantly secreted by the stomach [54, 55]. Patients with obesity-related Mets have reduced ghrelin circulating levels. Ghrelin has important vascular actions; it acutely stimulates production of NO in vascular endothelium through a PI3-kinase-dependent mechanism involving phosphorylation of Akt which directly phosphorylates and activates eNOS leading to increased production of NO [56]. This signaling pathway

is similar to that used by insulin to promote increased production of NO in vascular endothelium. Moreover, we have demonstrated that intra-arterial ghrelin administration acutely improves endothelial dysfunction by increasing nitric oxide (NO) and decreases ET-1-dependent vasoconstriction, thereby restoring the physiological balance between these opposing vascular mediators in patients with central obesity [57, 58].

Thus, therapeutic interventions including weight loss, exercise, or pharmacological therapies that increase plasma ghrelin levels could to contribute to this strategies by mimicking and/or augmenting beneficial effects of increased insulin sensitivity.

Dysregulation of adipokines synthesis and release into the blood stream occur in obese patients and play a critical role in promoting IR [59–61]; diabetes and dyslipidemia are characterized by low adiponectin levels and elevated levels of inflammatory adipokines such as TNF-alpha (TNF-α) [62].

Adipose tissue also expresses a local renin-angiotensin system (RAS). Adipocytes express RAS receptors and synthesize and secrete angiotensinogen and angiotensin peptides [63]. RAS is a hormonal cascade that governs vascular tone, fluid-electrolyte balance, and blood pressure [64].

4. Adipokines and Cardiac Function

Many studies have shown effects on the heart of various adipokines. TNF-α has been considered to be a critical factor in the pathogenesis of cardiac contractile dysfunction and heart failure. Transgenic mice with overexpression of TNF-α develop severe dilated cardiomyopathy [11], and TNF-α directly depresses cardiomyocyte contractility and induces apoptosis of cardiomyocytes *in vitro* [65]. TNF-α has negative inotropic effects on cardiomyocytes in vitro, and leads to heart failure in mice [66–72]. In addition, elevated serum TNF-α levels have been associated with the progression of heart failure in patients [66].

Experimental findings have shown that adiponectin has several beneficial effects in the cardiovascular system. Adiponectin plays an essential role in the maintenance of heart architecture, as the cytokine may attenuate angiotensin II-induced cardiac hypertrophy [73] and attenuate cardiomyocyte contractile dysfunction in *db/db* diabetic obese mice via a mechanism possibly related to c-Jun and IRS-1 phosphorylation [74].

Moreover, adiponectin represses atherosclerotic lesions in a mouse model of atherosclerosis, and adiponectin-deficient mice exhibit an accelerated vascular remodeling response to injury [75]. In addition, adiponectin stimulates nitric oxide production in endothelial cells through AMPK-dependent and AMPK-independent phosphorylation of endothelial nitric oxide synthase (eNOS) [76, 77] and hypoadiponectinemia is associated with the progression of left ventricular hypertrophy (LVH), which is accompanied by diastolic dysfunction [78].

An association between serum leptin concentrations and various cardiovascular risks, including myocardial infarction [79], coronary heart disease [40], stroke [39], chronic heart failure [80], and left cardiac hypertrophy [81], has been observed.

Several works suggested that leptin could be an important link between obesity and development of cardiovascular disease [82]. This might be mediated through various effects of leptin including effect on blood pressure [83], inflammatory vascular response [42, 84], and platelet aggregation [85, 86]. High levels of leptin are associated with lower arterial distensibility [87] and have also been shown by several investigators to promote angiogenesis, enhance the calcification of vascular cells, and potentiate the prothrombotic platelet aggregation [86, 88] moreover, obese individuals possess higher plasma levels of prothrombotic factors such as fibrinogen, von Willebrand factor, factor VII, and plasminogen activator inhibitor-1 (PAI-1), which lead to a higher risk of thrombosis and atherosclerosis. The levels of pro-thrombotic factors such as fibrinogen, von Willebrand factor, factor VII, and plasminogen activator inhibitor-1 (PAI-1) are shown to be directly correlated with leptin levels [89].

Ghrelin is not produced by the adipose tissue; however, the functions of this gastric peptide are closely related to those of adipokine regarding metabolic and cardiovascular function.

Ghrelin has been demonstrated to have cardiovascular effects, both in animals and humans. Ghrelin protects the heart from ischemia in rats, and chronic administration of the peptide improves cardiac contractility in animals with chronic heart failure [90]. Furthermore, in the heart of rats subjected to ischemia followed by reperfusion, ghrelin reduces the infarct size [91], increases cardiac output, diastolic thickness of the noninfarcted wall, and attenuates the development of cardiac cachexia in rats with heart failure [92]. In humans, ghrelin administration reduces cardiac afterload and increases cardiac output and systemic vascular resistance, without changing heart rate [93]. Moreover, ghrelin administration increases exercise capacity and improves left ventricular function and muscle wasting in patients with chronic heart failure [94–96].

5. Adipose Tissue Inflammation

Recent observations from Kamei et al. [97] on transgenic mice have led to the concept that obesity contributes to IR and diabetes promoting a condition of chronic, low-grade inflammation of the adipose tissue because of additional infiltration and accumulation of inflammatory macrophages [98–102]. The macrophage content of adipose tissue is higher in visceral obesity compared to subcutaneous obesity, leading to the concept that visceral fat more than subcutaneous one plays a central role in the development of IR [103]. Macrophages appear to be recruited from the circulation, and adipocyte-derived factors might be involved in this process.

Monocyte chemoattractant protein-1 (MCP-1) is produced predominantly by macrophages and endothelial cells and is considered one of the most important potent chemotactic factors for monocytes. The increase of MCP-1 expression in adipose tissue contributes to the macrophage infiltration and IR associated with obesity.

The general low-grade chronic inflammatory state, closely related to obesity, may affect insulin action by suppressing insulin receptor signalling via serine phosphorylation of insulin receptor substrates at metabolically relevant sites [104]. Because favourable metabolic and hemodynamic actions of insulin share common intracellular transduction pathways [105], inflammation may simultaneously contribute to both IR and vascular dysfunction, two cardinal and interrelated features of the Mets. Moreover, macrophages become activated and secrete inflammatory cytokines such as TNF-alpha and IL.6 which in turn decrease insulin action on adipocytes, determine hypoadiponectin, and increase leptin production [98, 106]. TNF-α indeed plays a central role in the pathophysiology of IR and vascular damage in patients with obesity; the deletion of the TNF-α gene or the TNF receptors has proven effective to improve insulin action in both genetic and dietary models of rodent obesity. Overexpression of TNF-α has previously been reported in obese adipose tissue [62, 107], as well as in the skeletal muscle of insulin-resistant animals and humans and exposure to TNF-α acutely inhibits insulin-stimulated glucose uptake. Additionally, TNF-α-induced vasculopathy is characterized by increased vascular reactive oxygen species.

We have previously demonstrated that TNF-α neutralization with the monoclonal antibody infliximab ameliorates insulin-stimulated vascular reactivity in Mets [108]. Our findings suggest that increased oxidative stress is involved in mediating the effects of TNF-α on insulin-stimulated vasodilator capacity. The beneficial action on vascular reactivity demonstrated in our study proposes a novel mechanism by which TNF-α activation might be involved, viaincreased oxidative stress, in the pathophysiology of vascular dysfunction in patients with obesity-related MetS.

The degree to which any particular adipose-derived inflammatory mediator enters the blood stream and plays a role in metabolic and cardiovascular disorders has not yet been established [109].

An emerging area of interest is the role of perivascular adipose tissue (PVAT) in regulating local vascular tone [110]. The presence of adipose tissue around the heart and the great vessels has been recently recognized as an independent cardiovascular risk factor. The perivascular adipose tissue (PVAT) is the potential source of the mediators leading to obesity-related vascular damage.

Because of the absence of the fascial boundaries, epicardial adipose tissue may locally interact and affect the coronary arteries and myocardium through paracrine actions of pro- and anti-inflammatory adipokines and other bioactive molecules [111].

Thus, the epicardial and perivascular adipose tissue could mechanically and functionally modulate the function of the myocardium and vasculature thereby possibly playing a role in obesity-related atherosclerosis [112].

Several studies demonstrated that epicardial fat produces a number of bioactive molecules as well as TNF-alpha, IL-6, IL-1, resistin, free fatty acid, and adiponectin that could affect cardiovascular morphology and function [113–117].

Moreover, recent studies have shown that perivascular adipocytes physiologically exert anticontractile effects which are both NO dependent and independent.

In particular, adipokines released from fat depots have local rather than systemic vasoregulatory effects, a mechanism defined as vasocrine signaling. In healthy subjects, PVAT seems to mediate an anticontractile effect in medium- and small-sized arteries [118, 119].

Adiponectin is the main candidate for this role based on the finding that the anticontractile properties of the fat are abolished entirely with an adiponectin type 1 receptor blocking fragment [119].

Importantly, this effect of PVAT is lost in patients with obesity-related metabolic syndrome, and conformational changes in perivascular fat have been shown to associate with lots of its anticontractile properties likely due to inflammatory, vasoconstrictor, and oxidative mechanisms. Recent studies has demonstrated a positive correlation between epicardial adipose tissues volume and coronary atherosclerosis using multislice computed tomography [120].

Moreover, Hosogai and colleagues demonstrated that PVAT of obese mice is hypoxic and that hypoxia stimulated an inflammatory phenotype and a loss of the anticontractile properties. This effect is mediated by endoplasmic reticulum stress and posttranscriptional regulation. Because hypoxia is a prominent feature of adipose tissue in obese individuals and is thought to cause adipocyte dysfunction and tissue inflammation [121], these findings further support a prominent role for PVAT-derived inflammatory cytokines in adversely modulating vascular function.

Of note, the obese phenotype could be reproduced by adding the inflammatory cytokines IL-6 or TNF-α to the PVAT around healthy vessels, which in turn could be blocked by cytokine antagonists.

In conclusion, these studies suggest that PVAT in obese individuals predominately exerts influence that contributes to vascular disease and may act both locally (paracrine) and downstream (vasocrine), through outside-to-inside signaling.

6. Renal Effects of Obesity

The most common types of morphological renal lesions observed in renal biopsies of obese patients are mainly focal and segmental glomerulosclerosis and glomerulomegaly [122]. The podocyte foot process effacement described in the ADP knockoutmice probably represents an earlier stage of kidney involvement. Early changes occurring in the presence of only mild metabolic abnormalities and mild hypertension in the absence of diabetes mellitus include increased glomerular cell proliferation, increased mesangial matrix, thicker basement membrane, and increased expression of glomerular transforming growth factor-beta [50].

In a recent study, Lamacchia and colleagues demonstrated that para- and perirenal fat thickness is an independent predictor of kidney dysfunction and increased renal resistance in patients with type 2 diabetes [123].

The mechanisms of obesity-induced renal injury are not fully understood and are likely to involve a combination of

hemodynamic and metabolic abnormalities. Many factors contribute to the increase in both glomerular filtration rate (GFR) and rise in renal plasma flow (RPF) observed in obese patients. The increased protein intake determines a rise in GFR [124]. Moreover, IR causes increase in the efferent arteriolar pressure because the reduction of noradrenaline-induced efferent arteriolar constriction by insulin action is blunted. Subsequently, the transcapillary pressure gradient increases resulting in hyperfiltration [124]. Augmented filtration determines microalbuminuria. Moreover, insulin stimulates the synthesis of IGF-1 and IGF-2, both promoting glomerular hypertrophy [122, 124]. The rapid and parallel increases in the prevalence of end-stage renal disease and obesity in the past two decades suggest that obesity may be a major risk for kidney disease through other mechanisms than diabetes and hypertension (see Figure 1) [125]. Additionally, obesity increases the risk of development of renal diseases from different aetiologies, such as primary immunoglobulin A nephritis or unilateral nephrectomy [126, 127]. Whether weight loss, in the long term, can slow down the progression of renal damage or reverse it is unknown at the present time. In the short term, weight loss usually leads to reduction of the proteinuria. Antiproteinuric effects of weight loss are also observed in obese patients with nephropathies due to other causes [126].

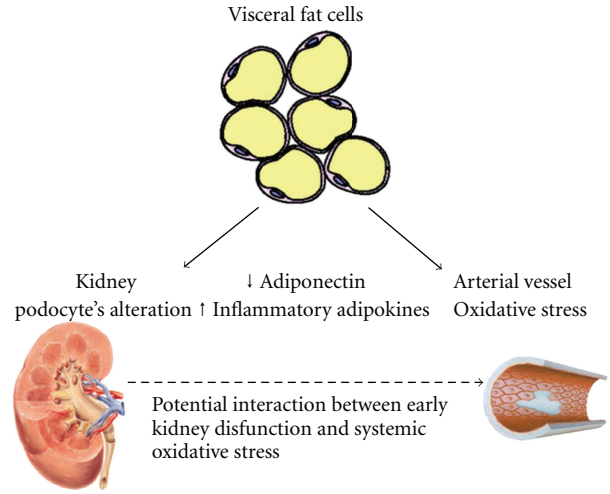

Figure 1: Possible dynamic interactions between obesity, CKD, and CVD. The increase of visceral mass determines both decreased production of ADN and increased production of inflammatory adipokines which result in increased insulin resistance.

7. Mechanisms of Vascular Damage in Obesity

Abdominal obesity is well recognized as a major risk factor for CVD, but the underlying mechanisms of vascular damage in obesity remain poorly understood.

One of the most important mechanisms by which obesity leads to the development of vascular diseases is the development of IR in skeletal muscle, adipose tissue, and liver. The adipose tissue excess, particularly visceral fat, is associated with a continuous production of mediators that impair insulin action in skeletal muscle, like free fatty acids (FFAs), and is associated with a decreased production of adiponectin, a mediator known to improve insulin sensitivity [128]. Plasminogen activator inhibitor-1 (PAI-1) is typically increased in the obesity/IR state and plays an important role in the genesis of vascular abnormalities [129]. In addition, obesity and IR are frequently associated with altered coagulation/fibrinolysis. In combination, all of the above abnormalities create a state of constant and progressive damage to the vascular wall, manifested by a low-grade progressive inflammatory process [130]. Endothelial dysfunction is defined as paradoxical or inadequate endothelial-mediated vasodilation and is characterized by loss of balance between vasoconstrictors and vasodilators, increased oxidative stress, and elevated expression of proinflammatory and prothrombotic factors.

Endothelial dysfunction is a fundamental initial step in the development and progression of atherosclerosis and has been considered an important event in the development of microvascular complications [130].

Adipose tissue can produce a significant amount of compounds able to affect endothelial function; the ability of adipokines to directly affect vascular homeostasis may represent an important mechanistic basis of vascular disease in patients with obesity. Central obesity is associated with increased levels of free fatty acid (FFA) that induces endothelial dysfunction by effect of insulin-mediated vasodilatation in humans and by impairment of nitric oxide-independent mechanism mediated by reduction of potassium-mediated vasodilatation [131]. The increased levels of FFA from the more lipolytically active intra-abdominal adipocytes decreased insulin sensitivity through the intracellular insulin signaling [132].

Moreover, FFAs are capable of utilizing the innate immune receptor TLR4 to induce proinflammatory cytokine expression in macrophages and adipocytes. In particular, the TLR4 signaling appears to be required for a component of insulin resistance induced by FFAs in adipocytes and in vivo after lipid infusion and high-fat diets [133].

Moreover, TNF alpha overproduction in obesity mediates the increased endothelial permeability by activating NADPH oxidase [129] and also inhibits transcriptional, as well as posttranscriptional, eNOS gene expression an effect that can account for the endothelial dysfunction.

In obese patients, an increase in reactive oxygen species has been demonstrated and could be the link between the low-grade inflammation, platelet activation, and nitric oxide destruction.

In IR and obesity, the dyslipidaemia is characterized by a different composition and distribution of LDL cholesterol, resulting in an increased concentration of the more atherogenic small dense LDL. Small dense LDL particles can move through endothelial fenestrations, entering the subendothelial space where inflammation and transformation into plaque can occur [134]. Moreover, the ox-LDL is mostly taken up by macrophage scavenger receptors, rather than the normal LDL receptor pathway, thus inducing atherosclerosis.

8. Vascular Dysfunction in Insulin Resistance and Metabolic Syndrome

Hyperinsulinemia and IR are established metabolic features of obesity. Vasodilator actions of insulin to stimulate production of nitric oxide (NO) from vascular endothelium lead to increased blood flow that further enhances glucose uptake in skeletal muscle [135, 136]. Insulin binding to its cognate receptor activates two major branches of insulin signal transduction network. Metabolic actions of insulin tend to be mediated by phosphatidylinositol 3-kinase- (PI3K-) dependent signaling pathways, whereas the nonmetabolic insulin signalling pathways (MAPK-dependent insulin signaling pathways) typically regulate growth, mitogenesis, and differentiation [137, 138] and also regulate the secretion of the vasoconstrictor endothelin-1 (ET-1) from endothelium.

The PI3K-dependent metabolic actions of insulin directly promote glucose uptake in skeletal muscle by stimulating translocation of insulin responsive glucose transporters (GLUT4). At the same time, PI3K-dependent vascular actions of insulin to increase blood flow and capillary recruitment substantially contribute to promoting glucose disposal under healthy conditions [3].

ET-1, a potent vasoconstrictor synthesized and secreted by vascular endothelium, plays an important role in endothelial dysfunction.

In humans, insulin-stimulated ET-1 production may influence skeletal muscle glucose disposal, and ET-1 infusion induces peripheral insulin resistance. NO, however, is known to inhibit ET-1 production and action [139]. Consequently, under healthy conditions, the effects of insulin-stimulated ET-1 on the metabolic actions of insulin are likely to be offset by insulin-stimulated production of NO [140].

IR is characterized by selective impairment in PI3K-dependent signalling in both metabolic and vascular insulin target tissues, and the diminished sensitivity to the actions of insulin in vascular endothelium contributes importantly to the clinical phenotype of this condition [3].

In insulin-resistant states, the insulin-mediated ET-1 secretion is augmented, and blockade of ET-1 receptors significantly improves insulin sensitivity and peripheral glucose uptake in the context of IR [141, 142].

Another important mechanism of insulin action is the increased microvascular perfusion of skeletal muscle leading to increased muscle blood flow and glucose uptake.

While the majority of previous studies have focused on the endothelium-dependent effect of insulin, we have suggested that the blunted vasodilator responsiveness to the exogenous NO seen in obese patients during hyperinsulinemia could be related to the facilitatory action physiologically exerted by insulin on vasorelaxation within VSMCs. Indeed, insulin enhances vasodilator responsiveness by reducing Ca^{2+} concentration in VSMCs, via activation of the Na^+, K^+-ATPase pump [143]. Similarly, in human VSMCs, insulin inactivates the small GTPase RhoA and its target, Rho-kinase, thereby leading to decreased phosphorylation of myosin light chain and subsequent vasodilation [144].

In a recent study, we have demonstrated that insulin exerts a facilitatory effect on vascular reactivity to a variety of vasoactive molecules (acetylcholine, sodium nitroprusside, and verapamil) by the increased delivery of substrates in skeletal muscle of healthy subjects, but in contrast with the results obtained in healthy subjects, the responsiveness of these vasodilators was not enhanced during hyperinsulinemia in the group of patients with the metabolic syndrome due to increased oxidative stress [145].

9. Conclusion

The rapid growth of obesity is contributing to an "epidemic" in Mets and diabetes and related renal and cardiovascular complications. Adipose tissue is an endocrine organ which produces a variety of "adipokines." Clinical management should be aimed to reduce risk factors by encouraging lifestyle modifications such as diet, aerobic exercise, and healthy eating as well as pharmacologic intervention to improve insulin sensitivity, dyslipidemia, and blood pressure control and protect the kidney from further injury. At the present time, there are few drugs available to produce significant long-term weight loss. Weight loss of about 10% can improve insulin sensitivity and lower blood pressure, reduce serum lipid levels, decrease plasma inflammatory cytokines, and increase circulating AND [97, 146]. Finally, an emerging area of interest is the potential role of the podocyte-specific drugs. Further research on adipokines action on renal cells is needed and will lead to novel treatment strategies aimed to fight the increased incidence of obesity-related chronic kidney and cardiovascular diseases.

