

The Relationship between Hyperinsulinemia, Hypertension and Progressive Renal Disease

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Abstract. The incidence of end-stage renal disease (ESRD) has risen dramatically in the past decade, mainly due to the increasing prevalence of diabetes mellitus, and both impaired glucose tolerance and hypertension are important contributors to rising rates of ESRD. Obesity, especially the visceral type, is associated with peripheral resistance to insulin actions and hyperinsulinemia, which predisposes to development of diabetes. A common genetic predisposition to insulin resistance and hypertension and the coexistence of these two disorders predisposes to premature atherosclerosis. A constellation of metabolic and cardiovascular derangements, which also includes dyslipidemia, dysglycemia, endothelial dysfunction, fibrinolytic and inflammatory abnormalities, left ventricular hypertrophy, microalbuminuria, and increased oxidative stress, is referred to as the cardiometabolic syndrome. The components of this syndrome, individually and interdependently, substantially

increase the risk of renal disease, cardiovascular disease (CVD) and mortality. Similar findings and cardiorenal risk factors can occur in subjects with android obesity without excess body weight.

Recently, microalbuminuria has been gaining momentum as a component and marker for the cardiometabolic syndrome, in addition to being an early marker for progressive renal disease in patients with this syndrome or in those with diabetes. Furthermore, it is now established as an independent predictor of CVD and CVD mortality. This review examines the relationship between insulin resistance/hyperinsulinemia and hypertension in the context of cardiometabolic syndrome, progressive renal disease and accelerated CVD. The importance of microalbuminuria as an early marker for the cardiometabolic syndrome is also discussed in this review.

The cardiometabolic syndrome is currently estimated to affect 24% of the adult population (1). In addition to diabetes, which is the leading cause of end-stage renal disease (ESRD) in westernized societies, other metabolic and cardiovascular abnormalities associated with the cardiometabolic syndrome contribute to progressive renal disease, cardiovascular disease (CVD), and CVD mortality (Table 1) (2). Of particular importance are hypertension and insulin resistance/hyperinsulinemia, which frequently coexist and contribute substantially to CVD and ESRD (3–10). There appears to be a common genetic predisposition to both insulin resistance and hypertension. Furthermore, insulin resistance/hyperinsulinemia contributes to the elevated BP through several mechanisms, one of which is tissue angiotensin II (AngII) and aldosterone actions, leading to vascular resistance to the effects of insulin (Figure 1) (6,7,9–

14). Other mechanisms include enhanced sympathetic nervous system (SNS) activity, dyslipidemia, atherosclerosis, enhanced oxidative stress, hypercoagulability, left ventricular hypertrophy (LVH), renal functional and structural changes and glomerulosclerosis, progressive renal disease, and eventually ESRD (3–5, 15–21) (Figure 2). Microalbuminuria, in addition to being an early marker for nephropathy, is an established marker for increased CVD morbidity and mortality in patients with hyperinsulinemia and hypertension (22). Furthermore, it is increasingly recognized as a marker for the cardiometabolic syndrome (23–26).

Epidemiology of Insulin Resistance, Associated Cardiometabolic Derangements and Progressive Renal Disease

There has been an alarming growth of the prevalence of chronic kidney disease (CKD) (Figure 3) and ESRD (Figures 4, 5, and 6) over the last decade, in concert with a striking increase in the burden of diabetes, the leading cause of ESRD (Figures 5 and 6). Additionally, increasing rates of obesity (Figure 4) and associated insulin resistance and hypertension (Figures 5 and 6) are major contributors to ESRD (2). The costs attributed to ESRD have risen from 4.8% a decade ago to 6.3% of all Medicare

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Table 1. Cardiovascular and renal risk factors associated with the cardiometabolic syndrome

1. Hypertension
2. Central obesity
3. Hyperinsulinemia/insulin resistance
4. Endothelial dysfunction
5. Microalbuminuria
6. Low HDL-cholesterol levels
7. High triglycerides levels
8. Small, dense LDL cholesterol particles
9. Increased Apo-lipoprotein B particles
10. Increased fibrinogen levels
11. Increased plasma activator inhibitor –1 levels
12. Increased C-reactive protein and other inflammatory markers
13. Reduced vascular compliance
14. Absent nocturnal dipping of BP and pulse
15. Salt sensitivity
16. Left ventricular hypertrophy
17. Hyperuricemia
18. Increased reactive oxygen species

expenditures, consuming a total of \$22.83 billion currently (2). ESRD treatment is initiated earlier, reflecting in part, an increasing burden of associated comorbidities, including diabetes and other cardiometabolic abnormalities (2), with increasing levels of inflammatory markers, correlating with a decline in kidney function (2). Furthermore, the USRDS 15th annual report projects that by the year 2030, the ESRD population will increase by 460,000 new cases annually and the prevalent population will reach 2.24 million, with two thirds of these numbers having diabetes as the primary cause of renal disease (2).

In parallel with the growth in kidney disease, the prevalence of obesity/insulin resistance and impaired glucose metabolism has been increasing rapidly, currently meeting epidemic proportions (1,27). The prevalence of diagnosed and undiagnosed diabetes combined, which constitute a major portion of the insulin-resistant population is estimated at 8% of adult population (21,27). An even greater number of patients have the cardiometabolic syndrome (24%) (1). Furthermore, obesity appears to be one of the most important risk factors for ESRD and is of increasing significance as its prevalence rises in this country.

This alarming growth of cardiometabolic abnormalities and resultant renal disease emphasizes the importance of prevention and control of these derangements (2,9). Indeed, the increasing awareness and improvement of control of these risk factors, although still suboptimal, may be the reason behind the slowing trend of ESRD incident rates between 1998 and 2001 (2).

Visceral Obesity

Visceral obesity triggers a litany of maladaptive cardiovascular, renal, metabolic, prothrombotic and inflammatory responses, some of which form the “cardio-metabolic syndrome”

