1 Insulin Resistance and the Metabolic Syndrome in Kidney Disease (e.g., the Cardiorenal Metabolic Syndrome)

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Introduction

The metabolic syndrome is a collection of abnormalities that are risk factors for the development of cardiovascular and chronic kidney disease (CKD). While current dogma suggest that obesity is at the core of this constellation of risk factors, the association between blood pressure and diabetes was described as early as 1921 [1–4]. Then during the 1988 Banting lecture, G.M. Reaven suggested that the clustering of risk factors in an individual including high blood pressure, impaired glucose tolerance, and dyslipidemia was associated with coronary artery disease. At that time he grouped these metabolic disorders and referred to them as "syndrome X." He proposed that resistance to insulin-stimulated glucose uptake and compensatory hyperinsulinemia contributed to the development of non-insulin-dependent diabetes mellitus, hypertension, and coronary artery disease [5]. This interest in "syndrome X" became an area of investigative interest for many in the 1990s and early 2000s that ultimately led to a better understanding of the relationship between obesity, insulin resistance, and cardiovascular and kidney disease.

In modern terms, the "metabolic syndrome" refers to a set of physical and laboratory parameters whose co-occurrence in an individual may help clinicians identify the presence of insulin resistance as a chance to intervene early in the course of cardiovascular disease [6, 7]. In addition to syndrome X, other terms that have been used to describe a similar group of risk factors are "insulin resistance syndrome," "dysmetabolic syndrome X," and also "Reaven's syndrome." Since then, a number of organizations have sought to name and define this syndrome including the National Cholesterol Education Program Adult Treatment Panel III (ATP III), World

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Health Organization, American Association of Clinical Endocrinologists, European Group for the Study of Insulin Resistance, and International Diabetes Federation among others. The common criteria for this syndrome consistently rely on the presence of obesity and insulin resistance. It should be noted the central difference between the various organizations in describing the syndrome is in measurement thresholds of insulin resistance, blood pressure, obesity, and/or the presence of microalbuminuria.

There is a well-described relationship between diabetes and CKD; however, over the past decade, there has been considerable interest in the effects of insulin resistance, distinct from that of diabetes, on CKD. Obesity and the presence of the compensatory hyperinsulinemia from insulin resistance have emerged as important contributors to the development of CKD. Thereby in this chapter, we will focus on the importance of the metabolic syndrome and insulin resistance in kidney disease and then review some of the important mechanisms that underlie this relationship [8–12].

Definition(s) of the Cardiorenal Metabolic Syndrome

Over the years, the diagnostic criteria for the identification of the metabolic syndrome have evolved. There have been a number of diagnostic criteria used in the cardiorenal metabolic syndrome to help identify the heightened risk for diabetes, cardiovascular, and, for our discussion, kidney disease. As per Reaven's original description, syndrome X referred to the following risk factors: glucose intolerance, dyslipidemia, and hypertension [5]. Reaven proposed a causative role for insulin resistance. However, his description did not mention central obesity, which is now viewed by most as the unifying feature of the syndrome.

In 1999, a World Health Organization (WHO) diabetes group proposed a definition that included impaired glucose tolerance or diabetes mellitus and/or insulin resistance together with two or more of the following: raised arterial pressure ≥160/90 mmHg, plasma triglycerides >150 mg/dl, HDL <35 mg/dl in men or <9 mg/dl in women, central obesity suggested by waist/hip ratio of >0.90 in men and >0.85 in women and/or BMI >30 kg/m^2, and/or microalbuminuria ≥20 μg/min or albumin/creatinine ratio ≥20 mg/gm [13]. Subsequently, the European Group for the Study of Insulin Resistance suggested some modifications to the WHO definition of metabolic syndrome. They excluded diabetic individuals as the current thought at that time was that there was no simple way to measure insulin resistance and suggested different cutoffs for other criteria [14]. The NCEP:ATP III proposed a definition that focused on facilitating diagnosis and risk reduction for individuals at high risk for cardiovascular disease [15]. The ATP III suggested the diagnosis of metabolic syndrome with the presence of three or more from the following criteria: waist circumference >40 inches in men or >35 inches in women, triglycerides ≥150 mg/dl, high-density lipoprotein cholesterol <40 mg/dl in men or <50 mg/dl in women, blood pressure ≥130/ ≥85 mmHg, and/or fasting glucose ≥100 mg/dl [15].

The existence of multiple definitions of the syndrome resulted in difficulties with comparison and interpretation of data between studies of the syndrome as well as confusion with application for clinical use [16]. It is important to note these groups did not consider in their recommendations ethnic differences in measurements of obesity and especially in waist circumference [16]. To address these concerns, a consensus group panel meeting arranged by the International Diabetes Federation (IDF) in 2004 proposed a "global" definition for use in clinical practice [17]. The working group of the IDF suggests the presence of obesity as measured by waist circumference that had values with ethnicity in mind in addition to two of the following factors: elevated triglycerides (≥150 mg/dl or on treatment), reduced HDL cholesterol (<50 mg/dl in females and <40 mg/dl in males), raised blood pressure (≥130 mmHg systolic or ≥85 mmHg diastolic or on treatment for hypertension), and fasting plasma glucose (fasting glucose ≥100 mg/dl or diagnosis of diabetes) [17]. Waist circumference cutoffs based on ethnicity included (1) Europoids, sub-Saharan Africans,

Eastern Mediterranean, and Middle East (Arab) populations, ≥94 cm for men and ≥80 cm for women; (2) South Asians, Chinese, Ethnic South, and Central Americans, ≥90 cm for men and ≥80 cm for women; and (3) Japanese, ≥85 cm for men and ≥90 cm for women [17].