Conflict of Interest

The authors declare no conflict of interest.

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Clinical Study

Height Constitutes an Important Predictor of Mortality in End-Stage Renal Disease

Tsuneo Takenaka, Takahiko Sato, Hitoshi Hoshi, Nobutaka Kato, Keita Sueyoshi, Masahiro Tsuda, Yusuke Watanabe, Hiroshi Takane, Yoichi Ohno, and Hiromichi Suzuki

Department of Medicine, Saitama Medical College, 38 Moro-hongo, Moroyama, Iruma, Saitama 395-0495, Japan

Correspondence should be addressed to Tsuneo Takenaka, takenaka@saitama-med.ac.jp

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Aim. Height is an important determinant of augmentation index (AI) that anticipates cardiovascular prognosis. There is a scanty of the data whether short height predicts survival in patients with end-stage renal diseases, a high risk population. *Methods*. Fifty two hypertensive patients with type 2 diabetic nephropathy receiving hemodialysis and 52 patients with nondiabetic nephropathy were enrolled. In addition to AI estimated with radial artery tonometry, classical cardiovascular risk factors were considered. Patients were followed for 2 years to assess cardiovascular prognosis. *Results*. Cox hazards regression revealed that both smoking and shortness in height independently contributed to total mortality and indicated that smoking as well as the presence of left ventricular hypertrophy predicted cardiovascular mortality. Our findings implicated that high AI, the presence of diabetes, and low high-density lipoprotein cholesterol were significant contributors to cardiovascular events. *Conclusions*. Our findings provide new evidence that shortness in height independently contributes to total mortality in hemodialysis patients.

1. Introduction

Recent technical advance enables noninvasive screening of arterial stiffness, and an increase in arterial stiffness is a character of atherosclerosis [1–9]. Pulse wave velocity (PWV) and augmentation index (AI) are good examples. Both PWV and AI predict cardiovascular survival in patients with hypertension or renal insufficiency [4–9]. Recently, ASCOT-CAFE study has clearly demonstrated that an elevated augmentation index (AI) is an important cardiovascular risk in hypertensive patients [9]. Although PWV could predict cardiovascular mortality in diabetes [5], there is scanty of data on AI. Furthermore, available data in diabetes failed to provide a consistent pattern. On the one hand, Lacy et al. demonstrated that diabetes showed an elevated PWV but a normal AI [10]. On the other hand, Westerbacka et al. reported that AI was associated with carotid intima-media thickness in diabetes [11]. AI is a dynamic index of arterial stiffness, reflecting not only elastic but also muscular artery stiffness [12, 13]. The stiffness of muscular artery is modulated by vasoactive agents including nitric oxide, angiotensin II, and autonomic nerve activity. Collectively, variations in these factors may elicit changes in AI. Indeed, we have demonstrated that AI in diabetes shows abnormal regulations following acute postural changes [14].

There is a debate on the relationship between height and cardiovascular disease. A recent meta-analysis demonstrated that short statue is associated with coronary heart disease [15]. In contrast, studies from South Korea indicated that height inversely related to mortality in both men and women without an association with coronary heart disease [16, 17]. Lee et al. reported an opposing relation of height with death from cardiovascular diseases and cancers among people in Asia-Pacific area [18]. Various mechanisms underlying this relation are proposed such as poor nutrition during childhood, increased LDL cholesterol, genetic liability, high pulse pressure, and systolic blood pressure in adults with short height [15–21]. Indeed, systolic blood pressure is suited to assess cardiovascular risk in Japanese [22]. Of interest, height is inversely related to AI, and high AI is

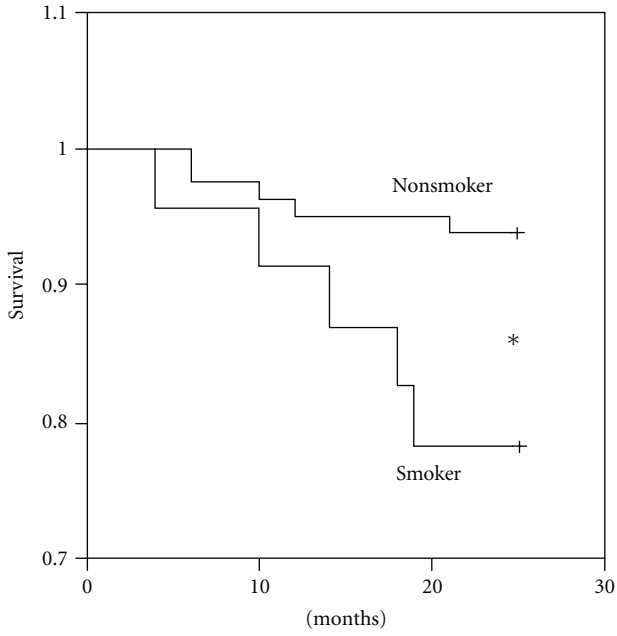

Figure 1: Kaplan-Meier analysis on whole hemodialysis patients showed that nonsmokers survived better than smokers. Log-rank test denoted that there was a significant difference in mortality between smoker and nonsmoker.

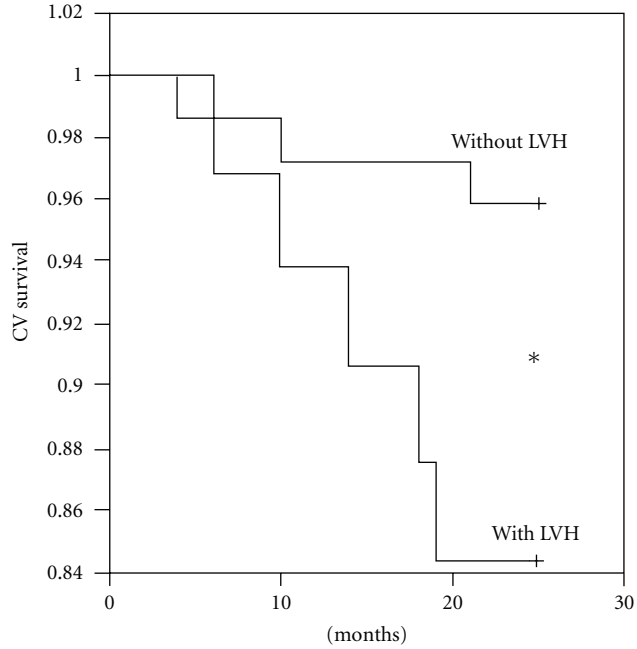

Figure 2: Kaplan-Meier analysis on whole hemodialysis patients showed that those without left ventricular hypertrophy (LVH) suffered cardiovascular death less than those with LVH. Log-rank test denoted that there was a significant difference in cardiovascular mortality between patients with LVH and those without.

a cardiovascular risk [9]. Cardiovascular diseases are major causes of death in hemodialysis patients [23]. The present study was performed to assess whether short height predicts mortality in renal patients.

Diabetes as well as hypertension is well-known cardiovascular risk factors. Recent data indicated that cardiovascular events occurred three times more frequently in patients with chronic kidney diseases [24]. Diabetes is now a primary disease, which requires renal replacement therapy [5, 25]. Moreover, although dialysis therapy saves their lives, it may also burden additional cardiovascular risks to them. In the present study, the relationship between cardiovascular risk factors including AI and cardiovascular prognosis was examined in hypertensive patients with diabetic and nondiabetic nephropathy receiving regular dialysis therapy. Our data provide the evidence that left ventricular hypertrophy (LVH) predicts cardiovascular events in diabetic patients undergoing hemodialysis. In addition, the present results indicate that nondiabetic patients with higher AI suffered from more cardiovascular events. Our findings implicate that smoking and LVH predict cardiovascular death, and further suggest that in addition to smoking, short statue is a risk for mortality in hemodialysis patients.

2. Methods

Patients who visited our offices to perform chronic hemodialysis were listed for the study when they accept the informed consent. The following patients were not enrolled: patients with myocardial infarction or stroke within 6 months, patients with unstable angina pectoris, patients with persistent arrhythmia, patients with heart failure or left ventricular ejection fraction of 40% or less, patients with peripheral artery disease (stage 3-4), and patients with overt secondary hyperparathyroidism [26]. Patient entry was started in 2003, and 52 type II diabetic patients with nephropathy entered the study. Age- and sex-matched 52 nondiabetic hemodialysis patients were enrolled as controls to perform case-control study. All 104 patients received hemodialysis therapy for 4 hours, 3 days a week. Dry weight was carefully determined for an individual patient to achieve edema-free state in references to blood pressure and cardiac thorax ratio. In selected patients, end-diastolic left ventricular diameter, inferior vena cava diameter, and plasma level of atrial natriuretic peptide were also assessed.

Radial AI was assessed using automated tonometry (HEM9010-AI, Omron Healthcare). This device was designed to automatically record pulse waves using series of tonometric sensors faced on radial artery. AI was determined by dividing reflection pressure by ejection pressure with variations of 4.4% [27]. This device also measures blood pressure using an oscillometric method. Two measurements were performed with the patient in the sitting position for 5 and 10 minutes, respectively, and the average of the 2 values was taken for the purpose efficacy analysis. This device was able to estimate central blood pressure expressed as SBP2 [28]. Electrocardiogram and blood samples were taken from all patients at the time of entry. The following criteria were used to diagnose LVH; Sokolow-Lyon voltage

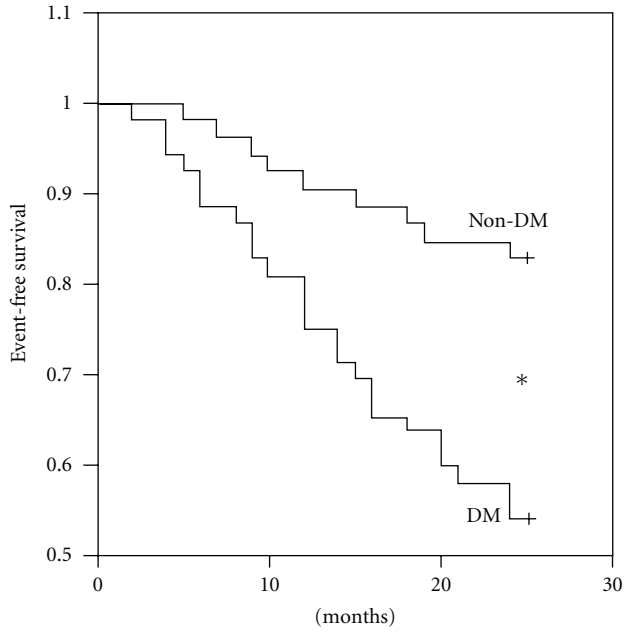

Figure 3: Kaplan-Meier analysis on whole hemodialysis patients showed that those without diabetes experienced cardiovascular events less frequently than those with diabetes. Log-rank test depicted that there was a significant difference in cardiovascular events between patients with diabetes and those without.

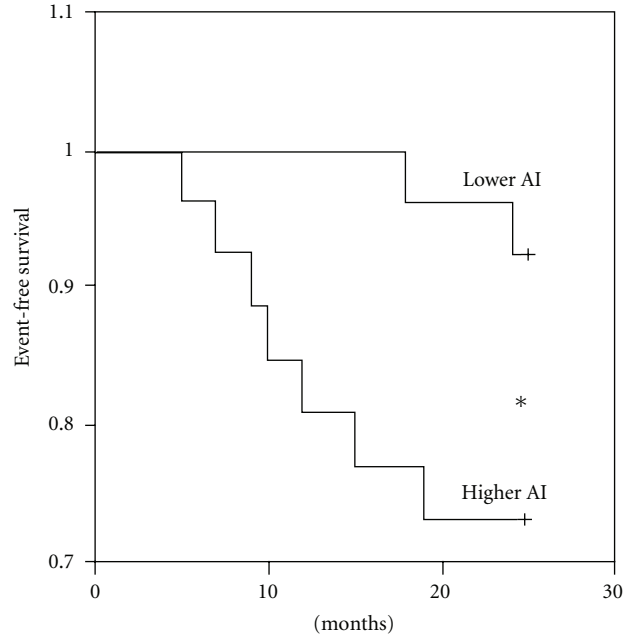

Figure 4: Kaplan-Meier analysis on nondiabetic hemodialysis patients showed that those with higher AI failed to live cardiovascular event-free lives similar to those with the lower AI. Log-rank test denoted that there was a significant difference in cardiovascular events between two subgroups.

amplitude of (SV1 + RV5 or RV6) > 3.5 mV, a Cornell voltage of (SV3 + RaVL) > 2.8 mV, or a Cornell product of [(SV3 + RaVL) × QRS duration] > 244 mV. Left ventricular strain was defined as a down-sloping ST-segment depression > 0.1 mV with T-wave flattening or inversion in leads V4 to V5 [29]. Blood sample was drawn after overnight fast for accuracy.

The patients were followed for 2 years or until cardiovascular events occurred. Cardiovascular events included coronary artery disease, stroke, and peripheral artery disease. Heart failure was excluded because pulmonary edema only due to fluid retention is common in this patient population [30]. Thus, the following patients were considered to possess cardiovascular events: patients with acute myocardial infarction, those with angina pectoris being treated by either bypass surgery or balloon angioplasty, patients with brain infarction or bleeding, and patients with peripheral artery disease who received limb amputation, balloon angioplasty, or bypass surgery.

Cox hazard analysis with Wald modification was performed to assess cardiovascular risk. In addition to AI, the presence or absence of LVH and diabetes, classical Flamingham risk factors including age, sex, height, weight, mean blood pressure (MBP), pulse rate (PR), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), and current smoking were used as independent variables. Nonclassical risk factors such as serum albumin, hemoglobin (Hb), hemodialysis duration, and KT/V were also considered as independent variables. AI showed significant relationship with SBP and SBP2 ($P < .01$). Since we used AI, an index of arterial stiffness, as an independent variable, MBP was selected as an independent variable of blood pressure component to decrease multi-co-linearity [31]. Kaplan-Meier analysis was performed to assess a contributor to cardiovascular events. Cox hazard model was also applied to consider cardiovascular risk in diabetic and nondiabetic groups, respectively. Age, sex, height, weight, MBP, PR, TC, HDL-C, TG, AI, the presence or absence of LVH and smoking were used as independent variables in subgroup analysis. The median of AI and HDL-C was used to divide patients into two groups. Stepwise regression analysis was used to assess which patient backgrounds determined AI. Receiver operation characteristic (ROC) analysis was used to assess cut-off value of AI to predict cardiovascular events. Fisher's exact test and Student t-test were used to compare patient background between groups. $P < .05$ was considered significant.

3. Results

Table 1 summarized patient background for two groups. In each group, there were 11 females and age was averaged 59 y/o at the time of study entry. Height, weight, MBP, PR, AI, TC, HDL-C, and the prevalence of smokers were similar between nondiabetic and diabetic groups. Twenty diabetic patients were on insulin therapy, and 10 took voglibose. The other 22 diabetes were diet therapy alone. Averaged HbA1c was 6.1 ± 0.3% in diabetes. LVH was more frequently observed in diabetes than nondiabetics, and TG was higher in diabetes. Although serum albumin

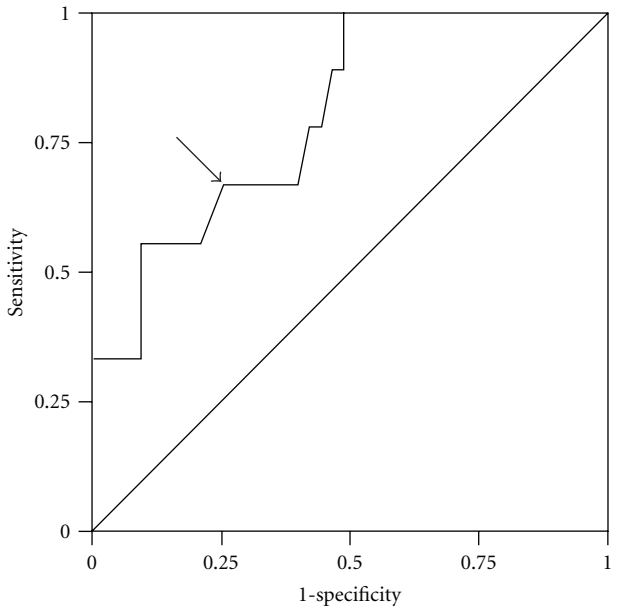

Figure 5: ROC curve for nondiabetic patients showed that AI of 87 was able to be used as a cutoff value to (arrow) predict cardiovascular events.

(3.8 ± 0.3 versus 3.8 ± 0.2 g/dl), Hb (10.0 ± 0.5 versus 9.9 ± 0.6 g/dl), and dialysis efficiency (KT/V; 1.1 ± 0.1 versus 1.1 ± 0.1) were similar between 2 groups, the duration of hemodialysis in diabetes was shorter than that of nondiabetic patients. Most patients took antihypertensives. Either an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker was prescribed for 87% of diabetic patients and 77% of nondiabetic patients. Statins were prescribed for 58% of diabetic patients and 54% of nondiabetic patients. No patients took fibrates, because Ministry of Health, Labor and Welfare Japan prohibited their application for patients with renal insufficiency. Erythropoietin was administered to treat renal anemia and titrated to maintain hemoglobin around 10 g/dl. The doses of erythropoietin were similar between diabetic (3800 ± 435 IU/week) and nondiabetic patients (3950 ± 383 IU/week).

Three patients died during 2 years in the nondiabetic group. The causes of death were stroke (2 cases) and gastric cancer. Eight diabetic patients died during observation periods. Three diabetic patients were dead from myocardial infarction, two from stroke, and one from peripheral artery diseases. The other two patients died from renal cell carcinoma and pneumonia. Thus, only 5% of patients were dead for a year in the present study. As with previous reports, our results support a significant small death rate of hemodialysis patients in Japan, compared to US or Europe [32].

Cox hazard analysis demonstrated that both smoking ($P < .05$) and shortness in height ($P < .05$) considerably contributed to total mortality (Table 2). Figure 1 depicted Kaplan-Meier analysis indicating a significant difference in survival curves between smokers and nonsmokers ($P < .05$). Cox hazard model selected both smoking ($P < .05$) and LVH ($P < .05$) as significant contributors to cardiovascular

Table 1: Demographic feature of participating patients.

	Non-DM	DM
Age (y/o)	59 ± 13	59 ± 12
Sex (M/F)	41/11	41/11
height (cm)	164 ± 9	163 ± 8
Weight (kg)	60 ± 10	60 ± 11
SBP (mmHg)	143 ± 19	146 ± 20
DBP (mmHg)	69 ± 13	67 ± 16
SBP2 (mmHg)	127 ± 16	129 ± 18
MBP (mmHg)	94 ± 12	94 ± 13
PR (bpm)	78 ± 18	79 ± 10
TC (mg/dl)	157 ± 42	158 ± 36
HDL-C (mg/dl)	40 ± 15	36 ± 11
TG (mg/dl)	115 ± 45	134 ± 52*
Smoking (%)	19	25
AI	78 ± 21	79 ± 20
LVH (%)	15	46*
HD duration (yrs)	12.4 ± 1.0	9.6 ± 0.8*

DM, HD, PR, TC, HDL-C, TG, AI, LVH, SBP, SBP2, DBP, and MBP depicted diabetes mellitus, hemodialysis, pulse rate, total cholesterol, high density lipoprotein cholesterol, triglyceride, augmentation index, left ventricular hypertrophy, systolic, central, diastolic and mean blood pressure, respectively. *indicates significance between groups.

Table 2: Cox hazard stepwise regression analysis for all mortality (whole patients). $\chi^2 = 8.54$, $df = 2$, $P = .014$.

Variable	β	SE	Wald	Probability
Smoking	1.65	0.65	6.35	0.012
Height	−0.082	0.038	4.80	0.028

SE; standard error.