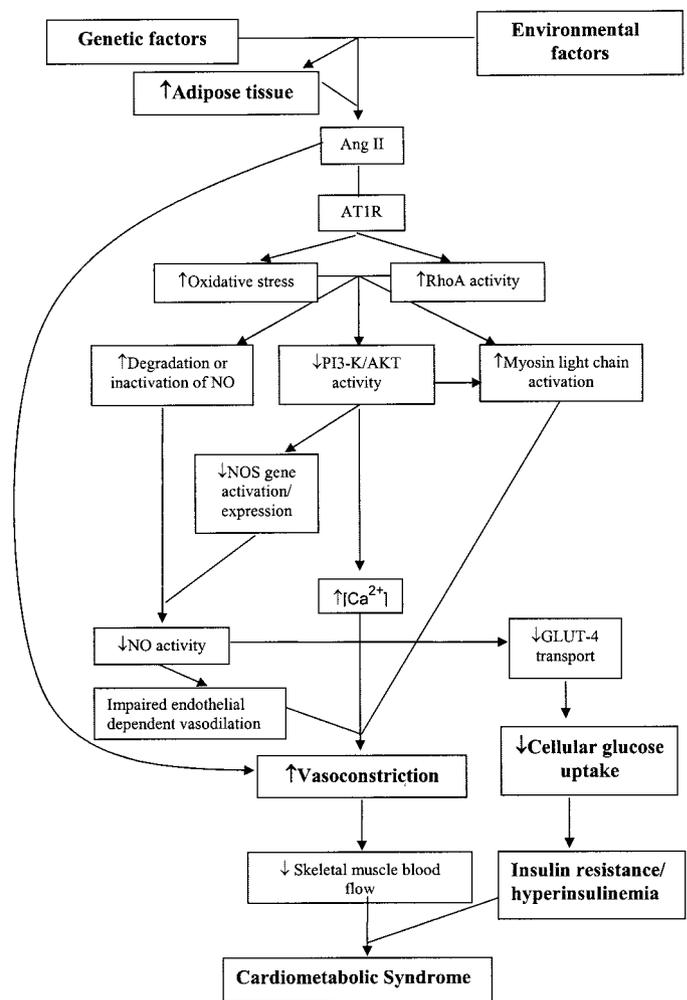


Figure 1. Inhibitory effects of AngII on insulin signaling contributing to the cardiometabolic syndrome.

(Table 1; Figure 2) (3–5,14). These responses, including hyperinsulinemia/insulin resistance, dysglycemia, dyslipidemia, hyperleptinemia, hypercortisolemia, altered vascular structure and function, enhanced SNS and renin-angiotensin-aldosterone system (RAAS) activities, hypercoagulability, and an altered Kallikrein-Kinin system, individually and interdependently, contribute to progressive renal disease/ESRD, hypertension, and other CVD morbidity and mortality (Figure 7) (3–5,16). In fact, the parallel increase in the prevalence of obesity and ESRD suggests that obesity is one of the most important precursors of ESRD (4) (Figure 4).

Insulin resistance and hyperinsulinemia in those with visceral obesity relate to the metabolic characteristics of the fat that is present in the omental and para-intestinal regions (13,14). Compared with peripheral fat cells, visceral fat is more resistant to the metabolic effects of insulin and more sensitive to lipolytic hormones (13). Consequently, increased release of free fatty acids (FFA) into the portal system provides increased substrate for hepatic triglyceride synthesis and may impair first pass metabolism of INS (13,14).

Furthermore, data from the NHANES survey show a re-

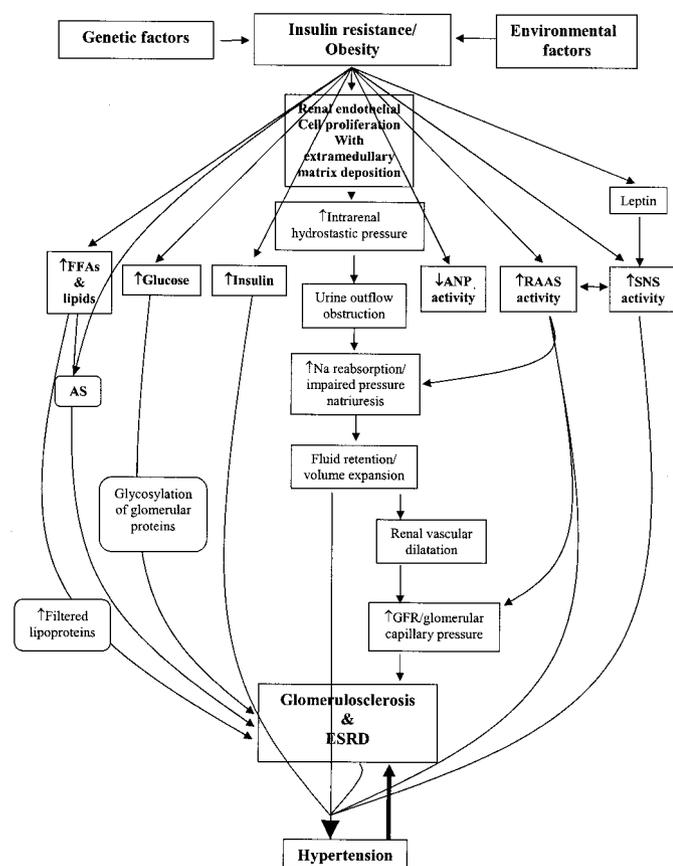


Figure 2. Mechanisms responsible for hypertension and progressive renal failure in the insulin-resistant state. Structural and functional alterations in the kidneys collaborate, resulting in activation of the sympathetic nervous system (SNS) and the renin-angiotensin aldosterone system (RAAS) and leading to fluid retention. Once ESRD develops, it perpetuates hypertension.

markable and linear relationship between rise in body mass index (BMI) and systolic BP (SBP), and diastolic BP (DBP), and pulse pressures in the American population (3). In regression models corrected for age-related increase in BP, a gain of 1.7 kg/m² for men and 1.25 kg/m² for women in BMI or an increase 4.5 cm for men and 2.5 cm for women in waist circumference corresponds to an increase in SBP of 1 mmHg (3). Obesity by itself possibly accounts for 78% and 65% of essential hypertension in men and women, respectively, according to data from the Framingham Cohort (19). Animal experiments and human studies have confirmed this causation and given insight into the mechanisms involved (3–5,14).

The role of inflammation in the insulin resistance syndrome has been gaining momentum (3,4,13). Central adipose tissue is currently recognized as a rich milieu and source of inflammatory cytokines, such as tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), and C-reactive protein (CRP), and plasminogen activator inhibitor (PAI-1). It is thought that the central adipocyte synthesizes TNF- α , which in turn stimulates IL-6, considered a major regulator in the production of acute phase reactants such as CRP, PAI-1, and fibrinogen from the hepatocyte (3,13). As such, obesity has been suggested to be a

low-grade inflammatory condition increasingly important in the causation and progression of hypertension and endothelial dysfunction (3,4,13). A direct cause-and-effect relationship, however, has not been clearly established. It is not known, for example, whether long-term treatment with nonsteroidal anti-inflammatory drugs reduces the level of inflammatory cytokines or alleviates hypertensive and vascular disease in obese patients (3).

Moreover, there are accumulating data to indicate that visceral obesity and attendant risk factors are associated with increased risk for CVD. In the Quebec Cardiovascular Study, a prospective investigation in which more than 2000 middle-aged men were followed over 5 yr, two clinical characteristics associated with visceral obesity were the strongest independent risk factors for coronary heart disease (CHD): fasting hyperinsulinemia and increased apolipoprotein B concentrations (13). Visceral obesity is often accompanied by insulin resistance and hyperinsulinemia. This hyperinsulinemia may, in turn, contribute to increased CVD (12–14).

Extensive studies also confirmed the role of obesity in the development of progressive renal disease (3–6). Obesity is associated with activation of RAAS and SNS activities, hyperinsulinemia/insulin resistance, dyslipidemia, dysglycemia, endothelial dysfunction, which individually and interdependently contribute to renal functional and structural changes, progressive renal disease, and eventually, ESRD (3,4,6,10).

Collectively, the interaction among the various metabolic and hemodynamic abnormalities associated with visceral obesity and insulin resistance/hyperinsulinemia predispose patients to atherosclerosis, premature CVD, including hypertension, progressive renal disease and eventually, ESRD.

Insulin Resistance/Hyperinsulinemia and Hypertension: Coexistence and Genetic Predisposition

The association of hypertension, insulin resistance, and resultant hyperinsulinemia is well established (3–10,14). In untreated essential hypertensive patients, fasting and postprandial insulin (INS) levels are higher than in normotensive controls, regardless of the BMI, with a direct correlation between plasma INS concentrations and BP. Insulin resistance and hyperinsulinemia also exist in rats with genetic hypertension such as Dahl hypertensive and spontaneously hypertensive rat (SHR) strains (3). On the other hand, the association of insulin resistance and essential hypertension does not occur in secondary hypertension (6). This suggests a common genetic predisposition for essential hypertension and insulin resistance, a concept that is also supported by the finding of altered glucose metabolism in normotensive offspring of hypertensive patients (8). This concept is further supported by the discovery of some genetic defects in people with combinations of insulin resistance, obesity, dyslipidemia, dysglycemia and hypertension (28,29). These defects include a mutation in the β 3-adrenergic receptor, which regulates lipolysis in visceral fat, and the presence of two mutated genes on chromosome 7q, one that controls insulin levels and hypertension and the other, leptin, a

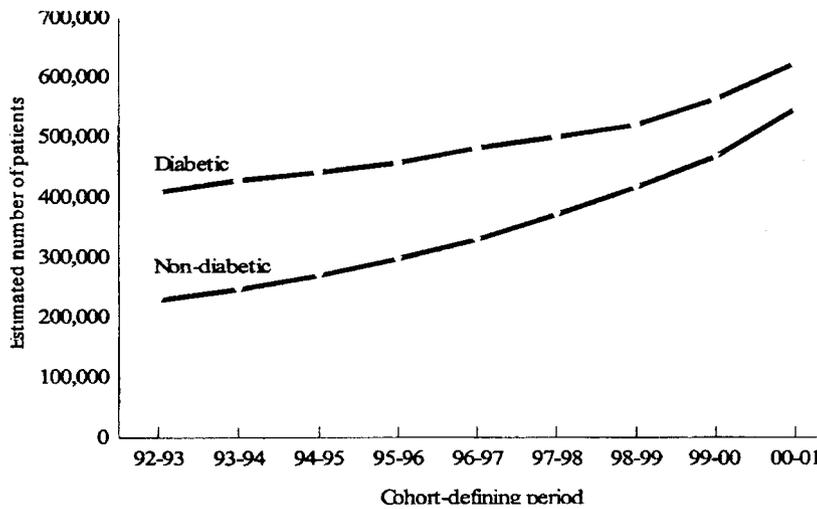


Figure 3. Trends in the size of Medicare CKD population by diabetes status reported by the United States Renal Data Systems Survey (USRDS) 15th annual report, 2003 (2).

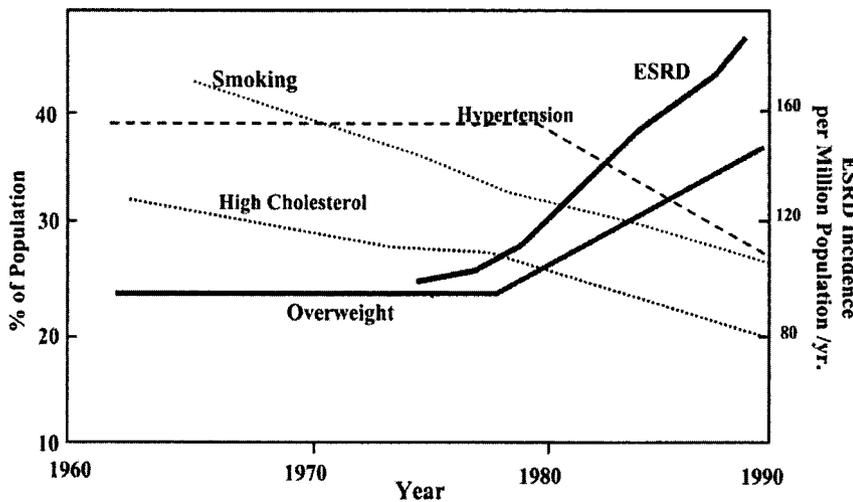


Figure 4. Estimated prevalence of cardiovascular risk factors as assessed by the National Health and Nutrition Examination Surveys I, II, and III incidence of ESRD reported by the USRDS, 2001 (40).

peptide that regulates food intake (3,28). Deficiency in CD36, a known fatty acid transporter, is also believed to be involved in the predisposition to insulin resistance and hypertension in Asians (29).

A genetic predisposition to insulin resistance and hypertension is present in type 2 diabetic patients, who constitute a large chunk of the insulin-resistant population, and elevated BP in these subjects is primarily due to essential hypertension (7,8). However, in type 1 diabetes mellitus, hypertension is often secondary to overt nephropathy (7). Elevated BP, in turn, exacerbates nephropathy; thus these comorbid states reinforce each other (3,13).

In addition to the genetic predisposition, insulin resistance/hyperinsulinemia is incriminated in the development of hypertension through abnormalities in insulin signaling and associated cardiovascular and metabolic derangements (6–9). These would include cell membrane ion exchange, enhanced SNS and RAAS and suppressed atrial natriuretic peptide (ANP) activities, sodium retention, volume expansion, progressive renal disease/ESRD, cardiac hyperactivity, LVH, dyslipidemia, dysglycemia and increased oxidative stress (7) (Figures 1 and 2).

Of importance is that there is little direct or experimental evidence that hyperinsulinemia, *per se*, can raise BP despite the correlation of insulin/resistance/hyperinsulinemia and hypertension in clinical studies. People with insulinomas do not appear to have increased arterial pressure (30). Furthermore, insulin-infused dogs do not have an increase in BP (31). On the other hand, there is experimental evidence for the role of insulin resistance in the etiology of hypertension. Insulin, acting through PI3-k/AKT pathways, leads to increased NO production from the endothelial cells (EC) and decreased myosin light chain activation/vasoconstriction in VSMC, ultimately a vasodilator effect. In the insulin-resistant state, there is inhibition of these INS signaling pathways, thus contributing to vasoconstriction (12).