Table 3: Cox hazard stepwise regression analysis for cardiovascular mortality (whole patients). $\chi^2 = 10.22$, $df = 2$, $P = .006$.

Variable	β	SE	Wald	Probability
Smoking	1.858	0.731	6.45	0.011
LVH	1.372	0.713	3.52	0.041

SE and LVH indicate standard error and left ventricular hypertrophy.

mortality (Table 3). As shown in Figure 2, patients with LVH survived less than those without ($P < .05$). As shown in Table 4, however, Cox hazard analysis showed that the presence of diabetes ($P < .05$), high AI ($P < .05$), and low HDL-C ($P < .05$) contributed to cardiovascular events in this study. Figure 3 depicted that diabetic patients suffered more cardiovascular events than nondiabetic patients ($P < .05$).

Subgroup analysis was also performed. In nondiabetic patients, Cox hazard model failed to find significant contributors to total and cardiovascular mortality. However, it selected high AI as a contributor to cardiovascular events (Table 5). Figure 4 exhibits Kaplan Meier analysis which showed that patients with low AI enjoy cardiovascular event-free lives longer than those with high AI. As illustrated in Figure 5, ROC analysis has shown that the cutoff value of

Table 4: Cox hazard stepwise regression analysis for cardiovascular events (whole patients). $\chi^2 = 23.3$, $df = 3$, $P = .0001$.

Variable	β	SE	Wald	Probability
AI	0.026	0.009	8.499	0.004
HDL-C	−0.045	0.018	6.208	0.013
DM	1.155	0.394	8.593	0.003

SE, AI, HDL-C, and DM depicted standard error, augmentation index, high density lipoprotein cholesterol, and diabetes mellitus.

Table 5: Cox hazard stepwise regression analysis for cardiovascular events (nondiabetic patients). $\chi^2 = 11.42$, $df = 1$, $P = .001$.

Variable	β	SE	Wald	Probability
AI	0.064	0.021	9.090	0.003

SE and AI described standard error and augmentation index.

Table 6: Cox hazard stepwise regression analysis for cardiovascular events (diabetic patients). $\chi^2 = 10.07$, $df = 2$, $P = .007$.

Variable	β	SE	Wald	Probability
HDL-C	−0.047	0.021	4.819	0.028
LVH	0.987	0.425	5.405	0.020

SE, HDL-C, and LVH denoted standard error, high density lipoprotein cholesterol, and left ventricular hypertrophy.

Table 7: Stepwise regression analysis for AI (nondiabetic patients). $R^2 = 0.428$, RMSE 16.52, $F = 18.33$, $P < .001$.

Variable	β	SE	t	P
Age	0.644	0.198	3.249	0.002
Height	−0.926	0.306	−3.029	0.004

AI and SE represented augmentation index and standard error.

Table 8: Stepwise regression analysis for AI (diabetic patients). $R^2 = 0.303$, RMSE 16.58, $F = 10.65$, $P < .001$.

Variable	β	SE	t	P
MBP	0.404	0.178	2.268	0.028
Height	−1.140	0.289	−3.940	0.001

AI, SE, and MBP indicated augmentation index, standard error, and mean blood pressure.

87 for AI predicts the occurrence of cardiovascular events in nondiabetic hemodialysis patients with sensitivity and specificity of 67% and 74%, respectively. In diabetic patients, Cox hazard model failed to find significant contributors to total and cardiovascular mortality as the case with nondiabetic patients. However, Cox hazard analysis chose the presence of LVH ($P < .05$) and low HDL-C ($P < .05$) as the predictors of cardiovascular events (Table 6). Figure 6 demonstrated that hemodialysis patients with the lower HDL-C failed to live cardiovascular event-free lives similar to those with the higher HDL-C. Stepwise regression analysis on patient backgrounds in each group described that age and height significantly contributed to AI in nondiabetic group (Table 7) and showed that MBP and height determined AI in diabetic group (Table 8).

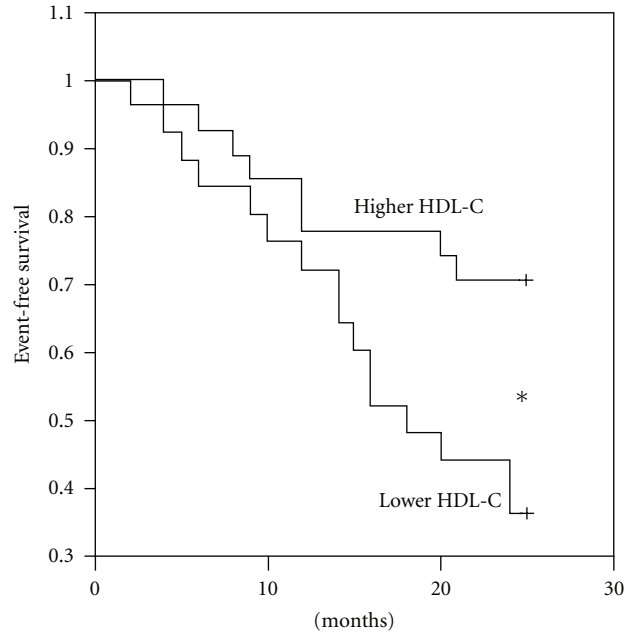

Figure 6: Kaplan-Meier analysis on diabetic hemodialysis patients showed that patients with higher HDL-C AI enjoy cardiovascular event-free lives longer than those with lower HDL-C. Log-rank test denoted that there was a significant difference in cardiovascular events between the two subgroups.

4. Discussion

Cardiovascular diseases are a major cause of death in hemodialysis patients [23]. Early detection of cardiovascular diseases and prevention of cardiovascular events appear important also in hemodialysis patients. We have previously reported that cardio-ankle vascular index, another index of arterial stiffness, is useful for this purpose, because it provides the cutoff value of 7.55 to predict the presence of cardiovascular diseases in hemodialysis patients [30]. Consistent with Covic et al. [33], our study suggests that the measurement of AI is also useful to screen the presence of cardiovascular diseases even if asymptomatic. ROC analysis showed that the cutoff value of 87 for AI predicted the occurrence of cardiovascular events in nondiabetic hemodialysis patients. Together, the present findings indicate that nondiabetic hemodialysis patients possessing AI over 87 should receive further medical examinations for the presence of cardiovascular diseases and implicate a critical role of central blood pressure in the development of cardiovascular events in hemodialysis patients.

Our results constitute a novel finding that the shortage in height contributed to total death in the present study. Shortness in height would reduce the time required for reflection wave to reach ascending aorta, thereby increasing AI [13]. Indeed, stepwise regression analyses demonstrated that the determinant of AI consisted of the height in both diabetic and nondiabetic groups. However, Kaplan-Meier analysis failed to attain statistical significance when a comparison was made to mortality between tall and short patients. Although precise reasons for the discrepancy are not

readily apparent from the present study, several confounding factors could be involved. Smokers prevailed in the tall patients (16 smokers) more than short ones (7 smokers). ASCOT-CAFÉ study demonstrated the advantage of lower AI for better cardiovascular outcomes in hypertensive patients [9]. As discussed (bide infra), AI measured in the sitting position, however, may be inappropriately low in diabetic group possibly due to the presence of neuropathy [14]. Taken together, these observations could account for that the shortness of height, an important determinant of AI, but not AI itself, was picked up as a risk factor of mortality. It is tempting to speculate that patients with short height are exposed to high AI and high central blood pressure, even if brachial blood pressure is controlled similarly to tall patients. Indeed, Asians who suffer more cerebrovascular attacks than coronary heart disease are generally shorter than Caucasians [18]. The difference in body size as well as racial background may underlie high prevalence of stroke in Asia. Alternatively, the treatment goal of blood pressure for hypertensive patients should be individualized and adjusted by taking the influence of height on central blood pressure into consideration [34]. Taken together, these observations raise the possibility that blood pressure should be more carefully controlled for patients with short height such as women [35].

Several factors such as age, LVH, and arterial stiffness have been reported to predict cardiovascular prognosis.It seems controversial that AI constitutes a good predictor of cardiovascular complications in diabetes [10]. Indeed, AI was selected as an important contributor to cardiovascular events for nondiabetic but not diabetic patients in the present study. The present results support a recent investigation implicating that pulse pressure predicted cardiovascular survival in nondiabetic, but not diabetic hemodialysis patients [36]. In this study, however, LVH was selected as one of contributors to cardiovascular events in diabetes. Our previous data demonstrated that AI positively correlated to left ventricular mass Index in patients with nondiabetic CKD [27]. Our recent data demonstrated that patients with diabetic nephropathy manifested greater decreases in AI, brachial and central blood pressures when their postures alter from supine to sitting position than those with nondiabetic CKD [14]. The patient with diabetic nephropathy commonly suffers neuropathy as well [37]. Diabetic neuropathy could fade appropriate vasoconstriction following to postural changes, resulting in a large decrease in reflection wave. Alternatively, sleep may markedly increase central blood pressure in diabetes with neuropathy and facilitate the development of LVH. Collectively, blood pressure control at night in lying position would be important to prevent LVH, cardiovascular events, and death, especially in diabetes.

Atherosclerotic cardiovascular diseases constitute a major cause of death in diabetic patients [38]. Frequently, type II diabetes has already manifested atherosclerotic vascular lesions at the time of diagnosis, and the presence of atherosclerosis makes their survival shorter and may increase total medical cost. Thus, the prevention and detection of atherosclerosis and cardiovascular complications in diabetes should be of clinical significance. In addition to glycemic control, lipid-lowering drugs, and renin-angiotensin inhibitors appear as promising therapeutic tools to retard the development of atherosclerosis in diabetes [39, 40]. In consistent, this study demonstrated that diabetes was a significant contributor to cardiovascular events. The usage of RAS inhibitors and statins was similar between diabetic and nondiabetic group, suggesting that the differences in medication between groups might have played a small role [39–41]. Our recent data indicated that oxidized LDL was higher in diabetic patients than those without diabetes [26]. Thus, the present results are compatible with recent investigations which revealed that oxidative stress underlies diabetic nephropathy [42], and suggest that oxidative stress is also involved in the pathogenesis of cardiovascular diseases in diabetes.

Chronic kidney disease (CKD) is characterized by oxidative stress [43, 44]. In the case of hemodialysis, the contact of blood cells with dialyzer membrane may generate more oxidative stress to the patient. We have previously demonstrated that oxidized LDL was sky high in hemodialysis patients [45]. Our recent data suggest that oxidative stress induces insulin resistance, which is an important cardiovascular risk factor in hemodialysis patients [26]. It is easy to expect that the superimposition of exogenous oxidative stress on endogenous one would increase cardiovascular risk. Oxidative stress also causes the damage of DNA and histones, possibly underlying the pathogenesis of cancer [46]. Consequently, the present results that smoking strongly contributed to total and cardiovascular mortality are consistent with the above, and suggest that the prohibition of smoking is encouraged especially for CKD patients.

HDL-C plays a pivotal role in lipid metabolism by uptaking redundant cholesterol and carrying it back to liver for degradation. Recent investigations reveal that HDL-C possesses strong antioxidant activity [47, 48]. In the present study, low HDL-C was selected as the contributor to cardiovascular events when diabetic as well as whole patients were examined. Our previous data indicated that higher oxidized LDL resulted in lower ankle-brachial pressure index in hemodialysis patients [45], and that hemodialysis patients with low ABI exhibit a strong tendency to develop cardiovascular events [26]. Our data seem compatible with those by Nishizawa et al. that non-HDL-C such as intermediate density lipoprotein cholesterol is highly atherogenic in hemodialysis patients [49] and suggest that in patients with CKD, the efforts to maintain HDL-C level such as aerobic exercise are more important for vascular health than those without renal dysfunction.

This study shares several limitations. Although further larger scale study should be required before drawing conclusion, the present data suggest that the values of AI in sitting position as a predictor of cardiovascular prognosis in hypertensive patients with diabetic nephropathy might be less than our expectation. Prospective studies that utilize AI measured in lying position should be required to examine AI as a predictor of cardiovascular prognosis in diabetes. Second, the usage of echocardiographic LVH as a risk factor might give differing results because electrocardiographic LVH does not always reflect echocardiographic LVH [29].

Thirdly, although TG was higher in diabetes, HDL-C was similar between the 2 groups in this study. However, TG did not contribute to either cardiovascular death or events. While the reasons for this discrepancy are not readily clear, we should note that TG levels were not so high in diabetes and that blood glucose was fairly controlled, presumably accounting for this. Fourthly, nonclassical risk factors such as albumin and anemia were not selected as a significant contributor to mortality or cardiovascular events. We should note that the patients enrolled in the present study were relatively young and shared well nutrition. Finally, oxidative stress and central hypertension may cause crosstalk to each other. Oxidative stress should increase central blood pressure by attenuating the actions of nitric oxide on artery, and high central blood pressure could induce oxidative stress de novo.

In conclusion, the present observations provide new evidence that shortness in height independently contributes to mortality in hemodialysis patients.

Acknowledgments

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Research Article

Lipoprotein(a) Is the Best Single Marker in Assessing Unstable Angina Pectoris

Vidosava B. Djordjević,[1] Vladan Ćosić,[2] Ivana Stojanović,[1] Slavica Kundalić,[2] Lilika Zvezdanović,[2] Marina Deljanin-Ilić,[3] Predrag Vlahović,[2] and Lidija Popović[1]

[1] *Institute of Biochemistry, Faculty of Medicine, Niš, Serbia*
[2] *Centre for Medical Biochemistry, Clinical Center, Niš, Serbia*
[3] *Institute for Cardiovascular and Rheumatic Diseases, Niška Banja, Serbia*

Correspondence should be addressed to Predrag Vlahović, predrag_vlahovic@yahoo.com

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This study evaluated whether statin therapy changed a diagnostic validity of lipid and inflammatory markers in ischemic heart disease (IHD) patients. Levels of lipids, lipoproteins, apolipoproteins, inflammatory markers, and atherogenic indexes were determined in 49 apparently healthy men and women, 82 patients having stable angina pectoris (SAP), 80 patients with unstable angina (USAP), and 106 patients with acute ST-elevation myocardial infarction (STEMI) treated or not treated with statins. Diagnostic accuracy of markers was determined by ROC curve analysis. Significantly lower apoA-I in all statin-treated groups and significantly higher apoB in statin-treated STEMI group compared to non-statin-treated groups were observed. CRP showed the best ROC characteristics in the assessment of STEMI patients. Lp(a) is better in the evaluation of SAP and USAP patients, considering that Lp(a) showed the highest area under the curve (AUC). Regarding atherogenic indexes, the highest AUC in SAP group was obtained for TG/apoB and in USAP and STEMI patients for TG/HDL-c. Statins lowered total cholesterol, LDL-c, and TG but fail to normalize apoA-I in patients with IHD.

1. Introduction

Beside endothelial dysfunction leading to inflammatory reaction, lipid metabolism disorders represent the second key event in the initiation and rapid development of atherogenesis [1]. Many individual lipid and inflammatory markers have been considered as the factors playing an important role in atherogenesis and prognosis of related diseases. The atherogenic dyslipidemic profile, especially mild to marked elevation of apo-B containing lipoproteins, such as very low-density lipoproteins (VLDL), VLDL-remnants, intermediate-density lipoproteins (IDL), and low-density lipoproteins (LDL) (specifically small, dense LDL), and low levels of high-density lipoproteins (HDL) [2–4], appears to promote enhanced arterial cholesterol deposition and accelerate the progression of atherosclerotic disease. Despite the use of new and effective pharmacological drugs to lower plasma lipid concentration, cardiovascular diseases continue to be the main cause of death in western countries [5, 6]. Fenofibrate lowers the plasma level of cholesterol and triglyceride, corrects the abnormality in LDL metabolism, but has no effect on HDL-cholesterol (HDL-c) [7]. On the other hand, statins have a therapeutic effect on lipid metabolism and inflammation. They lower total and LDL-cholesterol (LDL-c), elevate HDL-c, and lower inflammatory markers such as C-reactive protein (CRP) [8–11]. Since antilipidemic drugs induce modifications in current lipid metabolism and inflammatory response, lipid and inflammatory markers become less convenient in assessing the activity of atherosclerotic process. This may be a reason for contradictory results related to CRP, which was until recently a promising marker in predicting cardiovascular events. Recent limited data have shown that lipoprotein(a) (Lp(a)) and the ratio of Tc/HDL-c may be used as much stronger

predictors in screening for high blood lipid [12], and Lp(a) is the best single marker for the presence of cerebrovascular disease [13].

The aim of this study was to determine which individual lipid or inflammatory biomarkers had the highest clinical accuracy by Receiver Operating Characteristic (ROC) curve analysis in patients with different stages of ischemic heart disease treated or not treated with statins.

2. Materials and Methods

2.1. Subject. The study evaluated patients admitted to the Institute for Cardiovascular diseases "Niška Banja" for the evaluation of chest pain. Patients were categorized into three groups based on the degree of ischemic heart disease (IHD): chronic stable angina pectoris (SAP group), unstable angina pectoris (USAP group), and acute ST-elevation myocardial infarction (STEMI group). The SAP group consisted of 52 male and 30 female (total 82, mean age 61.3 ± 6.5 years); the USAP group had 50 male and 30 female (total 80 mean age 60.8 ± 9.8 years); the STEMI patients included 72 male and 34 female (total 106, mean age 60.22 ± 12.7 years). Each group was divided into statin-treated (+) and non-statin-treated (−) groups. The SAP(+) group consisted of 34 males and 17 females, the SAP(−) of 18 males and 13 females, the USAP(+) of 35 males and 12 females, the USAP(−) of 15 males and 18 females, the STEMI(+) of 37 males and 18 females, and the STEMI(−) of 35 males and 16 females.

The patients in the SAP group gave a history consistent with stable angina for at least 3 months before entering the study and demonstrated objective evidence of ischemia on exercise electrocardiogram and/or stress echocardiogram. None of the patients in this group had previous myocardial infarction or myocardial revascularization, cardiac valve disease, cardiomyopathy, malignant arrhythmias, acute or chronic liver disease, renal failure, or inflammatory disease, and none of the patients were under consideration for coronary revascularization at the time of the inclusion into the study.

Unstable angina was defined according to Hamm and Braunwald [14]. All patients in the USAP group had chest pain of increasing frequency and severity or at rest during the last 48 hours before hospitalisation associated with ST segment changes, T wave changes, or both and without rise in cardiac enzymes and troponin I.

Acute myocardial infarction was based on the following criteria: chest pain persisting longer than 30 min, concomitant changes on the electrocardiogram at the admission to hospital and elevated troponin I levels. All patients had STEMI according to the Guidelines of the European Society of Cardiology [15]. In all patients, a detailed clinical analysis was performed just after admission, and all of them were asked for current medications. Additional explanation of the criteria for patients with ischemic heart disease selection was given in our previously published paper [16].

For the control group, we recruited 49 (30 male, 19 female) healthy volunteers—blood bank donors from the Department for Blood Transfusion of the Clinical Centre Niš. All controls were free of any acute infectious disease and any history of hypertension, diabetes or ischemic heart disease. All subjects gave informed consent prior to their enrolment in the study, and the study was approved by the local Ethics Committee.

2.2. Methods. Blood samples were obtained within 24 hours after admission after overnight fasting. Peripheral venous blood was drown into vacutainer tubes containing ethylene diamine-tetracetic acid (EDTA), citrate, or no anticoagulant. Troponin I and inflammatory markers were determined in serum, fibrinogen in citrate plasma, and lipid markers in EDTA plasma. Aliquots of plasma and serum for the determination of neopterin, iNOS, NO_2/NO_3, TNF-α, Lp(a), and oxidized LDL (oxLDL) were stored at 80°C until assayed. All other analyses were performed the same day the blood was collected.

Troponin I was determined on AxSYM (Abbott Ireland Diagnostics Division, Lisnamuck, Ireland). The diagnostic cutoff for acute myocardial infarction is 0.40 ng/mL. In apparently healthy population, 99th percentile is 0.04 ng/mL. Depending on patient hours after admission, sensitivity ranges from 60% (0–6 h) to 91.7% (12–24 h), and specificity 97.4% to 98.3%.