Direct Effects of INS/IGF-1 and AngII Counterregulatory Actions

In the insulin-resistant state, the selective resistance to INS and its homologous autocrine/paracrine peptide insulin like growth factor-1 (IGF-1) signaling in the endothelial, vascular smooth muscle cell (VSMC), and skeletal muscle cells is due,

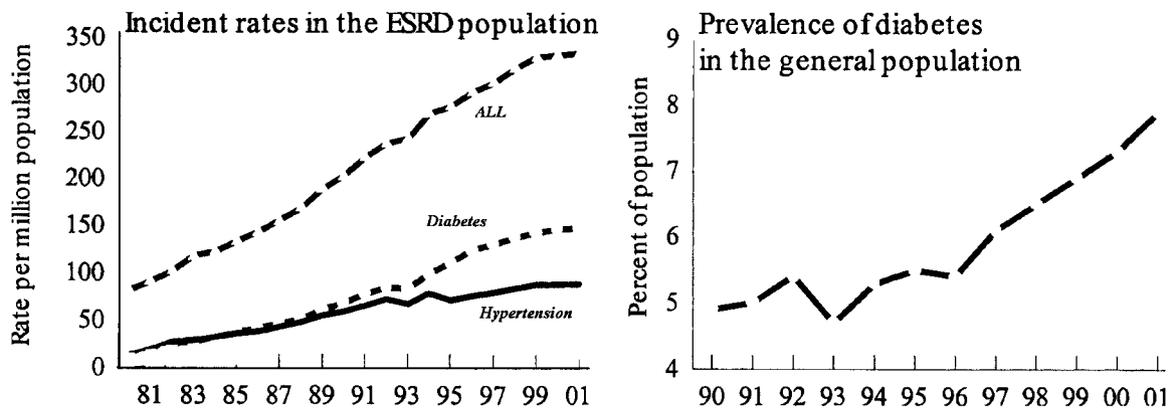


Figure 5. Adjusted ESRD incident rates, by primary diagnosis, and diabetes in the general population reported by the USRDS 15th annual report, 2003 (2).

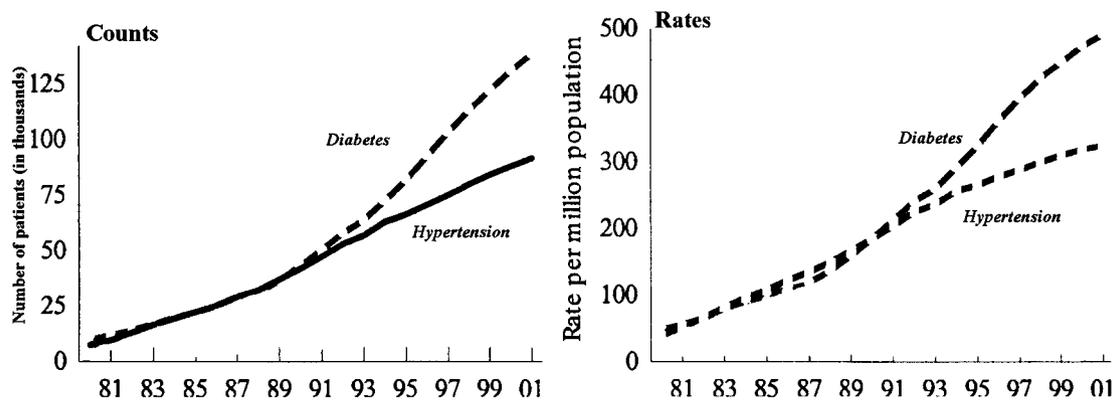


Figure 6. Prevalent counts and adjusted rates of ESRD patients, by primary diagnosis, reported by the USRDS 15th annual report, 2003 (2).

in part, to the antagonistic action of AngII (Figure 1) (10–14). AngII, acting through its ANG type 1 receptor (AT1R), inhibits the actions of INS in vascular and skeletal muscle tissue, in part, by interfering with INS signaling through phosphatidylinositol 3-kinase (PI3-K) and protein kinase β (AKT) metabolic pathways (12). This leads to decreases in nitric oxide (NO) production in EC, increased myosin light chain activation/vasoconstriction in VSMC, and reduced skeletal muscle glucose transport. In fact, one mechanism by which INS and (IGF-1) attenuate vascular contractility is through effects on VSMC divalent cation metabolism (7,10,12). These peptides reduce Ca^{2+} influx into VSMC by attenuating both voltage- and receptor-operated Ca^{2+} channels, limit the release of Ca^{2+} from intracellular organelles, and stimulate the $Na^+, K^+ - AT-Pase$ pump, leading ultimately to reduced intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) and thus contributing to vascular relaxation (7,12). Also, insulin and IGF-1 increase the cellular uptake of Mg^{2+} , an ultimately beneficial vasorelaxant effect. AngII, through increasing oxidative stress and RhoA activity inhibits these effects, thus contributing to vasoconstriction (7,12).

Both INS and IGF-1 exert their effects on vascular tone, in part via metabolic actions exerted on EC (7,9,12,14). Both peptides stimulate NO production, a process mediated by PI3-

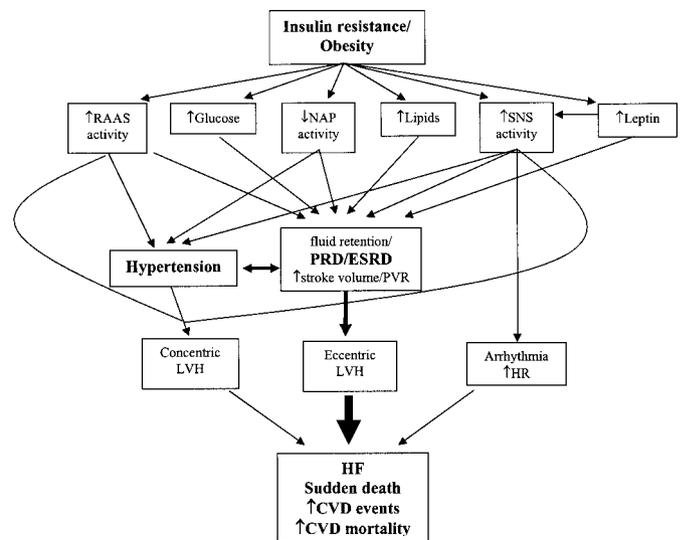


Figure 7. A summary of the mechanisms by which obesity/insulin resistance leads to cardiovascular morbidity and mortality. NAP - natriuretic peptide; SNS - sympathetic nervous system; RAAS - renin-angiotensin aldosterone system; HR - heart rate; PRD - progressive renal disease; ESRD - end-stage renal disease; LVH - left ventricular hypertrophy; HF - heart failure; \uparrow - increase.