HsCRP, total cholesterol (Tc), triglycerides (TG), LDL-c, HDL-c, apolipoprotein A-I (ApoA-I), apolipoprotein B (ApoB) were assayed on analyzer AU 400 (Olympus, Tokio, Japan). HsCRP was measured using a latex-enhanced immunoturbidimetric method on Olympus AU400. hsCRP reference values are <1 mg/L (manufacturer recommendation). This test is linear within a concentration range of 0.08–80 mg/L. The intra-assay precision for three different samples are between CV% 0.55 and CV% 4.32. Tc, TG, HDL-c, and LDL-c were measured by routine methods on analyzer AU 400. ApoA-I and apoB concentrations were determined using an immunoturbidimetric method (Olympus, Tokio, Japan).

The plasma concentration of Lp(a) was also assayed by a latex immunoassay (Sentinel CH Srl Diagnostics, Milan, Italy) on Olympus AU400. Lower detection limit was 3 mg/dL and the reference values were <30 mg/dL. The performance characteristics of Lp(a) test were as follows: the measuring range was 3.0–130 mg/dL; the intra-assay precision determined in two levels was CV% 2.00 and 1.26, respectively.

Serum neopterin concentrations were determined using a commercially available immunoassay (ELISA kit, IBL, Hamburg, Germany). The limit of detection was 0.7 nmol/L.

Serum iNOS activity was measured by a commercially available Quantikine human iNOS immunoassay (ELISA kit, R&D Systems Europe, LTD. UK). The limit of detection was 0.15 U/mL.

Quantikine human TNF-α immunoassay (R&D Systems Europe, Ltd. UK) was used for the estimation of serum TNF-α concentration.

Serum NO_2/NO_3 concentration was measured by the modified cadmium-reduction method of Navaro-Gonzálvez et al. [17] which is based on the produced nitrite determination by diazotization of sulfanilamide and coupling to naphthylene diamine. The lower and upper detection

Table 1: Demographic characteristics and blood lipid and inflammatory markers in patients with ischemic heart disease.

	SAP	USAP	STEMI	Controls
Male/female (N)	52/30	50/30	72/34	30/19
Age years	61.3 ± 6.5	60.8 ± 9.8	60.2 ± 12.7	59.1 ± 9.7
Troponin I, ng/mL	0.0 (0.0–1.68)	0.03 (0.0–3.7)*	12.8 (0.0–159.6)***	0.0 (0.0–0.01)
TG, mmol/L	1.88 (0.58–21.4)*	2.08 (0.56–7.6)***	1.90 (0.56–4.9)*	1.30 (0.46–4.18)
Tc, mmol/L	5.60 ± 1.20	5.78 ± 1.72	5.91 ± 1.57	5.48 ± 0.49
HDL-c, mmol/L	1.16 ± 0.28	1.00 ± 0.31***	1.06 ± 0.26***	1.15 ± 0.28
LDL-c, mmol/L	3.47 ± 1.05	3.55 ± 1.40	3.88 ± 1.28	3.51 ± 0.59
Lp(a), mg/dL	14.4 (3.6–67.8)***	22.7 (5.9–88.9)***	17.8 (4.8–79.0)***	5.6 (2.9–19.7)
ApoA-I, g/L	1.13 ± 0.30***	1.04 ± 0.29***	1.11 ± 0.17***	1.34 ± 0.21
ApoB, g/L	1.06 ± 0.38	1.17 ± 0.40	1.25 ± 0.31	1.17 ± 0.14
oxLDL, ng/mL	211 (11.7–1925)	143 (7–1550)*	140 (15–2105)	195 (18–705)
hsCRP, g/L	3.0 (0.4–84.35)*	5.8 (0.43–178.3)^{**,b}	18.0 (0.56–270)^{***,c}	1.5 (0.1–16.5)
Fibrinogen, g/L	4.29 ± 1.22	5.03 ± 1.49**	5.06 ± 2.46*	3.92 ± 1.03
Neopterin, nmol/L	14.9 (3–57)***	14.3 (1–105)^{**,a}	13.0 (1–52)	13.4 (1–19.6)
iNOS, U/mL	2.2 (0.5–4.7)	2.9 (0.9–6.0)	3.0 (0.9–6.2)	2.2 (0.6–9.3)
NO_2/NO_3, μmol/L	96 (35–197)	125 (52–199)^{**,b}	102 (61–243)	97 (57–230)
TNF-α, pg/mL	12.74 ± 1.25	13.78 ± 1.93	14.47 ± 2.15	13.60 ± 2.19

The results are presented as means ± SD for parametric, and median (min–max) for nonparametric values $^{*}P < .05$ versus controls, $^{**}P < .01$ versus controls, $^{***}P < .001$ versus controls, $^{a}P < .05$ versus STEMI, $^{b}P < .01$ versus SAP, $^{c}P < .001$ versus SAP.

limits were 2 and 250 μmol/L, respectively. Plasma oxLDL concentrations were estimated by a commercially available ELISA kit (Immune diagnostic AG, Bensheim).

2.3. Statistical Analysis. Most statistics were performed using SPSS (the Statistical Package for the Social Sciences) computer program. The comparison of the different patient groups to the control group was performed using ANOVA followed by a 2-sided Dunnett's test (for multiple comparisons), or Student's nonpaired t-test as appropriate. The clinical accuracy of the examined parameters was assessed using receiver operating characteristic (ROC) curve analysis. ROC plots were constructed, and the areas under the curves (AUC), standard errors, 95% confidence interval, sensitivity, and specificity as well as optimal cutoff were calculated using MedCalc computer program. Cutoff values at which the discrimination between the cases with positive and negative diagnosis was optimal were set. The comparisons of the areas under different ROC plots were made using univariate z scores. Multinomial logistic regression was used to assess wich of the lipid and inflammatory markers showing high sensitivity and specificity may be the best predictor of SAP, USAP or STEMI.

3. Results

Demographic characteristics in the studied patients showed the prevalence of males in all groups. The average age of groups was about sixty (Table 1). Statistical analysis using ANOVA showed that SAP patients had significantly higher concentrations of TG, Lp(a), hsCRP, neopterin, and significantly lower levels of apoA-I in comparison with healthy subjects. In addition to these parameters in the USAP group, three more markers were significantly increased, including troponin I, NO_2/NO_3 and fibrinogen, while HDL-c and oxLDL were decreased. In STEMI patients significant differences were observed in troponin I, TG, HDL-c, Lp(a), apoA-I, hsCRP and fibrinogen. Also, significant differences were found in hsCRP, neopterin and NO_2/NO_3 between different patient groups (Table 1).

However, the testing between statin-treated and non-statin-treated groups showed fewer differences. None of all studied inflammatory markers showed any significant difference between statin-treated and non-statin-treated groups (Table 2). Among lipid markers only apoA-I levels were significantly decreased in SAP(+)compared to SAP(−) patients. A significant decrease in apoA-I, HDL-c, and LDL-c/apoB was noted in USAP(+) patients, as well as a significant increase in apoB/apoA-I, LDL-c/HDL-c, and Tc/HDL-c, in comparison with the USAP(−) group. STEMI(+) patients showed a significant decrease in apoA-I and LDL-c/apoB and an increase in apoB, apoB/apoA-I, LDL-c/HDL-c and Tc/HDL-c compared to STEMI(−) patients (Table 3).

Since we did not find any significant difference in ROC curve analysis between statin-treated and non-statin-treated groups in any individual inflammatory or lipid marker, ROC curve analysis included both subgroups of each patient group.

The ROC curves for inflammatory markers are presented in Figure 2. In SAP patients no biomarker showed a significant difference related to any other although hsCRP had the highest area under the ROC (0.691 ± 0.079) (Table 4). The greatest sensitivity was found for NO_2/NO_3 (81.0%), TNF-α (88.0%), and neopterin (88.6%), but their specificities were low (30.4%, 42.1%, and 42.9%, resp.).

Table 2: Demographic characteristics, standard and inflammatory markers in statin-treated and non-statin-treated IHD patients.

	SAP(+)	SAP(−)	USAP(+)	USAP(−)	STEMI(+)	STEMI(−)	Controls
Male/female (*N*)	34/17	18/13	35/12	15/18	37/18	35/16	30/19
Age	61.4 ± 6.8	59.8 ± 8.4	63.2 ± 7.5	62.6 ± 6.4	63.2 ± 9.8	62.9 ± 11.4	59.1 ± 9.7
Glucose (mmol/L)	5.72 ± 1.56	5.95 ± 1.73	6.41 ± 0.48	5.98 ± 2.29	6.31 ± 2.17	6.99 ± 3.17	5.19 ± 0.59
Creatinine (μmol/L)	88.8 ± 15.9	97.2 ± 31.2	111.4 ± 38.9	117.2 ± 109.4	88.4 ± 21.8	103.0 ± 34.2	85.1 ± 13.9
Troponin I (ng/mL)	0.00 ± 0.01	0.08 ± 0.32	0.0 (0.0–21.4)	0.0 (0.0–19.5)	12.8 (0.37–227.8)	9.8 (0.001–22.8)	0
hsCRP (g/L)	2.7 (0.4–19.4)	3.1 (0.74–84.4)	6.2 (0.6–78.4)	4.7 (0.4–122.9)	12.8 (2.1–186.3)	20.9 (0.6–270.3)	1.3 (0.1–16.5)
Fibrinogen (g/L)	3.9 (2.1–7.0)	5.1 (2.6–5.6)	4.9 (2.0–7.6)	4.8 (3.7–8.5)	4.6 (0.3–7.8)	5.3 (2.5–11.4)	3.7 (2.1–7.3)
Neopterin (nmol/L)	14.5 (3.0–57.0)	17 (8.0–55.0)	14.3 (1.0–105.0)	14.5 (6.0–19.3)	12.8 (1.0–52.0)	13.2 (5.0–32.0)	13.4 (1.0–19.6)
iNOS (U/L)	2.5 (0.5–4.7)	1.4 (0.5–2.2)	2.3 (0.9–5.7)	3.0 (1.7–6.0)	2.8 (0.9–4.7)	3.2 (1.4–6.2)	2.2 (0.6–9.3)
NO_2^-/NO_3^- (μmol/L)	96.1 (34.9–194.9)	93.0 (67.4–197.4)	124.6 (78.6–196.6)	127.4 (51.8–154.3)	97.5 (61.5–243.0)	105.5 (75.0–224.9)	97 (57–229)
TNF-α (pg/mL)	12.7 (10.8–15.2)	13. (13.1–13.9)	13.1 (12.0–18.9)	13.2 (12.0–18.3)	15.1 (12.1–18.3)	13.6 (10.9–14.5)	13.1 (11.2–19.7)

The results are presented as means ± SD for parametric, and median (min–max) for nonparametric values.

Table 3: Lipid markers and atherogenic indexes in statin-treated and non-statin-treated IHD patients.

	SAP(+)	SAP(−)	USAP(+)	USAP(−)	STEMI(+)	STEMI(−)	Controls
TG (mmol/L)	1.69 (0.93–8.68)	1.98 (0.38–8.68)	1.9 (0.88–6.14)	2.0 (0.56–7.56)	1.9 (0.37–4.96)	1.9 (0.56–4.31)	1.4 (0.46–4.18)
Tc (mmol/L)	5.38 ± 1.25	5.76 ± 2.09	5.87 ± 1.57	5.82 ± 1.22	5.90 ± 1.63	5.72 ± 1.17	5.48 ± 0.49
HDL-c (mmol/L)	1.20 ± 0.29	1.17 ± 0.31	1.02 ± 0.27*	1.19 ± 0.30	1.05 ± 0.25	1.16 ± 0.28	1.15 ± 0.28
LDL-c (mmol/L)	3.26 ± 1.11	3.28 ± 1.08	3.67 ± 1.40	3.66 ± 1.01	3.85 ± 1.38	3.66 ± 1.01	3.51 ± 0.59
Lp(a) (mg/dL)	16.7 (4.0–68.0)	12.6 (7.0–22.0)	22.3 (5.9–59.7)	25.0 (20.4–36.6)	15.2 (5.0–64.0)	20.1 (14.0–37.2)	5.6 (2.9–19.7)
ApoA-I	1.28 ± 0.39*	1.46 ± 0.30	1.13 ± 0.33*	1.41 ± 0.33	1.12 ± 0.17**	1.44 ± 0.31	1.34 ± 0.21
Apo B (g/L)	0.98 ± 0.36	1.04 ± 0.26	1.18 ± 0.39	1.09 ± 0.22	1.25 ± 0.33*	1.11 ± 0.22	1.17 ± 0.14
oxLDL (ng/mL)	210 (12–1925)	230 (20–498)	153 (7–1550)	125 (42–657)	152 (15–2150)	72 (30–541)	195 (18–705)
TG/apoB	1.66 (0.67–3.42)	1.98 (0.67–5.32)	1.90 (0.69–4.73)	1.80 (0.41–5.52)	1.60 (0.71–4.07)	1.70 (0.68–5.07)	1.17 (0.68–1.91)
apoA/apoB	0.78 (0.27–1.66)	0.80 (0.39–1.33)	1.08 (0.45–1.99)**	0.77 (0.42–1.59)	1.10 (0.43–1.79)**	0.80 (0.25–1.55)	0.91 (0.41–0.56)
TG/HDL-c	1.51 (0.25–10.21)	1.62 (0.25–5.23)	3.70 (1.79–6.55)*	1.70 (0.40–9.33)	2.10 (0.66–5.90)	1.70 (0.54–5.60)	0.87 (0.24–2.73)
LDL-c/HDL-c	2.55 (0.85–6.58)	2.79 (1.21–4.69)	3.70 (1.79–6.55)	3.00 (1.72–4.71)	3.50 (1.35–6.45)*	3.20 (0.77–5.53)	2.47 (1.17–3.76)
Tc/HDL-c	4.52 (2.25–8.76)	4.92 (2.32–10.41)	5.90 (3.22–11.00)*	5.00 (3.10–8.80)	5.70 (2.65–9.18)*	5.10 (2.42–8.13)	4.44 (2.27–6.97)
LDL-c/apoB	3.22 (1.58–4.04)	3.01 (1.58–3.87)	3.10 (1.86–3.85)*	3.40 (2.10–4.05)	3.10 (1.60–3.98)*	3.40 (1.98–4.04)	3.40 (2.04–3.96)

The results are presented as means ± SD for parametric, and mediana (min–max) for nonparametric values $^{*}P < .05$ versus (−) group, $^{**}P < .001$ versus (−) group.

Table 4: The results of ROC curves analysis of inflammatory markers in ischemic heart disease patients.

		AUC	SE	95%CI	Specificity	Sensitivity	Criterion
SAP	CRP	0.691	0.079	0.533–0.821	66.7	72.7	>1.9
	Fibrinogen	0.557	0.087	0.399–0.706	59.5	75.9	>3.9
	iNOS	0.558	0.087	0.400–0.707	78.9	48.0	>2.8
	Neopterin	0.642	0.086	0.484–0.781	42.9	88.6	>11.9
	NO_2/NO_3	0.567	0.087	0.410–0.716	30.4	81.0	≤122.0
	TNF-α	0.596	0.088	0.437–0.741	42.1	88.0	≤14.0
USAP	CRP	0.808*	0.074	0.643–0.919	87.2	69.8	>4.1
	Fibrinogen	0.680	0.090	0.504–0.825	59.5	90.5	>3.9
	iNOS	0.610	0.095	0.433–0.767	78.9	52.6	>2.8
	Neopterin	0.709	0.086	0.534–0.848	94.3	34.9	>18.9
	NO_2/NO_3	0.698	0.088	0.523–0.839	47.8	92.7	>88.6
	TNF-α	0.548	0.097	0.374–0.714	31.6	94.7	>11.9
STEMI	CRP	0.923**	0.043	0.796–0.982	89.7	88.6	>4.7
	Fibrinogen	0.562	0.090	0.399–0.716	91.9	52.2	>5.0
	iNOS	0.602	0.088	0.437–0.751	21.1	100.0	>0.9
	Neopterin	0.725	0.081	0.563–0.852	100.0	19.0	>19.6
	NO_2/NO_3	0.627	0.087	0.462–0.772	47.8	74.4	>88.6
	TNF-α	0.604	0.088	0.439–0.753	89.5	27.3	>15.5

*$P < .05$ versus TNF-α, **$P < .05$ to $P < .001$ versus all other markers.

Also, in USAP patients AUC for hsCRP was the highest (0.808 ± 0.074), and significantly higher only in comparison with TNF-α (0.548 ± 0.097). Fibrinogen, NO_2/NO_3, and TNF-α showed very high sensitivity (90.5%, 92.7%, and 94.7%, resp.) for optimal cutoff values, and low specificity (under 59.5%). Neopterin showed high specificity (94.3%), and rather poor sensitivity (34.9%). The best predictor for disease activity was CRP with specificity of 87.2%, and sensitivity 69.8% when the cutoff was >4.1 mg/L.

In the STEMI group, ROC for hsCRP (0.923 ± 0.043) was significantly higher in comparison with all others. The highest sensitivity was obtained for iNOS (100%), but very low specificity (21.1%) excluded this marker from clinical use. Due to good sensitivity (88.6%) and specificity (89.7%) for cutoff >4.7, CRP alone may be satisfactory for patient screening.

The results related to ROC curves of lipid markers were shown in Figure 1 and Table 5. The highest AUC in SAP patients was obtained for Lp(a) (0.835 ± 0.049), which is significantly higher than AUC for oxLDL, LDL-c and apoB ($P < .001$). ApoA-I also had the AUC (0.780 ± 0.065) significantly higher than AUC for oxLDL and LDL-c ($P < .05$). However, sensitivity (81.8%), and specificity (80.0%) of Lp(a) were higher compared to all the other lipid markers.

In patients with USAP the highest AUCs were observed for Lp(a) (0.951 ± 0.025, significantly higher in comparison with LDL-c, oxLDL, apoB and TG), and apoA-I (0.876 ± 0.051, significantly higher than apoB and oxLDL AUCs). Sensitivity and specificity for Lp(a) were very high (97.9% and 84.0%, resp.), while for apoA-I these values were 91.3% and 71.8%, respectively. So, these markers may be useful in assessing disease activity in more than 90% of patients. No difference between the ability of Lp(a) and apoA-I to correctly stratify the patients was found.

Further, in STEMI patients both Lp(a) and apoA-I had also the highest AUC in comparison with other studied markers. For Lp(a) AUC was 0.881 and statistically different in comparison with apoB, LDL-c, oxLDL ($P < .001$) and TG ($P < .01$), and for apoA-I it was 0.836 (significantly higher than AUCs for LDL-c and oxLDL; $P < .001$). OxLDL, apoB and LDL-c showed high specificity (96.7%, 89.7% and 87.2%, resp.), but very poor sensitivity (24.5%, 30.9%, and 25.5%, resp.), which made them unsatisfactory for diagnostic screening. Thus, Lp(a) with 84.9% sensitivity and 84.0% specificity stayed the best predictor, better than apoA-I whose sensitivity was 83.6% and specificity 71.8%.

Since hsCRP showed the best characteristics among all studied inflammatory markers, and Lp(a) was the best lipid marker, we compared these two and troponin I in patient groups and showed that (Table 6) there was a significant difference between their AUCs in USAP patients in whom AUC for Lp(a) was 0.957 ($P < .05$) in comparison with 0.859 for hsCRP AUC and 0.821 for troponin I AUC ($P = .015$). In SAP patients, there was no significant difference in AUC between the different markers although hsCRP AUC and Lp(a) AUC were significantly higher (($P < .05$), $P < .01$, resp.) than AUC for troponin I.

Generally, almost all atherogenic indexes showed acceptable discriminative ability for ischemic heart disease patients (Figure 3, Table 7). The ratio of TG to apoB had the highest AUC (0.89 ± 0.03) and significantly higher than AUCs for apoB/apoA (0.71 ± 0.06), LDL-c/apoB (0.77 ± 0.06), LDL-c/HDL-c (0.65 ± 0.06), and Tc/HDL-c (0.73 ± 0.06) in SAP patients. A similar relationship was observed for TG/HDL-c with AUC of 0.88 ± 0.04. Identical AUCs were found

Table 5: The results of ROC curves analysis of lipid markers in ischemic heart disease patients.