K/AKT signaling pathways, and AngII inhibits this vasorelaxant effect of insulin/IGF-1 (7,9,12). In addition, AngII antagonizes the INS-induced increase in GLUT-4 transport to the skeletal muscle cell membrane, thereby reducing cellular glucose uptake (7,12). The generation of reactive oxygen species (ROS) appears to be one of the mechanisms by which AngII interferes with INS and IGF-1 signaling in these tissues (12,13).

Another role for hyperinsulinemia in the etiology of hypertension related to insulin resistance is via upregulation of AT1R by posttranscriptional mechanisms such as stabilization of mRNA and prolongation of its half-life (12,13). This potentiates the physiologic actions of AngII, which include peripheral vasoconstriction and plasma volume expansion (12,13).

In concert with the above-described actions of insulin on vasculature, clinical studies have shown that lessening of insulin resistance improves BP control (7,11). For instance, aerobic exercise training has been shown to improve insulin sensitivity and lower BP among sedentary, non-diabetic, hypertensive subjects (7,16). Following an 8-wk treatment with an insulin-sensitizing agent, patients with essential hypertension and mild diabetes exhibited a significant improvement in BP control and glucose metabolism (11). These findings were enhanced by a recent study, using another insulin-sensitizing agent in which treatment of nondiabetic hypertensive patients increased insulin sensitivity, reduced SBP and DBP, and induced favorable changes in markers of cardiovascular risk (17). Another oral hypoglycemic agent, metformin, improved BP control in a rodent model of insulin resistance (18). Collectively, these findings suggest that insulin resistance and hypertension are interrelated processes that are responsive to drugs that target insulin sensitivity.

Sympathetic Nervous System Changes

Both animal and human studies suggest that increased SNS activity, where vascular and renal INS actions are selectively preserved, may be another mediator of hypertension in insulin resistance/hyperinsulinemia state via stimulating renal sodium reabsorption with subsequent volume expansion and increasing cardiac output (CO) (7,32). This is especially true in obese subjects. Although there are variations between different ethnic groups, insulin resistance and hyperinsulinemia are more pronounced and are more strongly associated with hypertension in obese subjects than lean individuals (6). In the Normative Aging Study, SNS activity was elevated with hyperinsulinemia and correlated with BMI (33). In this study also, both insulin concentrations and urinary norepinephrine excretion correlated significantly with BP, a relation that persisted even after adjustment for BMI and other variables (33). Further evidence for the involvement of SNS in the relation between hyperinsulinemia and hypertension comes from diet studies and the pathogenesis of obesity-hypertension. It has been found that obese subjects have elevated SNS activity, measured both directly and indirectly (4,6,34). To support the hypothesis further, sympathetic denervation of the kidneys has a significant negative effect on renal sodium retention and thereby on obesity hypertension (4,5). In dogs fed a high-fat diet, renal nerves

appear crucially important for sodium retention and hypertension (35). In dogs with denervated kidneys, sodium retention was markedly attenuated, thereby leading to a lower BP. It therefore appears that renal nerves play a pivotal role in salt retention, impaired pressure natriuresis, and hypertension (35,36). Furthermore, food intake, primarily, fat and carbohydrate, increases SNS activity, whereas fasting and weight loss decrease it in both animal and humans (32,36). INS is believed to partially mediate this effect of diet centrally; it stimulates the uptake and metabolism of glucose in the regulatory cells anatomically related to the ventromedial nucleus of the hypothalamus, suppressing an inhibitory pathway between these cells and the brainstem, and subsequently disinhibiting the sympathetic outflow from the brainstem (37). This would preserve energy balance through regulating thermogenesis, although an unwanted byproduct results, which is the sympathetic stimulation of the heart, kidneys, and vasculature, contributing to hypertension. In insulin resistance, which is selective with preserved insulin effects on the sympathetic system, the associated hyperinsulinemia leads to exaggeration of the SNS response to diet, contributing to the pathophysiology of hypertension in hyperinsulinemia. Other mechanisms and mediators postulated as causative in the genesis of enhanced adrenergic activity in the insulin-resistant state include renal afferent nerves stimulated by increased intrarenal pressures and subsequent activation of renal mechanoreceptors, plasma FFA, AngII, elevated leptin levels, potentiation of central chemoreceptor sensitivity, and impaired baroreflex sensitivity (4–6, 34, 36).

Systemic and Adipose Tissue RAAS Changes

Adipose tissue, especially visceral type, possesses a local RAAS, which has more significant local paracrine as well as systemic effects than the subcutaneous fat (4,10). In insulin resistance/hyperinsulinemia, which is frequently associated with visceral obesity, RAAS activity is increased (4,10). This contributes to the cardiometabolic derangements associated with insulin resistance, including increased SNS activity, sodium retention and volume expansion, progressive renal disease, elevated BP, inhibition of INS signaling, and concentric LVH (3–6,13).

In addition to the increased adipose tissue RAAS activity, systemic RAAS effects are also enhanced in the insulin-resistant/hyperinsulinemic state, despite a state of sodium retention and volume expansion (3–5,13). It has been postulated that increased FFA, through their effects on the liver, may be contributing to the elevated aldosterone in insulin resistance (3). Also, it has been reported that AngII, angiotensin-converting enzyme (ACE) levels and plasma renin activity (PRA) correlate with BMI (5). Furthermore, weight loss, on short-term basis, resulted in significant reduction in PRA, aldosterone, and mean arterial pressure (MAP) in a study of 25 obese patients, supporting the relation between BMI and RAAS activity in insulin resistance (34).

RAAS also seems to play an important role in insulin sensitivity. Several large trials, including the Captopril Prevention Project (CAPPP) (38) and the Heart Outcomes Prevention Evaluation

Study (HOPE) (39) generated data suggesting that ACE inhibitors decrease the propensity to develop type 2 diabetes in hypertensive and high-risk patients, respectively. Also, there is a similar beneficial effect for angiotensin receptor blockers (ARB) in preventing development of diabetes (40). These beneficial effects of RAAS blockade on insulin sensitivity have been confirmed by *in vivo* studies where AT1R blocking agents resulted in an improvement in INS-mediated glucose utilization in INS-resistant rodents (41). These studies and the fact that hypertension *per se* is an insulin-resistant state (7,13,14) suggest that RAAS may have a crucial role in the pathophysiology of insulin resistance and that ACE inhibitors and ARB may improve insulin sensitivity. Two postulated mechanisms for this insulin-sensitizing effect of ACE inhibitors include improvement in microvascular blood flow to peripheral tissues and reversal of the inhibitory effects of AngII on INS signaling (42).

Alterations in Natriuretic Peptide System

The natriuretic peptide system consists of the atrial natriuretic peptide (ANP), the brain natriuretic peptide (BNP), and the C-type natriuretic peptide (CNP), each encoded by a separate gene. They are synthesized predominantly in the heart, brain, and kidneys and work via specific receptors, namely NPr-A, NPr-B, and NPr-C (3). The natriuretic peptides have a protective role on the development of hypertension due to their natriuretic and vasodilator effects as well as due to their inhibitory effect on the SNS and the RAAS (3). In obesity/hyperinsulinemia, overexpression of NPr-C receptor and lower levels and function of ANP with a possible role for a promoter variant at position –55 in the NPr-C gene, have been reported, contributing to increased sodium retention (3,43,44). Nannipieri *et al.* (45) assessed the interaction between insulin and ANP in type 2 diabetes compared with healthy subjects. They concluded that there was dual disruption of ANP levels and function control in type 2 diabetic persons. ANP release was resistant to volume stimulation in type 2 diabetic patients, and natriuresis was resistant to ANP action. This further emphasizes the role of ANP in BP regulation in the insulin-resistant state. Weight loss may partially reverse these abnormalities in patients with the cardiometabolic syndrome and in those with type 2 diabetes mellitus (44).

Progressive Renal Disease

Natural History: Functional and Structural Changes, Compensatory Responses, and Late Nephron Damage

Insulin resistance/hyperinsulinemia state is associated with activation of both RAAS and SNS activities, contributing to increased renal sodium reabsorption, associated fluid retention and hypertension (Figure 2) (3–6,13,32,34,36). Also, this state is accompanied by increased EC proliferation and intrarenal lipid and hyaluronate deposition in the matrix and inner medulla (Figure 2) (3–5,44,46). These depositions increase intrarenal pressure and volume in the tightly encapsulated kidney, leading to parenchymal prolapse and urine outflow obstruction, which result in slow tubular flow and subsequently increased sodium reabsorption, especially in the loop of Henle (4,5). This leads to inappropriately small natriuretic response to saline

load at mean and glomerular pressure, often referred to as “impaired pressure natriuresis” (4–6,13,46).

These functional and structural changes in the kidney provoke compensatory lowered renal vascular resistance, elevated kidney plasma flow, glomerular hyperfiltration, and stimulation of RAAS, despite volume expansion. Neurohumoral factors like AngII, sympathetic system, and cytokines are synergistically involved in these compensatory mechanisms. For instance, AngII, in addition to its systemic effects on BP, directly contributes to increased glomerular capillary pressure through vasoconstriction of the efferent arterioles and upregulation of renal injury response (7,44,46). These alterations with the hypertension associated with the insulin-resistant state help overcome the increased tubular reabsorption and maintain sodium balance (3,4,44,46). Although no glomerular damage has yet occurred, persistence of these compensatory responses, increasing glomerular wall stress, in the presence of hypertension, dyslipidemia and dysglycemia, will precipitate gradual nephron loss, glomerulosclerosis and eventually ESRD (Figure 2) (4,7,46). This glomerulosclerosis in the hyperinsulinemic/insulin-resistant kidney is peculiar and characterized by lower rate of nephrotic syndrome, fewer lesions of segmental sclerosis and a greater glomerular size compared with the idiopathic variety (4,12).

Hypertension is believed to contribute to renal disease by increasing glomerular capillary pressure, proteinuria, endothelial dysfunction, and sclerosis, leading to nephron damage (7). Dyslipidemia, on the other hand, enhances renal dysfunction through filtered lipoproteins, damaging glomerular and tubular cells, in addition to enhancing endothelial dysfunction and atherosclerosis and participating in the aforementioned deleterious renal functional and structural changes, eventually leading to nephron damage (3). Dysglycemia is not only involved in the aforementioned renal changes, but it also exerts a direct toxic effect on nephrons through glycosylation of glomerular proteins (46–48).

In summary, persistence of insulin resistance and suboptimal control of associated cardiometabolic abnormalities cause renal injury with functional as well as structural nephron loss contributing to elevated BP, which in turn leads to further renal injury, thereby setting off a vicious circle of events leading to further elevated BP and renal injury. Interestingly enough, it is difficult to dissociate the “cause” from “effect” in this circle, because the overall burden of insulin resistance may be strongly time-dependent (Figure 2) (4).

Renal Disease and Insulin Resistance: Ethnic Differences and Relative Weight of Risk Factors

Overt nephropathy is detected simultaneously with diagnosis of type 2 diabetes, while it develops later on in type 1 diabetes. This emphasizes the role of insulin resistance and associated abnormalities in the etiology of renal disease, since type 2 diabetic patients are insulin-resistant long before they develop overt diabetes (12,13). Also, the parallel increase in the prevalence of obesity and ESRD (Figure 4) besides the close association between obesity and type 2 diabetes and hypertension which are the 2 major risk of ESRD, has led to

speculate that obesity, which is frequently associated with insulin resistance/hyperinsulinemia, may account for at least half of the ESRD in the United States (4), supporting the role of insulin resistance in renal disease. In fact, insulin resistance is now an established modifiable risk factor for chronic kidney disease (CKD) and ESRD and an independent predictor of CVD mortality in people with ESRD (49). Furthermore, people with renal disease have higher insulin resistance compared with subjects with normal renal function (49). Adipocytokines, including TNF- α , IL-6, and leptin, are believed to mediate increased insulin resistance in ESRD (50). In uremic patients, the levels of these adipocytokines are even higher, further worsening insulin sensitivity (2,12,50).

The effect of insulin resistance and associated cardiovascular and metabolic derangements on renal function is heterogeneous between different ethnicities, suggesting a possible genetic role (2,47). The adjusted incidence of ESRD in African-Americans and Native Americans is about 4 times that in the rest of the US population and is disproportionate to their percentage of the population (2,47). Also, the relative weight of risk factors on progressive renal disease in the insulin-resistant state varies with ethnicity (7,47). For instance, the role of hypertension in progressive renal disease is more enhanced in African-Americans, with higher salt sensitivity and endothelin-1 levels, and native American Indians; the target organ damage at any level of BP is greater than in other ethnicities (47). Thus, it comes of no surprise that hypertension is the leading cause of ESRD in the African-American population (7,47).