		AUC	SE	95%CI	Specificity	Sensitivity	Criterion
SAP	ApoA-I	0.780[a]	0.065	0.660–0.873	71.8	77.3	≤1.28
	ApoB	0.542[b]	0.076	0.414–0.666	92.3	38.6	≤0.9
	LDL-c	0.539[b]	0.076	0.411–0.664	87.2	40.9	≤3.06
	Lp(a)	0.835[c]	0.049	0.722–0.915	80.0	81.8	>8.2
	oxLDL	0.552	0.075	0.423–0.675	80.0	43.2	>280
	TG	0.704	0.065	0.578–0.811	48.7	86.4	>1.31
USAP	ApoA-I	0.876[C]	0.051	0.773–0.944	71.8	91.3	≤1.28
	ApoB	0.557	0.074	0.430–0.678	89.7	21.7	>1.41
	LDL-c	0.588	0.075	0.461–0.707	64.1	60.9	≤3.49
	Lp(a)	0.951[B]	0.025	0.869–0.988	84.0	97.9	>8.2
	oxLDL	0.529	0.075	0.403–0.652	93.3	32.6	>460
	TG	0.742[A]	0.060	0.621–0.841	71.8	69.6	>1.94
STEMI	ApoA-I	0.836****	0.057	0.732–0.911	71.8	83.6	≤1.26
	ApoB	0.626**	0.068	0.506–0.735	89.7	30.9	>1.41
	LDL-c	0.514	0.073	0.395–0.631	87.2	25.5	≤3.07
	Lp(a)	0.881***/*****	0.038	0.785–0.994	84.0	84.9	>8.2
	oxLDL	0.505	0.074	0.387–0.623	96.7	24.5	>4.80
	TG	0.664*	0.065	0.546–0.769	56.4	69.1	>1.49

[a]$P < .05$ versus LDL-c and oxLDL, [b]$P < .05$ versus TG, [c]$P < .001$ versus oxLDL, LDL-c and ApoB, [A]$P < .05$ versus ApoB and OxLDL, [B]$P < .001$ versus LDL-c, oxLDL, ApoB and TG, [C]$P < .001$ versus ApoB, LDL-c and oxLDL, *$P < .05$ versus ApoA, LDL-c, **$P < 0.01$ versus ApoA, LDL-c, ***$P < .01$ versus TG, ****$P < .001$ versus LDL-c, oxLDL, *****$P < .001$ versus ApoB, LDL-c, OxLDL.

Table 6: Comparison of CRP and Lp(a) and troponin I ROC curves analysis.

		AUC	SE	95%CI	Specificity	Sensitivity	Cutoff
SAP	CRP	0.758**	0.057	0.640–0.853	57.6	75.7	>1.9
	Lp(a)	0.843***	0.046	0.736–0.919	80.0	81.8	>8.2
	Troponin I	0.568	0.049	0.480–0.654	96.9	17.6	>0
USAP	CRP	0.859	0.043	0.750–0.930	87.2	69.8	>4.1
	Lp(a)	0.957*	0.023	0.880–0.990	84.0	97.9	>8.2
	Troponin I	0.821	0.038	0.743–0.883	96.8	63.5	>0
STEMI	CRP	0.946	0.024	0.870–0.984	89.7	88.6	>4.7
	Lp(a)	0.888	0.036	0.796–0.948	84.0	84.9	>8.2
	Troponin I	1.000	0.000	0.971–1.000	100.0	93.4	>0.01

*$P < .05$ versus CRP and troponin I in USAP patients, **$P < .05$ versus troponin I in SAP patients, ***$P < 0.001$ versus troponin I in SAP patients.

for apoB/apoA and TG/HDL-c ratios (0.89 ± 0.03) and a little bit lower AUC for Tc/HDL-c (0.87 ± 0.03) in USAP patients. All three AUCs were significantly higher than AUC for LDL-c/HDL-c. The highest sensitivity and specificity were observed for TG/HDL-c (80.0% and 82.4%, resp.), and for Tc/HDL-c (73.3% and 71.4%, resp.). In STEMI patients AUC for TG/HDL-c was the highest (0.91 ± 0.03), followed by Tc/HDL-c (0.89 ± 0.03), and apoB/apoA (0.87 ± 0.04). Satisfactory sensitivity and specificity were noted for TG/apoB (78.6% and 74.3%, resp.).

Multinomial logistic regression was used to adequately predict ($H = 203.12$, $df = 15$, $P < .0005$) a classification of cases into evaluated groups. This model classified evaluated cases into the SAP group with an accuracy of 87.9%, control group 82.6%, STEMI group with 78.4%, and USAP group with 57.6%. Pearson ($H = 337.53$, $df = 402$, $P = .99$) and Deviance ($H = 173.73$, $df = 402$, $P = 1$) confirmed that this model adequately fited the data. Obtained model explained about 82% of variation in evaluated groups. Likelihood ratio test showed that Lp(a), apoA-I, TG, and CRP were predictors significantly ($P < .0005$) contributing to the obtained model. In comparison to the control group, Lp(a) (OR = 1.27, 95% CI 1.11 to 1.45, $P = .001$) and apoA-I (OR = 8.295, CI 95% 1.22 to 56.35, $P = .03$) represented significant, while TG (OR = 0.23, 95% CI 0.04 to 1.52, $P = 0.13$), CRP (OR = 1.36, 95% CI 0.97 to 1.90, $P = .07$), and neopterin (OR = 1.05, 95% CI 0.96 to 1.15, $P = .26$) unsignificant predictors in the SAP group. In the USAP group, Lp(a) (OR = 1.29, 95% CI 1.12 to 1.48, $P < .0005$), TG (OR = 3.32, 95% CI 1.11 to 9.93, $P = .03$), apoA-I (OR = 0.004, 95% CI 0 to 0.37, $P = .02$), and CRP (OR = 1.56, 95% CI 1.11 to 2.18, $P = .01$) were significant predictors in comparison with the

Table 7: The results of ROC curves analysis of atherogenic indexes in patients with ischemic heart disease.

		AUC	SE	95%CI	Specificity	Sensitivity	Criterion
SAP	apoB/apoA[b]	0.717	0.062	0.594–0.820	78.2	64.1	>0.93
	LDL-c/apoB[d]	0.771	0.062	0.652–0.865	52.7	76.9	≥3.14
	LDL-c/HDL-c	0.657	0.067	0.531–0.769	65.5	86.2	>3.24
	Tc/HDL-c[d]	0.737	0.060	0.615–0.837	63.6	74.3	>5.08
	TG/apoB[a,c]	0.897	0.037	0.798–0.958	80.0	54.3	>1.19
	TG/HDL-c[d,e]	0.883	0.040	0.781–0.949	87.0	55.9	>0.88
USAP	apoB/apoA**	0.896	0.034	0.807–0.953	56.8	82.1	>1.08
	LDL-c/apoB	0.745	0.063	0.635–0.836	68.2	76.9	>3.14
	LDL-c/HDL-c	0.840	0.043	0.741–0.912	53.3	93.1	>3.40
	Tc/HDL-c**	0.873	0.038	0.780–0.937	73.3	71.4	>4.97
	TG/apoB	0.787	0.050	0.681–0.871	61.4	97.1	>1.85
	TG/HDL-c*	0.896	0.034	0.808–0.953	80.0	82.4	>1.54
STEMI	apoB/apoA[A,C]	0.879	0.040	0.778–0.945	81.0	41.0	>0.74
	LDL-c/apoB	0.784	0.061	0.668–0.874	76.2	59.0	≤3.33
	LDL-c/HDL-c	0.800	0.052	0.686–0.887	36.4	100.0	>3.76
	Tc/HDL-c[B]	0.889	0.038	0.790–0.952	45.5	77.1	>5.22
	TG/apoB	0.849	0.045	0.742–0.923	78.6	74.3	>1.49
	TG/HDL-c[A,D]	0.912	0.034	0.819–0.960	88.6	55.9	>0.88

[a]$P < .05$ versus apoB/apoA, LDL-c/apoB and Tc/HDL-c, [b]$P < .01$ versus LDL-c/HDL-c, [c]$P < .01$ versus LDL-c/HDL-c, [d]$P < .001$ versus LDL-c/HDL-c, [e]$P < .001$ versus Tc/HDL-c, *$P < .05$ versus LDL-c/apoB and LDL-c/HDL-c, **$P < .05$ versus LDL-c/HDL-c, [A]$P < .05$ versus LDL-c/apoB, [B]$P < .05$ versus LDL-c/HDL-c, [C]$P < .01$ versus LDL-c/HDL-c, [D]$P < .01$ versus TG/apoB.

control group. Finally, in AIM group, only Lp(a) (OR = 1.25, 95% CI 1.09 to 1.43, $P = .001$) and CRP (OR = 1.59, 95% CI 1.14 to 2.22, $P = .007$) represented significant predictors comparing to the control group.

4. Discussion

The results of this study clearly demonstrated that none of the studied standard and inflammatory markers showed any significant difference between statin-treated and non-statin-treated patients. However, among lipid markers significantly lower apoA-I values were observed in all statin-treated groups, as well as significantly higher apoB ones in STEMI(+) group in comparison with non-statin-treated patients. Since almost all our patients differed only in the statin treatment, observed differences indicate that the statins did not have the same effects on all lipid markers, which made them less sensitive markers.

In this multimarkers study, we showed that Lp(a) was the marker with the best clinical accuracy, being the marker with the largest AUC and the best sensitivity and specificity among other lipid markers, as well as atherogenic indexes in all patient groups. Of all inflammatory studied markers, hsCRP was found to show significantly higher AUC in comparison with all other inflammatory markers in patients with STEMI. In USAP patients, hsCRP also had the highest AUC although this gained significance only compared to TNF-α.

The comparison of hsCRP and Lp(a) ROC curves showed that AUC for Lp(a) was higher than for hsCRP in SAP and USAP patients, and a significant difference existed only in USAP patients. In the STEMI group, hsCRP AUC was higher than Lp(a) AUC, but the difference was not significant. These findings showed that Lp(a) would be a marker with better clinical accuracy, particularly in patients with USAP what was also confirmed by multinomial logistic regression.

Studies in the past [18] showed that the relationship between coronary artery disease and Lp(a) was weak and that Lp(a) may be a marker at only high levels. It could not be used for widespread initial screening because the benefits might be small. Others have observed that the free apo(a) had a better diagnostic test performance in atherosclerotic risk assessment than Lp(a) testing [19]. Elevated Lp(a) level is also considered to be the best single marker for the presence of ischemic cerebrovascular disease, and the increased portion of the smaller-molecular-weight apo(a) isoforms in patients and individuals with a sonography score >0 points toward an inherited predisposition for this disease [13]. Erbağci et al. [20] showed that for optimal cutoff values for Lp(a) of 22.6 and 9.8 mg/dL, the diagnostic values of 0.612 and 0.596 in men and women, respectively, with coronary heart disease with or without angiographically demonstrable lesion were found. Our results showed that Lp(a) had better AUC characteristics and may be more useful than other multimarkers in SAP and USAP patients especially in statin-treated ones.

It was also noted that optimal cutoff levels for hsCRP in women and men were found as 2.1 and 3.0 mg/L with the diagnostic values of 0.792 and 0.770, respectively. Contrary to these results, we found much higher diagnostic values of 0.843, 0.957, and 0.888 for Lp(a) in SAP, USAP, and STEMI patients, as well as higher diagnostic values of 0.859 and 0.946 for hsCRP in USAP and STEMI patients, and the

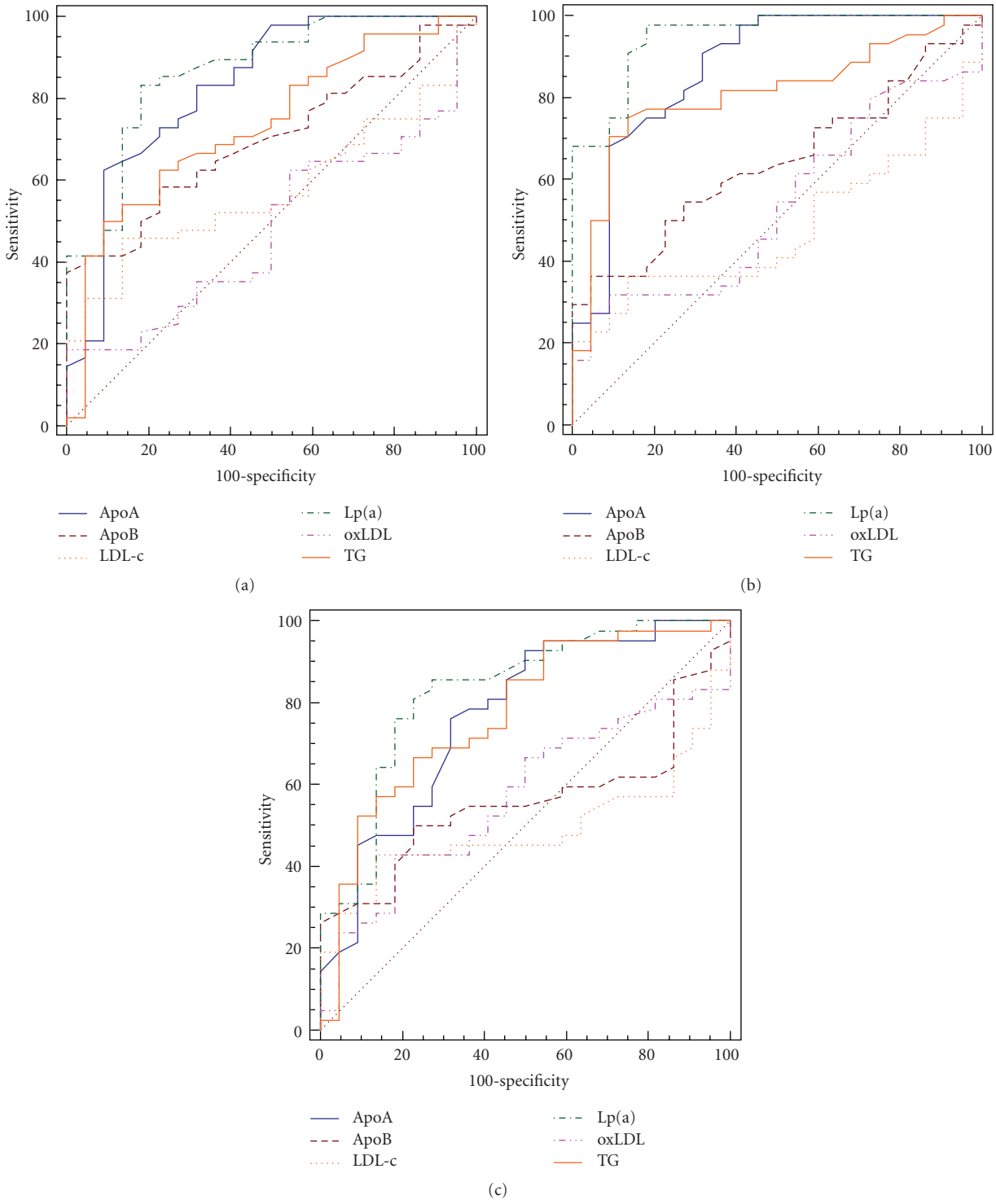

Figure 1: ROC curves of lipid markers: ApoA-I, ApoB, Lp(a), LDL-c, oxLDL, and TG in STEMI patients (a), USAP patients (b), and SAP patients (c).

difference between these two markers was significant in the USAP group. This finding is essential as, taking into account optimal cutoff level as >8.2 for Lp(a), Lp(a) is a better independent predictor than CRP in SAP and USAP patients on chronic treatment with statins. The Atherosclerosis Risk in Communities (ARIC) study showed that including some of the additional risk factors in the basic model containing only traditional risk factors might improve predictivity. So, they frequently found that the biggest contributors to the highest increase in AUC, outside the basic model, were albumin, fibrinogen, and Lp(a) [21]. Bennet et al. [22] noted that baseline Lp(a) levels had little or no correlation with

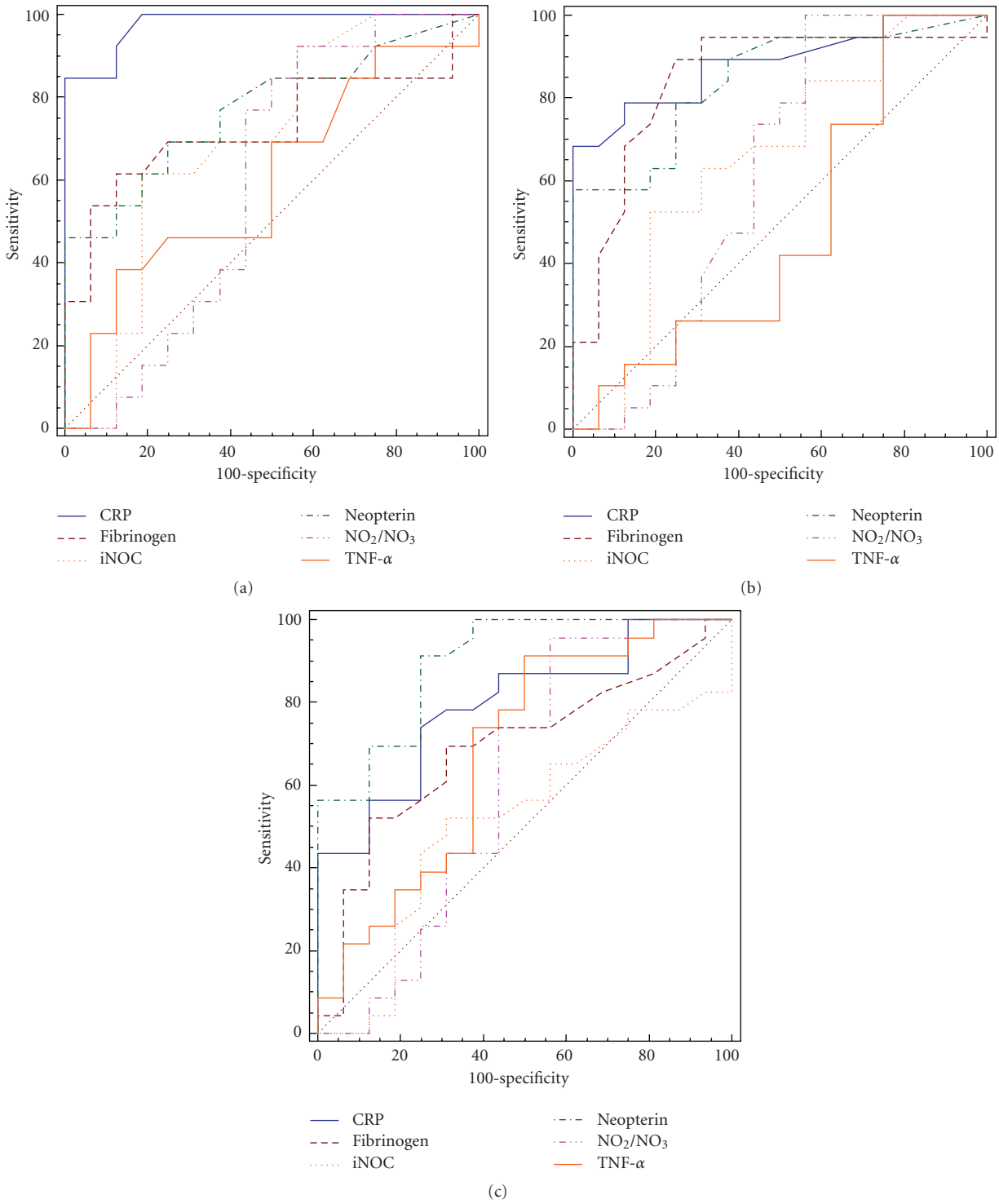

Figure 2: ROC curves of inflammatory markers: CRP, fibrinogen, iNOS, neopterin, NO_2/ NO_3, and TNF-α in STEMI patients (a), USAP patients (b), and SAP patients (c).

known cardiovascular risk factors including age, sex, total cholesterol level, and blood pressure. They concluded that the levels of Lp(a) were highly stable within individuals across the time and that there were independent, continuous associations between Lp(a) levels and a risk of coronary heart disease in a broad range of individuals. It seems that nontraditional risk factors could become more useful in predicting cardiovascular risk since clinical trials of statin therapy have demonstrated that baseline or treated LDL-c levels are only weakly associated with a net coronary angiographic change or cardiovascular events [23]. Statins reduce cardiovascular disease events and improve outcomes.