Microalbuminuria: A Marker of the Cardiometabolic Syndrome, Endothelial Dysfunction, Progressive Renal Disease, and CVD

Accumulating data indicate that microalbuminuria, defined as urine albumin excretion of 20 to 200 $\mu\text{g}/\text{min}$ or 30 to 300 mg/d , clusters with several metabolic and vascular abnormalities of the cardiometabolic syndrome (23,32,51) and is indeed a part of and even an early marker for this syndrome (23–26). Among others, the use of quartiles, different cut-off levels for abnormal values, different measures for insulin resistance and obesity, and different statistical methodologies led to inconsistent reporting of various components of the cardiometabolic syndrome as the strongest associated abnormality with microalbuminuria. However, enough evidence has been garnered confirming the association between microalbuminuria and each of hypertension (23,32) and central obesity (24). Also, studies confirmed the association of microalbuminuria with salt sensitivity, the absence of nocturnal drops in both SBP and DBP, dyslipidemia, and LVH (13,14,48). Furthermore, although researchers have reported mixed results on the association between microalbuminuria and hyperinsulinemia, multiple studies confirmed this relation with an additional association between microalbuminuria and high fasting blood sugar (FBS) values (23,24,48,52). The Insulin Resistance in Atherosclerosis Study revealed that an increasing degree of insulin sensitivity

was associated with a decreasing prevalence of microalbuminuria (24). Others reported that microalbuminuria in type 2 diabetes was associated with insulin resistance, a relation that was independent of BP or glucose levels (48). Also, an investigation of 5659 men and women from the Third Health and Nutrition Examination Survey (NHANES III), which is one of the most comprehensive and nationally representative surveys, confirmed the association between MA and the cardiometabolic syndrome, with the strongest association being with high FBS and high BP (23). Furthermore, the Framingham follow-up on glucose-intolerant normotensive subjects showed a twofold higher prevalence of MA in comparison with normal controls (52).

More importantly, microalbuminuria is now established as a modifiable predictor of CVD and CVD mortality (22,23,48,51). Of the individual components that constitute the cardiometabolic syndrome, microalbuminuria confers the strongest risk of cardiovascular death (23). However, despite its strong association with CVD, the exact pathogenetic mechanisms that link microalbuminuria to CVD remains unknown. Evidence has been garnered that microalbuminuria is a marker of generalized endothelial dysfunction and consequently a risk factor for CVD (18,22). In recent studies, this endothelial dysfunction has been characterized by the presence of transmembrane leakiness (32). It is presently unclear whether transmembrane leakiness should be viewed as the culminating event of different atherogenic factors acting in concert to promote endothelial dysfunction or whether it should be considered as the underlying substrate that enhances the atherogenicity of the different components of the cardiometabolic syndrome. For one, the increase in vascular permeability can promote the penetration of atherogenic lipoprotein particles in the arterial wall. One possible explanation is that endothelial dysfunction might promote increased penetration of atherogenic lipoprotein particles in the arterial wall, but glucose control, insulin resistance, procoagulant state, and adhesion molecules have all been implicated in the pathogenesis (53). In addition, microalbuminuria has also been associated with alterations in hemodynamic and vascular responses. This is exemplified by studies that have demonstrated that the compensatory vasodilation seen after relief from prolonged ischemia or infusion of vasodilators such as nitroglycerin is blunted in people with microalbuminuria (32). In general, microalbuminuria can be construed as a signal from the kidney that abnormalities in endothelial function and vascular responses are present and can be seen as an early marker of generalized endothelial dysfunction, atherosclerosis, increased CVD risk, and progressive renal disease (48). In this light, the reduction of microalbuminuria should be implemented as a therapeutic goal to reduce overall CVD risk (48).

In recent studies, measures that normalize the different components of cardiometabolic syndrome resulted in significant reductions in urine microalbumin excretion. For instance, weight loss can reduce microalbuminuria. Reductions in urine microalbumin excretion correlated significantly with weight loss as little as 5% from baseline (32). Measures that enhance insulin sensitivity, reduce BP, and improve glycemic control

have all been shown to reduce microalbuminuria (7,32,54). The use of statins for the treatment of dyslipidemia has been shown to improve endothelial function and reduce microalbuminuria, beneficial effects that extend well beyond its lipid-lowering properties (13). Even lowering plasma triglyceride levels has been shown to stabilize urine albumin excretion (32).

In summary, microalbuminuria can be viewed as a part of and an early marker for the cardiometabolic syndrome, including endothelial dysfunction and progressive renal disease, and a modifiable predictor for CVD and CVD mortality. The reduction of microalbuminuria may reflect the adequacy with which the different components of the cardiometabolic syndrome are controlled and should be instituted as a therapeutic goal in an effort to reduce overall CVD risk, including progressive renal disease, and mortality.

Atherosclerosis and Cardiovascular Alterations

Atherosclerosis

Several studies confirmed the role of insulin resistance, hyperinsulinemia and associated cardiometabolic abnormalities as important risk factors in the development of both incident and prevalent atherosclerosis, renal disease, stroke, CVD, and CVD mortality (Figure 7) (55–57). One such trial, the Insulin Resistance in Atherosclerosis study, which investigated 1600+ triethnic cohort, measured insulin sensitivity directly via frequently sampled intravenous glucose tolerance test (FSIVT), which correlates well with the gold standard measure of insulin sensitivity, the euglycemic hyperinsulinemic clamp technique, in relation to carotid intimal medial thickness (IMT) (56). Another study, the Atherosclerotic Risk in Communities (ARIC), measured insulin sensitivity indirectly via assessing fasting serum INS and glucose levels, in relation to carotid-IMT (55). Other measurements for insulin resistance included 2-h INS levels after glucose load and proinsulin levels. Measures for assessment of atherosclerosis also included coronary angiograms (57). In fact, several large studies revealed that hyperinsulinemia is not only associated with but also a predictor of CHD (13,57). An important study from Quebec on 2103 men confirmed the association between hyperinsulinemia and CHD using an insulin assay without crossreactivity with proinsulin to measure fasting insulin levels (20). These studies confirmed a positive association between atherosclerosis and reduced insulin sensitivity, hyperinsulinemia, hyperglycemia, hypertension, dyslipidemia, elevated plasma fibrinogen and plasminogen activator inhibitor (PAI)-I levels, central obesity and physical inactivity.

Several mechanisms have been proposed to explain the role of insulin resistance, hyperinsulinemia, and associated abnormalities in the development of atherosclerosis. These include both direct effects on the arterial wall and indirect actions on lipid and glucose metabolism, neurohumoral and hormonal factors, ultimately leading to endothelial injury, LDL uptake by subendothelial macrophages to foam cells, VSMC proliferation, and eventually atherosclerotic plaque formation (7,12,13). The direct effects could be through insulin participating in cholesterol transport into VSMC, stimulating cholesterol syn-

thesis and proliferation of these cells. The indirect effects are mediated by the major CVD risk factors clustering with hyperinsulinemia. In fact, elevated FFA (secreted by visceral adipocytes) and abnormalities in lipoproteins, neurohumoral and hormonal factors, acting on the liver and other target organs, lead to a constellation of lipid, glucose, fibrinolytic and inflammatory abnormalities in levels and composition as well as perturbations of the interaction between these factors and cellular receptors, contributing to the development of atherosclerosis, thrombosis, and eventually CHD and CKD (3). Furthermore, the progressive decline in renal function associated with insulin resistance is accompanied by a reduction in the clearance of insulin, proinsulin, other neurohumoral and hormonal mediators, believed to contribute to atherosclerosis (2,49). Also, it exacerbates hypertension, insulin resistance, and other associated cardiometabolic disorders, contributing further to accelerated atherosclerosis, increased CVD events, and mortality, as well as establishing a vicious cycle whereby progressive renal disease and CVD exacerbate each other (2).

Vascular Adaptations

An alteration in ions at the cellular and molecular level appears to be important in regulating vascular smooth muscle tone. These, as previously mentioned, may be deregulated in the obese/insulin-resistant resulting in abnormal vascular responsiveness (3). Weight loss may reverse this deregulation, resulting in a clearly significant decrease in PVR and MAP (58).

Cardiac Adaptations

The vascular and cardiometabolic disorders associated with insulin resistance, including volume expansion, hypertension, LVH, and dyslipidemia, synergistically increase CVD risk as confirmed by the PROCAM study (Figure 7) (4,5,7). Lean hypertensive individuals tend to have a concentric LVH in response to sustained hypertension, leading eventually to cardiac dilation and heart failure (HF) (3). On the other hand, the predominant pattern of cardiac hypertrophy noted in insulin-resistant hypertensive individuals is eccentric (4,5). The presence of both insulin resistance and hypertension in the same patient results in a mixed pattern of cardiac hypertrophy, caused by an elevation in both cardiac preload and afterload, and a heavier heart (4). Insulin resistance results in increased preload due to an expanded vascular volume, and the high afterload can be accounted for by the presence of hypertension and sympathetic system activation. Since LVH by itself is a major risk factor for sudden death and death due to progressive cardiac decompensation, it may partially explain the increased incidence of CVD morbidity and mortality in the obese/insulin-resistant (3). Furthermore, HF is twice as common in obese/insulin-resistant subjects compared with normal individuals, even after adjustment for comorbid conditions. Also, the myocardium in the obese/insulin-resistant individual shows the presence of mononuclear cell infiltration in and around the sinoatrial node with fat deposition all along the conduction system. Lipomatous hypertrophy of the interatrial septum has also been noted in these patients. All these changes make the

myocardium in the insulin-resistant hypertensive patient an ideal substrate for cardiac arrhythmia and sudden death (3).

Recommendations on the Management

Several metabolic, cardiovascular, and renal abnormalities contribute to the elevated CVD risk in patients with hyperinsulinemia and hypertension or the cardiometabolic syndrome (3,14,21,32). Hence, multitargeted-approaches, preferably population-based, to prevent or control these derangements need to be implemented (21). Weight reduction is warranted with diet, lifestyle/behavior modification and moderate physical activity of at least 30 min a day, 3 times a week (3). However, most patients with the cardiometabolic syndrome will benefit from tight glycemic control, antithrombotic therapy with ASA, cholesterol-lowering therapy with HMG-CoA reductase inhibitors (to an LDL-Cholesterol goal of less than 100 mg/dl), and aggressive BP control, frequently more than two agents (ACE inhibitors, ARB, diuretics, CCB, β - and α -blockers) to a BP goal of <130/80 mmHg and ideally <115/75 mmHg (21).

RAAS blockade with ACE inhibitors and ARB seem to be particularly helpful in patients with the cardiometabolic syndrome. In patients with DM, the role of these agents in improving the clinical outcomes and attenuating the progression of renal disease, both through BP-dependent as well as BP-independent effects has been established (21). ARB significantly reduce the progression of type 2 diabetic nephropathy (doubling of serum creatinine, ESRD, and death), both at early and late stage of renal disease with reduction in proteinuria, effects that go above and beyond BP-dependent benefits (56). Similar effects of ACE inhibitors in patients with type 1 diabetes have been confirmed, again with BP-dependent and BP-independent (21), while their renoprotective benefits in patients with type 2 diabetes are still to be revealed. On the basis of these studies, the use of ACE inhibitors, ARB, or both is recommended as first-line therapy in patients with diabetes and renal disease (59). Overt nephropathy is diagnosed at the onset of type 2 diabetes, and progressive renal disease is initiated in the prediabetic insulin-resistant state; it is therefore wise to extend these recommendations to include patients with the cardiometabolic syndrome and renal disease. Whether RAAS blockade with ACE inhibitors or ARB reduces renal injury better than other antihypertensive agents, especially in diabetic nephropathy, is still debatable. Studies reported mixed results on this subject and invariably demonstrated slightly better control of BP in the groups of the active drug. Randomized double-blinded head-to-head comparison trials with similar BP control in active and control groups are needed to further clarify this issue (60).

Further support for the importance of RAAS blockade in patients with the cardiometabolic syndrome comes from completed trials suggesting an insulin-sensitizing effect of ACE inhibitors (39) and ARB (40), with a potential of preventing the development of DM. Two ongoing trials, the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medications (DREAM) study, evaluating an ACE inhibitor (ramipril), a thiazolidinedione (rosiglitazone), or a combination of both agents

versus placebo, and the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR), evaluating an ARB (valsartan), a rapid on/off insulin secretagogue (nateglinide), or both *versus* placebo, should lead to more definite important conclusions on the role of these agents in the prevention of diabetes.

Detailed recommendations on the management of CVD and renal disease risk factors in the cardiometabolic syndrome have been elaborately discussed in our previous articles (3,14,21).

Conclusion

Hyperinsulinemia and hypertension are integral components of the cardiometabolic syndrome that frequently coexist with a possible common genetic predisposition. They contribute significantly to progressive renal disease and elevated CVD morbidity and mortality associated with this syndrome. Resistance to the effects of insulin on peripheral tissues and vasculature, as well as central actions of insulin stimulating the SNS activity and renal effects enhancing renal sodium reabsorption, all contribute to the etiology of hypertension in the insulin-resistant state. Other mechanisms involved would include endothelial dysfunction, LVH, cardiac hyperreactivity, dyslipidemia, hyperglycemia, enhanced RAAS activity, altered renal structure and function with impaired pressure natriuresis leading to sodium retention, volume expansion, progressive renal disease, and eventually ESRD.

Other derangements in the cardiometabolic syndrome include hyperuricemia, an altered Kinin-Kinin system, a prothrombotic and proinflammatory state, and microalbuminuria. Currently microalbuminuria is recognized as not only a component of the cardiometabolic syndrome, but also as an early marker of this syndrome and a reflection of a generalized endothelial dysfunction, atherosclerosis, progressive renal disease, and increased CVD morbidity and mortality.

In view of the complexity and diversity of the CVD and renal risk factors associated with the cardiometabolic syndrome, multi-targeted approaches to risk factor modification are recommended in patients with this syndrome, with particular emphasis on RAAS blockade and reduction of microalbuminuria. This would lessen the enormous burden of this syndrome, with rising prevalence and its complications for healthcare systems.

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