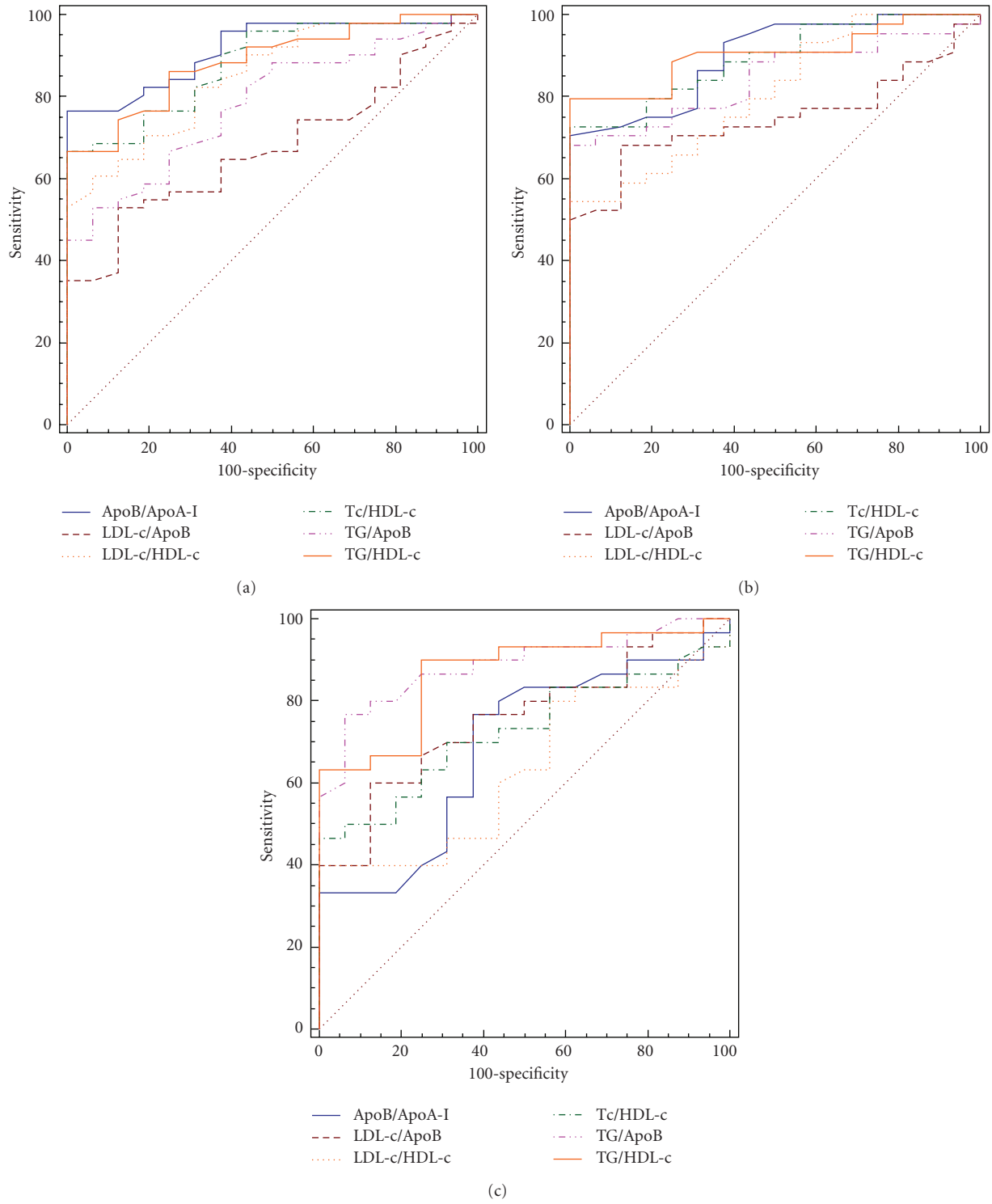

Figure 3: ROC curves of atherogenic indexes: ApoB/ApoA-I, LDL-c/ApoB, LDL-c/HDL-c, Tc/HDL-c, TG/ApoB, and TG/HDL-c in patients with STEMI (a), USAP (b), and SAP (c).

Large clinical trials indicate that statin-treated individuals have significantly smaller chance of cardiovascular disease, irirespective levels, and that the treatment is particularly effective among patients with high CRP levels. Beside the reduction of lipid and CRP levels [23], statins express additional effects resulting in the improvement of endothelial function, antiinflammatory and antiproliferative response, and the regression of human atherosclerotic lesions [23–25]. Contrary to previous findings, in patients with type IIa hypercholesterolemia, both atorvastatin and simvastatin,

significantly reduced Lp(a) levels but not apolipoprotein (a) fragment levels after six-week treatment [26]. In spite of these findings, we did not find any significant difference in Lp(a) concentration between the statin-treated and non-statin-treated patients, but we observed significantly lower apoA-I values in all patient groups, and significantly higher apoB in STEMI patients treated with statins.

In a prospective cohort study of more than 15000 healthy women aged 45 years or older, treated with aspirin and vitamin E and followed up over a 10-year period, it was noted that non-HDL-c and Tc/HDL-c were as good as, or better than, apolipoprotein fraction in the prediction of future cardiovascular events [27]. While these results support the use of standard lipid measurements, rather than apolipoproteins A-I and B in primary risk detection, in a randomized trial of lovastatin, the levels of apoB and the ratio of apoB/apoA-I were better predictors of future cardiovascular events than LDL-c, when participants were receiving the treatment [28]. On this basis, it has been suggested that the measurement of apoB could replace the current lipid status evaluation among patients taking statins [29]. Since our study showed that apoB significantly changed only in STEMI patients, it is not reliable for the evaluation ischemic heart disease patients taking statins. According to our results, it can be Lp(a).

In conclusion, considering our results, the best marker in assessing ischemic heart disease seemed to be CRP in STEMI, TG/apoB in SAP, and Lp(a) in USAP patients, respectively.

Statement

The study was approved by the Clinical Centre Niš Ethical Committee and all the subjects included in study provided written informed consent.

There was no possible conflict of interests considering acception of any funding or support by any organization gaining or loosing from the results of this study. There were no any other conflicting interests at all.

V. B. Djordjević desined the study and wrote the first draft of the manuscript. M. Deljanin-Ilić and L. Popović recruited the patients and wrote the clinical protocol. V. Ćosić and L. Zvezdanović took the blood samples, collected and undertook standard biochemical analyses. I. Stojanović determined nitrite/nitrate concentration in plasma. V. Ćosić, V. B Djordjević, P. Vlahović, and S. Kundalić undertook the determination of TNF-α, neopterin, iNOS, and oxLDL. V. B. Djordjević and P. Vlahović undertook the statistical analysis and managed the literature searches and analysis. All authors contributed to and have approved the final paper.

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Research Article

Association of Inflammatory and Oxidative Stress Markers with Metabolic Syndrome in Asian Indians in India

Veena S. Rao,[1] Radhika K. Nagaraj,[2] Sridhara Hebbagodi,[2] Natesha B. Kadarinarasimhiah,[1] and Vijay V. Kakkar[1,2]

[1] *Tata Proteomics and Coagulation Unit, Thrombosis Research Institute, Narayana Hrudayalaya, 258/A Bommasandra Industrial Area, Anekal Taluk, Bangalore 560099, India*
[2] *Emmanuel Kaye Bioinformatics Centre, Thrombosis Research Institute, Bangalore 560099, India*

Correspondence should be addressed to Veena S. Rao, veenasrao@triindia.org.in

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Metabolic syndrome (MetS) is a primary risk factor for cardiovascular disease and is associated with a proinflammatory state. Here, we assessed the contribution of inflammatory and oxidative stress markers towards prediction of MetS. A total of 2316 individuals were recruited in Phase I of the Indian Atherosclerosis Research Study (IARS). Modified ATPIII guidelines were used for classification of subjects with MetS. Among the inflammatory and oxidative stress markers studied, levels of hsCRP ($P < .0001$), Neopterin ($P = .036$), and oxLDL ($P < .0001$) were significantly higher among subjects with MetS. Among the markers we tested, oxLDL stood out as a robust predictor of MetS in the IARS population (OR 4.956 95% CI 2.504–9.810; $P < .0001$) followed by hsCRP (OR 1.324 95% CI 1.070–1.638; $P = .010$). In conclusion, oxLDL is a candidate predictor for MetS in the Asian Indian population.

1. Introduction

Metabolic syndrome (MetS) is a constellation of metabolic abnormalities that confer increased risk of cardiovascular disease (CVD) and diabetes mellitus (DM) [1]. The criteria for the metabolic syndrome have evolved since the original definition by the World Health Organization in 1998 [2], reflecting growing clinical evidence and analysis by a variety of consensus conferences and professional organizations [3, 4]. The major features of MetS include central obesity, hypertriglyceridemia, low HDL cholesterol, hyperglycemia, and hypertension.

The accepted and unifying hypothesis to describe the pathophysiology of metabolic syndrome is insulin resistance, caused by a defect in insulin action that is not fully understood. Free fatty acids (FFAs) are released in abundance from an expanded atherogenic adipose tissue mass leading to hyperinsulinemia [5]. Recent evidence indicates that a proinflammatory state is superimposed and contributes to the insulin resistance produced by excessive FFAs [6, 7]. Adipose tissue-derived macrophages may be the primary source of proinflammatory cytokines [8], and it has been reported that enhanced secretion of interleukin 6 (IL-6) and tumor necrosis factor (TNF-α) by adipocytes and monocyte-derived macrophages leads to more insulin resistance and lipolysis of adipose tissue triglyceride stores increasing circulating levels of FFAs [9]. IL-6 and other cytokines also enhance hepatic glucose production, VLDL production by the liver, and insulin resistance in the muscle. Cytokines and FFAs are also known to increase hepatic production of fibrinogen and adipocyte production of plasminogen activator inhibitor 1 (PAI-1) resulting in a prothrombotic state [5]. Higher levels of circulating cytokines stimulate the hepatic production of C-reactive protein (CRP) [10] and reduced production of the anti-inflammatory and insulin sensitizing cytokine, adiponectin has been associated with MetS [11]. Studies using cellular and animal models have described the role of oxidized LDL in the pathophysiology of incident MetS [12, 13]. This hypothesis is supported by population-based prospective human studies. The CARDIA study found increased incidence of MetS in individuals with higher circulating levels of ox-LDL with accumulation of

three of its risk factor constituents: obesity, hyperglycemia and hypertriglyceridemia [14]. Both oxidative stress and inflammatory stress associated with MetS have been found to initiate and propagate atherosclerotic macrovascular disease [15].

The multitude of risk factors amalgamating into MetS is increasing in Indians to reach epidemic proportions, which may present the common ground that enhances CVD risk in this ethnic group. The peculiar dyslipidemic obesity phenotype of Asian Indians with higher truncal and abdominal fat at lean body mass predisposes this ethnic group to the consequences of a proinflammatory and prothrombotic state [16]. Thus it is appealing to pursue a comprehensive CAD risk assessment with an understanding of the association of inflammation between MetS. Here, we assessed the association of inflammatory biomarkers with MetS and their independent ability to predict MetS in the studied population.

2. Materials and Methods

The Indian Atherosclerosis Research Study (IARS) is an ongoing, family-based epidemiological study investigating the genetic, conventional and environmental factors associated with CAD in Asian Indians living in the Indian subcontinent. Novel biomarker discovery is a specific aim of this study. For the study, families were enrolled from two Indian cities: Bangalore and Mumbai. Subjects were recruited through a proband who showed: (i) angiographic evidence of CAD (males $\leq$ 60 years and females $\leq$ 65 years at onset), (ii) a family history of CAD/CVD and, (iii) underwent therapeutic/surgical treatment at participating hospitals. Extended family members (both affected and unaffected) were enrolled, provided they met the recruitment age of 18 or above. Individuals with a history of any other major illness or concomitant infections were excluded from the study. Information pertaining to demographics; life style; anthropometrics; medical history of diabetes, hypertension and CAD; medication details, and a three-generation pedigree were recorded for each participant. Fasting sugar levels of >126 mg/dl were considered diabetic and, a systolic/diastolic blood pressure of >140/90 mm Hg was considered hypertensive. The study was conducted following the guidelines defined by the Indian Council of Medical Research and the Declaration of Helsinki for undertaking human clinical research. An institutional ethics committee approved the IARS and voluntary, signed informed consent was obtained from all participants.

Blood was collected by venipuncture after an overnight fast and processed using standardized protocols at each collection site. Blood was centrifuged for 10 min at 4°C, aliquoted in 0.5–1 mL volumes of sodium-citrate plasma, EDTA plasma and serum, and stored at −80°C within 2 h of venipuncture. For protein measurements, samples were thawed on ice and aliquoted into bar-coded Eppendorf tubes. The new sample aliquots were refrozen to −80°C until time of testing at which point they were thawed on ice again. Thus, samples from each collection site were exposed to identical numbers of freeze-thaw cycles for a given assay ensuring that sample handling does not contribute to any significant differences in protein levels.

2.1. Conventional Risk Factors. Serum total cholesterol and triglyceride were estimated by standard enzymatic analysis using reagents, standards and controls from Randox Laboratories Ltd. (Antrim, UK). The concentration of high-density lipoprotein (HDL)-cholesterol was estimated after precipitation of non-HDL fractions with a mixture of 2.4 mmol/L phosphotungstic acid and 39 mmol/L magnesium chloride. The concentration of low-density lipoprotein (LDL)-cholesterol was calculated using the Fridewald formula.

2.2. Measurement of Candidate Biomarkers. The candidate protein markers of vascular disease were measured in plasma (EDTA or citrate) or serum using solid-phase immunoassays and immunoturbidometric assays with commercially available reagents. Plasma interleukin (IL) 6 level and adiponectin was measured by enzyme-linked immunosorbent assa, (ELISA) from R & D Systems (Minneapolis, USA) and plasma hsCRP level was measured using the Roche latex Tina quant kit (Roche Diagnsotics, Basel, Switzerland). Levels of secretory phospholipase A2 (sPLA2) were determined using a sandwich immunometric assay (Cayman Corporation, Michigan, USA); myeloperoxidase using the sandwich enzyme immunoassay using kits from Mercodia (Uppasala, Sweden), neopterin using the enzyme immunoassay kit from IBL (Hamburg, Germany), oxLDL using the commercially available sandwich ELISA kit from Mercodia (Uppasala Sweden) and Leptin using the ELISA kit from Bio-Line (Bruxelles, Belgium). In the oxLDL ELISA, murine monoclonal antibody, mAb-4E6 was used as capture antibody and the second antibody was a peroxidase-conjugated anti-apolipoprotein B antibody recognizing ox-LDL bound to the solid phase.

2.3. Quality Control. Our quality control program included evaluation of intra-assay variations between duplicate sample measurements and inter-assay variations between independent repeat experiments. Sample measurements with coefficient of variation, CV > 15% were either retested or excluded from the dataset. The inter-assay CV for the commercial controls and NHP ranged from 4.9% to 7.0% for total cholesterol, 6.1% to 7.7% for triglyceride, 7.1% to 12.2% for HDL-cholesterol, 3.3% to 5.2%. The inter-assay CV for IL-6 relative to NHP was 4.3%; for plasma hsCRP 7.85%; secretory phospholipase A2 (sPLA2) was 5.37%; the inter-assay CV for NHP and the low and high controls provided by the manufacturer along with the kit ranged from 5.99 to 11.8% for neopterin and from 4.4 to 16% for oxLDL.

2.4. Statistical Analysis. SPSS ver. 17.0 statistical packages were used in the analysis. A P-value < .05 was considered statistically significant. The modified NCEP-ATPIII procedure was used to classify the IARS cohort into those with/without MetS based (Table 1). A cross-classification of MetS groups and CAD status was obtained.

Table 1: Metabolic syndrome: diagnostic criteria.

Modified ATPIII criteria	WHO criteria
(i) Abdominal density as defined by waist circumference cuts off ≥90 cm for men and ≥80 cm for women	(i) Fasting blood glucose level of ≥110 md/dl (6.1 mmol/L) or Diabetic
(ii) BMI cuts off at >23 kg/m^2	(ii) WHR of ≥0.89 in men, >0.81 in women and BMI > 23 kg/m^2
(iii) Serum TG ≥ 150 mg/dl (1.7 mmol/L)	(iii) Hypertriglyceridemia with TG > 150 mg/dl
(iv) HDL-C < 40 mg/dl in men (1.03 mmol/L) and < 50 mg/dl (1.29 mmol/L) in women	(iv) HDL-C <35 mg/dl in men and < 39 mg/dl in women
(v) Blood pressure ≥130/85	(v) High Blood Pressure >140/90 mm Hg or documented evidence of anti-hypertensive therapy
(vi) Fasting blood glucose level of ≥110 md/dl (6.1 mmol/L)	

Logarithmic transformation was performed to normalize skewed variables. Both continuous and categorical forms of the distribution of these variables were used in the analysis. The retransformed mean and standard error of the mean (SEM) are shown in tables. Differences between continuous variables were assessed using Student's *t*-test and those between categorical variables using the Chi-square test. Analysis of covariance was used to test for significance after adjusting for potential confounding variables. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated using conditional logistic regression analysis.

The Sensitivity, Specificity and Area under ROC were calculated for each model to determine its discriminative capacity. This method tests the difference between two models in their estimated probability to correctly classify "case subject" as "case subject", and "control subject" in to a control group. This reveals the prediction ability of the model. To assess the predictive value of the biomarkers, all variables were entered into a conditional logistic regression model (taking into account the gender and age matching), and cumulative AUC was calculated using the predictive probability values.

Multinomial Logistic Regression was used to identify the contribution of the selected biomarkers using odds ratio and associated confidence interval. The groups 1 and 2 are: no MetS, and MetS with no CAD and groups 3 and 4 are MetS groups within CAD group. Multinomial Logistic Regression is similar to binary logistic regression with no restriction on the number of dependent variables.

To identify biomarkers that discriminate between MetS and no MetS groups, and to identify the threshold levels of these biomarkers for correct classification, a two-group discriminate analysis was used. The linear discriminate function is an objective statistical method used to obtain predictive scores based on two or more variables from group discrimination. The discriminate score is based on the overall mean values of each of the variables. Individuals were classified into one group or the other depending on whether the score of an individual is lesser or greater than the predictive score.

3. Results

3.1. Clinical and Demographic Characteristics of IARS Participants. The 2005 modified National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III) criteria [3] were used to define MetS in the study population (Table 1). A total of 2316 individuals were categorized into two groups of subjects with or without MetS, based on the presence of a minimum of 3 out of 5 of the defining risk factors (Table 1). As expected, subjects with MetS had significantly higher systolic blood pressure (BP), diastolic BP, body mass index (BMI), circulating levels of total cholesterol, triglycerides and LDL cholesterol than those without MetS. Similarly, HDL levels were significantly lower in MetS subjects with significantly more diabetics & hypertensive. There was no difference in the number of smokers in the two groups canceling the oxidative and inflammatory stress due to smoking on either group of subjects (Table 2). As anticipated subjects with MetS had significantly higher levels of leptin and decreased levels of adiponectin (Table 2).

Novel biomarkers for inflammatory and oxidative stress were assayed. Individuals with MetS showed most significant increases in ox-LDL ($P < .0001$) & hsCRP ($P < .0001$), although sPLA2 ($P = .028$), IL-6 ($P = .039$) and neopterin ($P = .036$) levels were also significantly increased (Table 3).

3.2. Prediction of MetS Incidence Using Markers of Inflammation and Oxidative Stress. We used multinomial logistic regression analysis to identify biomarkers that classify subjects with risk of developing MetS. The study population was divided into 4 groups as follows: group 1—subjects without MetS (as defined by the modified ATP-III guidelines) and CAD; group 2—subjects with MetS and no CAD, group 3—subjects without MetS and CAD affected, and group 4—subjects with MetS and CAD affected. This study design could indicate biomarkers with a specific role in MetS by comparing groups 1 and 2 while CAD-specific markers would be obtained by comparing groups 1 and 3. Of the four inflammatory markers studied, only hsCRP identified subjects with risk of developing MetS (OR 1.492 95% CI 1.144–1.947; $P = .003$) (Table 4(a)). Among the oxidative stress markers, oxLDL best predicted MetS in our population (OR 6.031 95% CI 2.856–12.740; $P < .0001$). IL-6 emerged as a CAD-specific marker and neopterin seemed to be a marker for subjects with both MetS and CAD (Table 4(b)).

Having identified the key markers, we performed logistic regression analysis to assess the interaction between these markers. Using both forward and backward logistic regression analysis, we found that all the three markers qualified for the model indicating that they independently predict risk of developing MetS. The odds ratio for development of MetS was highest for oxLDL (OR 4.956 95% CI 2.504–9.810; $P < .0001$) compared to hsCRP (OR 1.324 95% CI 1.070–1.638; $P = .010$). In combination with oxLDL and hsCRP the odds of prediction of developing MetS was not significant for

Table 2: Clinical and demographic characteristics of the study subjects.

	Individuals with MetS ($n = 968$)	Individuals without MetS ($n = 1348$)	P-Value
CAD individuals (n) (%)	388 (40.1%)	385 (28.6%)	<.0001
Continuous variables—Mean ± SEM (retransformed mean)			
Age	51.689 ± 1.102	48.309 ± 1.209	.864
BMI (kg/M^2)	26.855 ± 0.383	25.036 ± 0.420	<.0001
Waist hip ratio	0.937 ± 0.006	0.918 ± 0.007	.372
Systolic blood pressure	129.326 ± 1.305	121.296 ± 1.432	<.0001
Diastolic blood pressure	84.838 ± 0.760	79.184 ± 0.834	<.0001
Total cholesterol mg/dL*	5.148 ± 0.021 (172.0869)	5.039 ± 0.023 (154.3156)	.004
Triglycerides mg/dL*	5.171 ± 0.036 (176.0908)	4.708 ± 0.039 (110.830)	<.0001
HDL-Cholesterol mg/dL*	3.591 ± 0.020 (36.2703)	3.762 ± 0.022 (43.0344)	<.0001
LDL-Cholesterol mg/dL*	4.550 ±0.034 (94.6324)	4.417 ± 0.037 (82.8473)	.051
Adiponectin ng/ml ($n = 766$)	8.308 ± 0.034 (4056.1924)	8.542 ± 0.038 (5125.5852)	.000
Leptin ng/ml ($n = 543$)	2.888 ± 0.070 (17.9573)	2.490 ± 0.090 (12.0612)	.001
Categorical Variables: n (%)			
Male	552 (57.0)	802 (59.5)	.226
Female	416 (43.0)	545 (40.5)	
Smoking			
Never	745 (77.3)	1076 (80.1)	.318
Ex-Smoker	138 (14.3)	164 (12.2)	
Occasional	11 (1.1)	19 (1.4)	
Current Smoker	70 (7.3)	85 (6.3)	
Hypertension	383 (39.6)	301 (22.4)	<.0001
Diabetes	313 (32.4)	196 (14.6)	<.0001
Statin	279 (29.3)	294 (22.0)	<.0001

* Log transformed variables represented as Mean ± Standard error (retransformed mean). P-value for categorical values was obtained using chi-square test and for continuous variables using for 2-sample t-test.

Table 3: Comparison of plasma levels of inflammatory and oxidative stress markers among subjects with and without metabolic syndrome.

Variable	Individuals with MetS	Individuals without MetS	P-value
	Mean ± SEM (retransformed mean)		
sPLA2 (pg/ml)	8.119 ± 0.046 (3357.6614)	7.963 ± 0.054 (2872.6780)	.028*
Interleukin 6 (pg/ml)	1.151 ± 0.064 (3.1613)	0.945 ± 0.076 (2.5728)	.039*
Myeloperoxidase (μg/L)	5.591 ± 0.042 (268.0034)	5.614 ± 0.049 (274.2390)	.723
Neopterin (nmol/L)	2.142 ± 0.038 (8.5164)	2.020 ± 0.044 (7.5383)	.036*
Fibrinogen (g/L)	1.468 ± 0.019 (4.3405)	1.431 ± 0.023 (4.1828)	.216
oxLDL (mU/L)	10.971 ± 0.027 (58162.72706)	10.789 ± 0.032 (48484.52724)	<.0001**
hsCRP (μg/ml)	1.024 ± 0.091 (2.7843)	0.515 ± 0.107 (1.6736)	<.0001**

neopterin ($P = .180$) (Figure 1). ROC curve analysis using the predictive probability for the above model evaluated the utility of assaying oxLDL, hsCRP and neopterin for risk prediction. When all 3 markers were used in combination, the AUC of the model was 0.71 ($P < .0001$) indicating that 71% of the study population could be classified correctly based on these markers (Figure 2).

3.3. Discriminant Analysis. To assess the percent contribution of the inflammatory and oxidative stress biomarkers to identify individuals with MetS we conducted linear discriminant analysis. As seen in Table 5(a), among all biomarkers studied, the structure correlation for ox-LDL is the highest (0.746) with a max contribution (37.99%) to a diagnosis of MetS. Based on the Discriminant scores obtained, we could classify 63.4% of the subjects correctly.

We obtained threshold levels for these biomarkers for the detection of MetS based on the Discriminant scores (Table 5(b)). Subjects with higher than the threshold value for ox-LDL have a 5-fold risk of developing MetS. Table 5(c) depicts the mean levels of these biomarkers obtained for the four groups based on the predictive classification.

Table 4

(a) Multinominal regression analysis: Odds ratio and 95% CI for inflammatory and oxidative stress markers for subjects with and without MetS

	OR (95% CI)	*P*-value
Inflammatory markers		
sPLA2	0.967 (0.64–1.455)	.874
Interleukin 6	1.298 (0.934–1.804)	.120
hsCRP	1.492 (1.144–1.947)	.003**
Fibrinogen	0.525 (0.168–1.634)	.266
Oxidative stress markers		
Myeloperoxidase	1.262 (0.810–1.969)	.304
Neopterin	2.934 (1.809–4.758)	<.0001**
oxLDL	6.031 (2.856–12.740)	<.0001**

Reference category: individuals without MetS and without CAD.

(b) Multinominal regression analysis: odds ratio and 95% CI for various inflammatory and oxidative stress markers for subjects with MetS and CAD

	OR (95% CI)	*P*-value
Inflammatory markers		
sPLA2	0.670 (0.435–1.030)	.068
Interleukin 6	4.716 (3.120–7.130)	<.0001**
hsCRP	0.967 (0.738–1.268)	.810
Fibrinogen	0.313 (0.102–0.964)	.043*
Oxidative stress markers		
Myeloperoxidase	1.842 (1.105–3.072)	.019*
Neopterin	6.209 (3.549–10.864)	<.0001**
oxLDL	2.992 (1.327–6.747)	.008**

Reference category: individuals without MetS and without CAD.

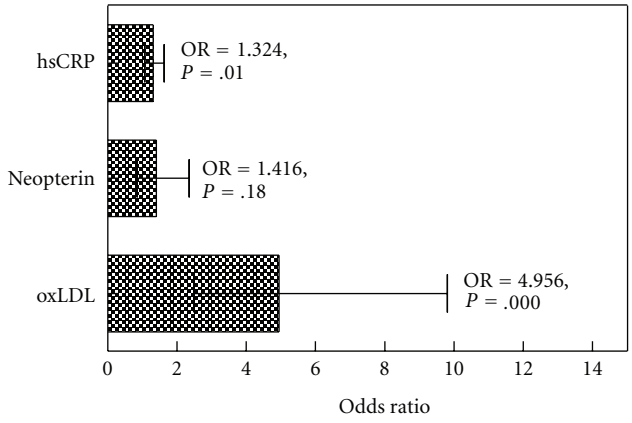

Figure 1: Error bar plot showing the odds ratio and 95% CI for hsCRP, neopterin and oxLDL towards risk of developing metabolic syndrome.

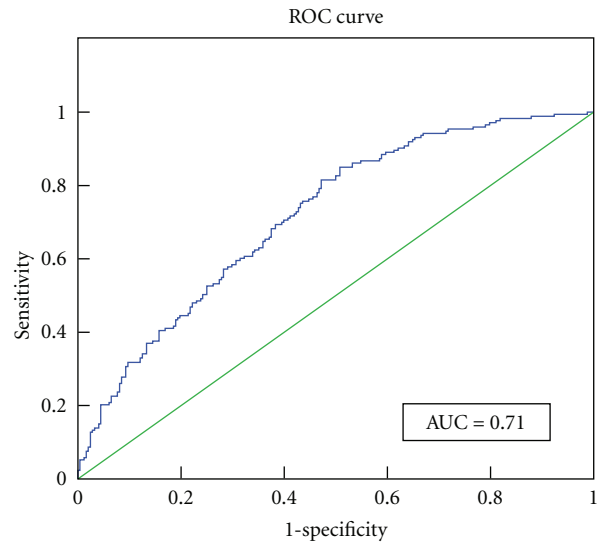

Figure 2: Area under the ROC curve for prediction of metabolic syndrome using a combination of three biomarkers viz oxLDL, hsCRP and neopterin

As expected, mean levels of these markers were significantly different between groups 1 (without MetS) and 2 (with MetS) indicating the importance of these 3 biomarkers in identifying subjects at risk of MetS.

4. Discussion

Increased oxidative stress and inflammatory biomarkers are known to play an important role in the initiation and progression of atherosclerotic vascular disease [17, 18], a major cause of morbidity and mortality in the world [19]. The presence of vascular risk factors led to the identification of a unique pathophysiological condition called metabolic

Table 5

(a) Discriminant analysis results

	Structure matrix	
	Function 1	Contribution (%)
Ln_oxLDL	.746	37.99
Ln_HsCRP	.639	27.87
Ln_Neopterin	.522	18.59
Ln_sPLA2	.411	11.53
Ln_Interleukin6	.242	3.99

(b) Threshold levels for the biomarkers obtained using Discriminant score

oxLDL	39922.68 mU/L
hsCRP	4.00 μg/ml
Neopterin	7.0596 nmol/L

63.4% of cases were correctly classified using discriminant analysis.

(c) Mean levels of biomarkers for discriminant groups

Variables	Discriminant group (see Table 5(d))	Mean ± S.E (retransformed mean)	P-value for group differences
hsCRP (μg/ml)	1	−0.066 ± 0.080 (0.9361)	<.0001**
	2	1.240 ± 0.102 (3.4556)	
	3	0.393 ± 0.128 (1.4814)	<.0001**
	4	1.219 ± 0.092 (3.3838)	
OxLDL (mU/L)	1	10.623 ± 0.022 (41068.6362)	<.0001**
	2	11.005 ± 0.028 (60174.2621)	
	3	10.682 ± 0.036 (43564.5924)	<.0001**
	4	11.106 ± 0.026 (66569.3806)	
Neopterin (nmol/L)	1	1.766 ± 0.035 (5.8474)	<.0001**
	2	2.231 ± 0.045 (9.3091)	
	3	1.896 ± 0.056 (6.6592)	<.0001**
	4	2.223 ± 0.040 (9.2349)	

(d) Discriminant groups

Actual group	Predicted group	Discriminant group
Unaffected	Unaffected	1
Unaffected	Affected	2
Affected	Unaffected	3
Affected	Affected	4

syndrome [1], now known to be characterized by elevated inflammatory markers and increased oxidative stress that can predict cardiovascular events such as the risk of myocardial infarction, stroke, and peripheral arterial disease [6, 20–22]. Importantly, the risk for Coronary Heart Disease (CHD) is markedly greater in obese individuals with MetS compared with those without it [23, 24]. However, the association and effect of MetS on plasma biomarkers of inflammation and oxidative stress is largely unknown. In this study we tested our hypothesis that markers of inflammation and oxidative stress can differentiate between individuals with or without MetS. We also studied the individual ability of these biomarkers in predicting MetS in an otherwise healthy person.

In this first report looking at the contribution of inflammatory markers to MetS in Asian Indians from India, we find that MetS enhances inflammatory and oxidative stress and found significantly higher circulating levels of oxLDL, hsCRP, sPLA2, IL-6 and neopterin in subjects with MetS compared to those without. These findings are

consistent with contemporary data [20–23]. To identify biomarkers with potential to diagnose MetS, we divided the study cohort into 4 groups: with/without MetS and those with/without CAD. This was done to identify novel plasma biomarkers specifically associated with MetS (Table 4(a)) and CAD (Table 4(b)). Multinomial logistic regression analysis of these groups of subjects revealed that among all the inflammatory biomarkers and markers of oxidative stress studied, hsCRP and oxLDL identified individuals with risk of developing MetS. IL-6 was the best marker of CAD risk and neopterin identified subjects with both CAD and MetS. Further analysis revealed that of the three markers only hsCRP and oxLDL identified individuals with MetS and oxLDL is the best predictor of MetS. This was despite the lack of large variations in oxLDL levels between CAD affected and unaffected groups in the study cohort.

OxLDL is known to be a potent inducer of (a) foam cells, that make a hallmark of atherosclerosis-fatty streaks, and (b) systemic inflammation alongside propagation of atherosclerosis [12, 14, 17, 25]. This may explain our robust findings with respect to this biomarker.

ROC curve analysis using predictive probability models revealed that a combination of oxLDL, hsCRP and neopterin identifies 71% of individuals with MetS. Discriminant analysis revealed the percent contribution of each of the biomarkers studied towards MetS. OxLDL contributed maximally and on the basis of the discriminant scores 63.4% of the cohort was classified accurately (Table 5(a)). Having obtained threshold values of ox-LDL for recognition of MetS using discriminant score, we found that subjects with higher values showed a 5-fold greater risk of developing MetS. The propensity of the LDL particles for oxidation decides the concentration of oxidized LDL in circulation. Small dense LDL contains fewer anti-oxidants, and therefore is more prone to oxidation [14]. MetS has been reported to be associated with a higher prevalence of small dense LDL [26] and among ethnic groups, Asian Indians are reported to show higher levels of small dense LDL particles [27, 28]. As found in our research, the fact that people with MetS are at an increased risk of macro vascular disease and death [29] appears to further explain the strong association of MetS with high concentrations of oxLDL. Our findings are concurrent with studies in various populations [14, 30–32], but this is the first report on Asian Indians from India.

In conclusion, our population data from families of Asian Indians with strong family histories of CAD shows that metabolic syndrome is associated with high inflammatory and oxidative stress. Diagnosis of MetS adds weight to the comprehensive CAD risk assessment of individuals. Further, novel biomarkers oxLDL, hsCRP and neopterin can be utilized to identify people with MetS in the Asian Indian population. OxLDL has been identified as the best predictive biomarker for MetS in Asian Indians and contributes maximally to the dysmetabolic state in comparison to all other biomarkers. Further research will validate its use to diagnose people with MetS compared to internationally defined criteria to ultimately yield a cost-effective method for MetS diagnosis and CAD risk stratification.

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Research Article

The Association of the Metabolic Syndrome with PAI-1 and t-PA Levels

Christopher S. Coffey,[1] Folkert W. Asselbergs,[2] Patricia R. Hebert,[3] Hans L. Hillege,[4] Qing Li,[5] Jason H. Moore,[6] and Wiek H. van Gilst[7]

[1] *Department of Biostatistics, College of Public Health, University of Iowa, Iowa City, IA 52242, USA*
[2] *Division of Heart and Lungs, Department of Cardiology, University Medical Center Utrecht, 3508 GA Utrecht, The Netherlands*
[3] *Charles E. Schmidt College of Biomedical Science, Florida Atlantic University, Boca Raton, FL 33431, USA*
[4] *Department of Cardiology, University Medical Center Groningen, University of Groningen, 9700 RB Groningen, The Netherlands*
[5] *Clinical Affairs and Medical Communications, ConvaTec, Inc., Skillman, NJ 08558, USA*
[6] *Departments of Genetics and Community and Family Medicine, Dartmouth Medical School, Lebanon, NH 03756, USA*
[7] *Department of Experimental Cardiology, University Medical Center Groningen, University of Groningen, 9700 RB Groningen, The Netherlands*

Correspondence should be addressed to Christopher S. Coffey, christopher-coffey@uiowa.edu

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Background. We used a random sample ($n = 2,495$) from the population-based Prevention of Renal and Vascular End-stage Disease (PREVEND) study population to examine the association of the metabolic syndrome (Met S) with plasminogen activator inhibitor type 1 (PAI-1) and tissue plasminogen activator (t-PA) antigen levels. *Results*. The overall prevalence of the Met S was 18%, was dependent on age and gender, and was positively associated with higher antigen levels of both PAI-1 and t-PA. These significant effects were maintained after adjustment for age, gender, BMI, elevated C-reactive protein, smoking status, urinary albumin excretion, and insulin levels. We found no significant interactions between the Met S and other covariates on PAI-1 and t-PA levels. *Conclusions*. Our study demonstrates that those with the Met S have significantly higher levels of PAI-1 and t-PA antigen, factors known to increase the risk of cardiovascular disease.

1. Introduction

The metabolic syndrome (Met S)—characterized by insulin resistance, abdominal obesity, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol, hypertension, and hyperglycemia—is becoming increasingly common. The Met S has been demonstrated to be a risk factor for cardiovascular disease [1] and type 2 diabetes [2]. Reported differences in the prevalence of the Met S among various ethnic groups [3] highlight the need to use population-based studies to examine descriptive epidemiology of the syndrome. Further, limited information is available on its association with plasminogen activator inhibitor type 1 (PAI-1) and tissue-type plasminogen activator (t-PA) antigen levels, both of which are biomarkers of fibrinolysis associated with an increased risk of cardiovascular disease [4–6].

We were also interested in how two more recently identified risk factors for cardiovascular disease—high-sensitivity (hs) C-reactive protein and microalbuminuria—might affect associations observed between the Met S and PAI-1 and t-PA antigen levels. High sensitivity C-reactive protein is a sensitive indicator of low-grade inflammation. C-reactive protein has been demonstrated to be an independent risk factor for cardiovascular disease [7, 8], and it is positively associated with both the Met S [9] and PAI-1 antigen levels [10]. Microalbuminuria, generally defined as a urinary albumin excretion of 30–300 mg per 24 hours [11], has been demonstrated to be an independent risk factor for

cardiovascular disease and mortality [12, 13]. Its appearance in the urine, in addition to renal pathology, indicates early vascular and endothelial damage in the vascular tree in general [14], and it is positively associated with both the Met S [15] and PAI-1 levels [16, 17].

While previous studies have generally reported positive associations between the Met S and PAI-1 and t-PA antigen levels [3, 18], few, if any, large population-based studies have controlled for C-reactive protein levels or albuminuria status or considered possible interactions between the Met S and other key variables on PAI-1 and t-PA antigen levels. The availability of a large population-based sample of subjects with detailed clinical data provided an opportunity to describe the Met S in a Dutch population and to examine the association of the Met S with PAI-1 and t-PA antigen levels, taking into account potential confounders and/or effect modifiers.

2. Materials and Methods

2.1. PREVEND Sample. This study is part of the ongoing Prevention of Renal and Vascular ENd-stage Disease (PREVEND) study, a large prospective study among inhabitants of the city of Groningen, the Netherlands. Details of the study protocol have been described elsewhere [12]. In brief, all inhabitants of the city between the ages of 28 and 75 (85,421 subjects) were asked to send in a morning urine sample and to fill out a short questionnaire on demographics and cardiovascular history. A total of 40,856 (47.8%) responded. From this group, 30,890 subjects had a urinary albumin concentration <10 mg/L and 9,996 subjects had a urinary albumin concentration of ≥10 mg/L in their morning urine sample. After exclusion of subjects with type 1 diabetes mellitus and women who were possibly pregnant, all subjects with a urinary albumin concentration ≥10 mg/L ($n = 7,768$) and a randomly selected control group with a urinary albumin concentration <10 mg/L ($n = 3,395$) were invited for further investigations in an outpatient clinic (total $n = 11,163$). The screening program in the outpatient clinic consisted of two visits. At the first visit, participants completed a self-administered questionnaire regarding demographics, cardiovascular and renal history, and drug use. At the second visit, blood was drawn after an overnight fast for determination of plasma glucose and serum creatinine. Finally, 8592 subjects completed the total screening program and form the baseline PREVEND cohort. From this cohort, we selected a random sample of 2,527 subjects representative of the entire PREVEND cohort. Of these, 32 subjects were missing a sufficient number of components of the Met S such that it could not be determined whether or not they had the Met S. Hence, this analysis is based on the subset of 2,495 subjects in the random sample with complete information regarding the Met S. The PREVEND study was approved by the local medical ethics committee and conducted in accordance with the guidelines of the declaration of Helsinki. All participants who attended the outpatient clinic gave written informed consent.

2.2. Measurements. Stored plasma samples collected at baseline were thawed and assayed by the Haemoprobe laboratory (Groningen, The Netherlands) using ELISA kits from Technoclone GmbH (Vienna, Austria). These assays measured both free and bound PAI-1 and t-PA antigen levels and have been described in detail elsewhere [19].

The metabolic syndrome was the primary independent variable of interest. For the purposes of the described analyses, the Met S was defined using the modified criteria of the National Cholesterol Education Program, Third Adult Treatment Panel [20]. Individuals with 3 or more of the following components were categorized as having the overall syndrome: (1) abdominal obesity (waist measurement >102 cm for men and >88 cm for women); (2) hypertriglyceridemia (>1.69 mmol/L (150 mg/dL)); (3) low HDL cholesterol (≤1.03 mmol/L (40 mg/dL) in men and ≤1.29 mmol/L (50 mg/dL) in women); (4) high blood pressure (≥130 mm Hg systolic and/or ≥85 mm Hg diastolic BP); (5) high fasting glucose (>5.5 mmol/L (100 mg/dL)). Waist and hip measurements were performed by several research nurses and medical students at the outpatient clinic for the PREVEND study. Waist circumference was measured on bare skin at the natural indentation between the 10th rib and iliac crest. Systolic and diastolic BPs were calculated as the average of the last two measurements taken at two clinic visits. After removal of shoes and heavy clothing, weight was measured to the nearest 0.5 kg using a Seca balance scale (Seca Vogel & Halke GmbH & Co, Hamburg, Germany). Height was measured to the nearest 0.5 cm. Blood samples were drawn after an overnight fast. Glucose was determined by Kodak Ektachem dry chemistry (Eastman Kodak, Rochester, NY, USA), an automatic enzymatic method. Triglycerides were measured enzymatically. A commercially available assay system was used to assess HDL cholesterol (Abbott Inc., Abbott Park, IL, USA). High-sensitivity C-reactive protein was determined by nephelometry with a threshold of 0.175 mg/L and intra- and interassay coefficients of less than 4.4% and 5.7%, respectively (BNIN, Dade Behring, Marburg, Germany).

Age was subdivided into categories of <40, 40–60, and >60 years of age. Smoking was defined as a current smoker or cessation of smoking less than a year before the study. BMI was subdivided into categories of <25, 25–30 (overweight), and >30 (obese) kg/m^2. Elevated C-reactive protein was defined as a level >3 mg/L. Urinary albumin excretion (UAE) was measured as the mean of two 24-hour urine collections. Participants were categorized as having normoalbuminuria (<30 mg/24 h), microalbuminuria (30–300 mg/24 h), or macroalbuminuria (>300 mg/24 hr). Insulin levels were subdivided into categories of <8, 8–12, and >12 μU/mL. Diabetes was defined as a fasting plasma glucose level >7.0 mmol/L, a nonfasting plasma glucose level >11.1 mmol/L, or the use of glucose-lowering medication.

2.3. Statistical Analyses. We initially described the prevalence of the Met S by gender and age. Logarithmic transformations were used to normalize the distributions of PAI-1 and t-PA levels. Although reported P values are for comparisons of the log-transformed means, we report medians and interquartile

Table 1: Characteristics of the study population by presence or absence of the metabolic syndrome.

	Metabolic syndrome		P value
	Present ($N = 440$)	Absent ($N = 2055$)	
Age at baseline			<.0001[1]
<40 yrs (%)	8.9	91.1	
40–60 yrs (%)	17.5	82.5	
>60 yrs (%)	26.9	70.1	
Gender			<.0001[1]
Male (%)	20.9	79.1	
Female (%)	14.8	85.2	
BMI			<.0001[1]
<25 kg/m^2 (%)	3.7	96.4	
25–30 kg/m^2 (%)	22.7	77.3	
>30 kg/m^2 (%)	53.1	47.0	
Smoker			.506[1]
Yes (%)	18.4	81.6	
No (%)	17.3	82.7	
C-reactive protein			<.0001[1]
≥3.0 mg/L (%)	33.0	67.0	
<3.0 mg/L (%)	13.4	86.6	
Urinary albumin excretion			<.0001[1]
<30 mg/24 h (%)	15.7	84.3	
30–300 mg/24 h (%)	44.9	55.2	
>300 mg/24 h (%)	80.0	20.0	
Insulin levels			<.0001[1]
<8 μU/mL (%)	5.1	94.9	
8–12 μU/mL (%)	18.6	81.4	
>12 μU/mL (%)	45.3	54.7	
PAI-1 antigen (ng/mL) (median (IQR))	126.7 (81.4, 194.2)	57.3 (35.5, 99.7)	<.0001[2]
t-PA antigen (ng/mL) (median (IQR))	3.9 (2.8, 6.0)	2.9 (2.2, 4.2)	<.0001[2]

BMI: body mass index; PAI-1: plasminogen activator inhibitor type 1; t-PA: tissue-type plasminogen activator; IQR: interquartile range.
[1]Chi-square test, [2]T-test based on log values.

ranges (IQR) for summary statistics since such comparisons are more similar to a comparison of medians than means in the original metric. Univariate linear models were used to examine the individual effects of the Met S, age at baseline, gender, BMI, smoking status, elevated C-reactive protein, albuminuria status, and insulin levels with PAI-1 and t-PA levels. We also used multivariable linear regression models with backwards selection and split-sample validation to explore whether the association of the Met S with PAI-1 and t-PA levels held up after adjusting for the other variables. The full model of interest included all factors as well as all possible two-way interactions between each factor and the Met S. At each step, the interaction term with the highest P value (provided it was >.10) was removed from the model and the model was refit with all remaining terms. This process was continued until either no interaction terms remained or all remaining interactions were significant.

Since it is well known that models obtained using such data-driven methods are prone to increased type 1 errors [21], proper validation of such models is crucial. For this analysis, model validation was performed using the split-sample validation techniques as described in Muller and Fetterman [22]. Essentially, this involves splitting the analysis dataset into a training and hold-out sample. The shrinkage statistic is defined as the difference between the R^2 value in the final model obtained using the training sample and the cross-validity coefficient calculated from the holdout sample. Small values of relative shrinkage imply better generalizability of the final model. All statistical analyses were performed using SAS version 9.1.

3. Results and Discussion

3.1. Description of Met S in the Population. The average age of the study population was 48 years and 53% were women. The overall prevalence of the Met S in the population was 18% and rose with age in both genders. Although the overall prevalence was significantly higher in men than in women (21% versus 15%, $P < .01$), the prevalence was dependent on age and gender. As shown in Figure 1, in subjects less than 40 years, the prevalence was significantly higher in men (13% versus 6%, $P < .01$). In contrast, there was no significant

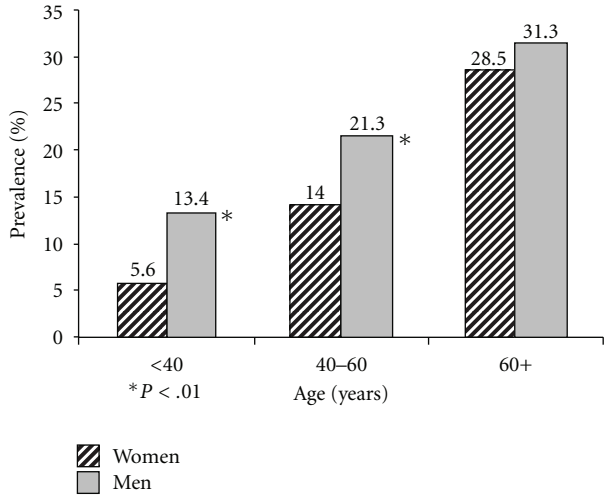

Figure 1: Prevalence of the metabolic syndrome by gender and age.

difference in the prevalence for men and women over 60 years (31% versus 29%, $P = .46$).

Table 1 shows the characteristics of the study population by the presence or absence of the Met S. The Met S was positively associated with all covariates except smoking. We also examined the frequency of type 2 diabetes by the presence or absence of the Met S. The presence of diabetes was highly correlated with the Met S (75% of diabetics had the Met S versus 16% of nondiabetics, $P < .001$).

3.2. Association of Met S and Other Covariates with PAI-1 Antigen Levels. The results from the univariate models indicate that an older age at baseline, male gender, higher BMI, smoking, elevated hs C-reactive protein, elevated UAE, and elevated insulin levels were positively associated with PAI-1 antigen levels (Table 2). In addition, PAI-1 levels were significantly higher among those with the Met S as opposed to those without the Met S (median (IQR): 126 (81, 194) ng/ml versus 59 (36, 103 ng/ml), $P < .001$).

From the backwards selection algorithm using the training sample, there were no significant interactions. Cross-validation produced a negative shrinkage statistic which implies a reasonable fit. The results from the final multivariable model applied to the combined datasets are shown in Table 2. The previously observed associations between PAI-1 levels and both UAE and hsCRP went away after adjustment for the other variables. All other variables, including the Met S, continued to have a significant relationship with PAI-1 levels after adjustment.

3.3. Association of Met S and Other Covariates with t-PA Antigen Levels. The results from the univariate models (Table 3) indicate that increasing age at baseline, male gender, higher BMI, not smoking, elevated C-reactive protein, and elevated insulin levels were positively associated with t-PA levels. Further, median t-PA levels were significantly higher among those with the Met S as opposed to those without the Met S (median (IQR): 3.9 (2.8, 6.0) ng/ml versus 2.9 (2.2, 4.2) ng/ml, $P < .001$).

From the backwards selection algorithm using the training sample, as before, there were no significant interactions. Furthermore, cross-validation produced a near zero shrinkage statistic which implies a reasonable fit. The results from the final multivariable model applied to the combined datasets are shown in Table 3. The previously observed relationships between t-PA levels and BMI, smoking status, and C-reactive protein disappear after adjustment. After adjustment for all other covariates, the Met S, increasing age at baseline, male gender, and elevated insulin levels continued to have a significant effect on t-PA levels.

3.4. Prevalence of Met S. The overall prevalence rate of 18% in our Dutch population and the greater prevalence in men as compared to women are similar to findings reported for other adult European populations. Hu et al. [23] reported an overall prevalence of the Met S of 15% in nondiabetic adult Europeans based on 11 study cohorts. If those with type 2 diabetes are removed from our Dutch population, the prevalence of the Met S is reduced to 16%, similar to that found in the study by Hu and others.

3.5. Association of Met S with PAI-1 and t-PA Antigen Levels. There remained a significant positive association between the Met S and both PAI-1 and t-PA antigen levels after adjustment for the covariates of interest. These associations also remained when participants with type 2 diabetes were excluded from the models (results not shown). Further, after adjustment all other covariates with the exception of UAE continued to have a significant effect on PAI-1 levels, whereas, in addition to the Met S, only age, gender, and insulin levels had significant effects on t-PA levels.

Our findings of an association between the Met S and PAI-1 and t-PA antigen levels are generally consistent with the findings of previously conducted studies [3, 18]. Anand et al. [3] also demonstrated a reduction in clot lysis time after induced ischemia by venous cuff occlusion, further supporting impaired fibrinolytic function in those with the Met S. Our study extends previous findings of an association between the Met S and PAI-1 and t-PA antigen levels by adjusting for a number of covariates and by exploring potential interactions between the Met S and these covariates.

The link between PAI-1 and Met S is complex, and several mechanisms could contribute to the elevated PAI-1 concentrations in Met S patients [24]. One of the proposed mechanisms is the contribution of the rennin-angiotensin system on PAI-1 synthesis. Angiotensin-converting enzyme inhibition has been shown to reduce PAI-1 levels in obese patients [25], and angiotensin II promotes PAI-1 excretion in human adipocytes [26]. In addition, the expression of rennin-angiotensin system genes is regulated differently in obese subjects [27], and a combination of variants in rennin-angiotensin system genes was associated with the Met S. Interestingly, our group previously found that polymorphisms in genes from the rennin, angiotensin, and

Table 2: PAI-1 antigen levels (ng/mL) for the association of the metabolic syndrome and other covariates.

	Median (IQR)	Univariate models	Multivariable model
Age at baseline		<0.001	<0.001
<40 yrs	51 (32, 89)		
40–60 yrs	72 (42, 123)		
>60 yrs	80 (47, 138)		
Gender		<0.001	<0.001
Male	75 (46, 132)		
Female	59 (34, 107)		
BMI		<0.001	<0.001
<25 kg/m^2 (%)	49 (31, 79)		
25–30 kg/m^2 (%)	80 (49, 143)		
>30 kg/m^2 (%)	115 (71, 189)		
Smoking status		<0.001	<0.001
Current/former	70 (43, 126)		
Nonsmokers	64 (37, 114)		
C-reactive protein		<0.001	0.633
≥3.0 mg/L	84 (45, 152)		
<3.0 mg/L	63 (38, 109)		
Urinary albumin excretion		<0.001	0.303
<30 mg/24 h (%)	66 (39, 116)		
30–300 mg/24 h (%)	80 (48, 154)		
>300 mg/24 h (%)	104 (68, 134)		
Insulin levels		<0.001	<0.001
<8 μU/mL (%)	52 (34, 82)		
8–12 μU/mL (%)	77 (44, 128)		
>12 μU/mL (%)	114 (71, 181)		
Metabolic syndrome		<0.001	<0.001
Present	126 (81, 194)		
Absent	59 (36, 103)		

PAI-1 levels were missing in 29 (1.2%) of subjects.

bradykinin system were related to PAI-1 and t-PA levels and this relationship was dependent on body size as assessed by body mass index and waist-to-hip ratio [28, 29]. Further research is needed to further elucidate the underlying mechanisms responsible for the observed relation between PAI-1, t-PA, and the Met S.

The positive associations of PAI-1 with age, male gender, BMI, smoking, and insulin levels as well as the positive associations of t-PA with age, male gender, and insulin levels have been reported elsewhere [10, 30–35]. The lack of association between C-reactive protein with PAI-1 and t-PA levels is interesting and may suggest that the elevation of PAI-1 may be due to production of PAI-1 by adipose tissue and less as a response to changes in inflammatory status. This lack of association has been reported previously [36]. The lack of association of UAE with PAI-1 levels and of smoking and obesity with t-PA levels was unanticipated since associations have been previously reported [16, 17, 31, 37].

3.6. Strengths and Limitations. Strengths of our research include the fact that the sample used for analysis was population-based and therefore more representative of the general adult population than would be other population groups. Further, our sample size was relatively large and we had data available on a large number of variables including hs C-reactive protein and UAE, novel risk factors for cardiovascular disease associated with both the Met S and PAI-1 antigen levels.

There were also several limitations of our study. As our study was cross-sectional, although the associations between the Met S and PAI-1 and t-PA antigen levels remained after control for other covariates, we are unable to evaluate causality. One possibility, consistent with the hypothesis that the increase in cardiovascular disease among individuals with the Met S occurs at least in part through thrombotic mechanisms, is that the Met S causes elevations of PAI-1 and t-PA levels. Alternatively, it has been hypothesized that PAI-1 levels may play a causal role in the development of obesity and the Met S [24]. This is a promising hypothesis as PAI-1 was recently demonstrated to predict the development of type 2 diabetes in the prospective Insulinpagebreak Resistance Atherosclerosis Study (IRAS) [38]. Hence, the choice of PAI-1 and t-PA antigen levels as the endpoints for the study was somewhat arbitrary since, although the

Table 3: t-PA antigen levels (ng/mL) for the association of the metabolic syndrome and other covariates.

	Median (IQR)	Univariate models	Multivariable model
Age at baseline		<0.001	<0.001
<40 yrs	2.7 (1.9, 3.5)		
40–60 yrs	3.1 (2.3, 4.4)		
>60 yrs	3.7 (2.7, 5.7)		
Gender		<0.001	<0.001
Male	3.3 (2.4, 4.9)		
Female	2.8 (2.1, 4.0)		
BMI		<0.001	0.153
<25 kg/m^2 (%)	2.7 (2.1, 3.7)		
25–30 kg/m^2 (%)	3.4 (2.4, 5.1)		
>30 kg/m^2 (%)	3.6 (2.6, 4.9)		
Smoking status		0.042	0.391
Current/former	3.0 (2.2, 4.4)		
Nonsmokers	3.1 (2.3, 4.5)		
C-reactive protein		0.001	0.418
≥3.0 mg/L	3.3 (2.3, 4.9)		
<3.0 mg/L	3.0 (2.2, 4.3)		
Urinary albumin excretion		0.10	0.383
<30 mg/24 h (%)	3.0 (2.2, 4.4)		
30–300 mg/24 h (%)	3.3 (2.4, 5.0)		
>300 mg/24 h (%)	4.6 (4.2, 6.3)		
Insulin levels		<0.001	<0.001
<8 μU/mL (%)	2.8 (2.1, 3.8)		
8–12 μU/mL (%)	3.2 (2.3, 4.7)		
>12 μU/mL (%)	3.6 (2.6, 5.7)		
Metabolic syndrome		<0.001	0.002
Present	3.9 (2.8, 6.0)		
Absent	2.9 (2.2, 4.2)		

t-PA levels were missing in 26 (1.0%) of subjects.

Met S may influence PAI-1 and t-PA levels, PAI-1 has also been hypothesized to causally influence obesity and the Met S. It would also be of interest to know whether the subjects were on statin therapy, receiving other lipid lowering drugs, or receiving ACE inhibitors or ARBs. Unfortunately, the PREVEND database does not include detailed information regarding the use of statins or ARBs. Only a small percentage of subjects were found to be receiving any ACE inhibitor (4.4%) or any lipid lowering medication (5.0%), which suggests that this would have a minimal impact on the overall conclusions of the study. Finally, due to the size of the study and the curse of dimensionality, we did not explore interactions among the covariates of interest nor did we explore interactions higher than second order among the covariates and the Met S. Hence, we may have missed an important higher-order interaction among the variables of interest.

4. Conclusions

In conclusion, the present study demonstrates that those with the Met S have higher levels of PAI-1 and t-PA antigen, factors known to increase the risk of cardiovascular disease. However, prospective studies are needed to establish causality. To demonstrate that the Met S causes increases in PAI-1 and t-PA antigen levels that result in cardiovascular disease requires monitoring changes in these fibrinolytic variables, in addition to the development of clinical events,

in subjects with and without the Met S. Alternatively, to determine if PAI-1 is an underlying cause of the Met S would require examining the associations of baseline levels of PAI-1 with incident cases of the Met S. After causality is established, clinical trials will be needed to investigate whether lifestyle or pharmacologic interventions targeted to improve fibrinolytic function reduce cardiovascular events in subjects with the Met S or, alternatively, are effective in preventing the Met S.

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