Epidemiology of the Cardiorenal Metabolic Syndrome

The prevalence of metabolic syndrome varies with the diagnostic criteria used, region studied, as well as age and ethnicity of the population. In 2010, based on data from the National Health and Nutrition Examination Survey (NHANES), the age-adjusted prevalence of the cardiorenal metabolic syndrome in the adult US population was estimated to be ~23% [18]. The study utilized waist circumference cutoffs of ≥40 inches for men and ≥35 inches for women based on the ATP III definition while utilizing the cutoffs from the IDF definition for the other criteria. The use of more generous cutoffs for defining abdominal obesity may have led to an underestimation of that parameter in the US population. Comparison of the data from 1999 to 2000 and 2009 to 2010 revealed an improving trend for metabolic syndrome, blood pressure, triglycerides, and HDL cholesterol and a worrisome increasing trend in hyperglycemia and waist circumference. The improvement in blood pressure and lipid trends was thought to have corresponded to increases in awareness and incorporation of antihypertensive and lipid-lowering therapies [18]. Hispanic-American adults, especially females, have a higher prevalence compared to other US racial subgroups [18]. In an epidemiological study of 1800 adults in an urban population in India, the prevalence of the syndrome was ~13% [19]. Further, in another population, a cross-sectional study in the Guangdong province of South China using the NCEP:ATP III criteria showed an unadjusted prevalence of ~27% [20]. Along with other risk factors such as hypertension and diabetes, it is important to note the prevalence of the syndrome increases with age until 70 years and then declines [21].

While it is clear the cardiorenal metabolic syndrome is highly prevalent, there is sufficient additional evidence to support an association between insulin resistance and CKD. Observational data from NHANES III support a direct correlational relationship between insulin resistance and both the presence of microalbuminuria and overt CKD [11, 22]. Important in these observational data is the ability to distinguish between insulin resistance or overt diabetes and development of CKD. It is important to note then that insulin resistance has been documented in a nondiabetic population in early stages of CKD as well as in more advanced stages [12]. In one prospective cohort, the Atherosclerosis Risk in Communities (ARIC) study, there was an increased risk for the development of CKD in nondiabetics that met the definition of the syndrome. This occurred independent of baseline confounders such as diabetes and hypertension and even with their development over the duration of the study [9]. Additional data from the Framingham Heart Study support that in a cohort of individuals without diabetes followed over 7 years, insulin resistance was significantly associated with development of CKD following adjustments for confounders [10]. These collective data suggest a trend has emerged between CKD and the cardiorenal metabolic syndrome irrespective of overt diabetes.

The Cardiorenal Metabolic Syndrome and CKD

The syndrome is associated with an increase in risk for myocardial infarction, cardiovascular mortality, and stroke as well as all-cause mortality [23]. The presence of the cardiorenal metabolic syndrome has been associated with a greater risk for type 2 diabetes [24] and independently increases the risk of microalbuminuria and incident CKD [25, 26]. Hence, the presence of metabolic syndrome in one out of every four to five adults provides an opportunity to identify and treat risk factors that predispose to type 2 diabetes, CKD, as well as all-cause CKD-associated mortality. In this context, there has been much interest in the presence of microalbuminuria or

albuminuria as a risk predictor or as an actual outcome of the metabolic derangements associated with the cardiorenal metabolic syndrome. There have been a number of population level studies that have included microalbuminuria in nondiabetics with CKD to evaluate risk in this syndrome [27–30]. Further, microalbuminuria is an independent, modifiable predictor of risk and largely considered a marker of generalized endothelial dysfunction [31].

The contribution that visceral adiposity has to these metabolic-induced vascular abnormalities includes insulin resistance, lipoprotein abnormalities, as well as promotion of a pro-inflammatory/pro-oxidative milieu that induces systemic hemodynamic changes [32, 33]. While overweight/obesity status, sedentary lifestyle, as well as genetics predispose to these risks, a unifying mechanism is difficult to elucidate and is likely a conglomerate of factors [34]. Numerous metabolic abnormalities have been suggested that explain the association between obesity, insulin resistance, and albuminuria of which the most significant ones are inappropriate activation of the sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS) and the diminishing actions of protective cytokines [35]. Excessive visceral adipose tissue in obese individuals is a well-known source for pro-inflammatory adipokines which promote insulin resistance [35]. The resulting hyperinsulinemic state in addition to obesity-induced kidney structural and functional changes then potentiates glomerulosclerosis and thickening of glomerular basement membrane in animal models [35]. The following are some of the mechanisms thought to contribute to increased risk of CKD in individuals with the metabolic syndrome.

Insulin Resistance/Hyperinsulinemia

Insulin helps control energy homeostasis by facilitating the glucose uptake and glycogen storage in the liver and skeletal muscle tissue. In addition, insulin stimulates the storage of lipids as triglycerides in adipose tissue [36]. Insulin binds and activates the insulin receptor tyrosine kinase in skeletal muscle [36]. This leads to phosphorylation of insulin receptor substrate-1 (IRS-1) which then binds and activates phosphatidylinositol 3-kinase (PI3K) [36]. PI3K then promotes translocation of glucose transporter type 4 (GLUT4) to the plasma membrane, thereby leading to glucose uptake [36]. Impaired insulin metabolic signaling in the skeletal muscle, liver, and adipose tissue due to reduced binding or phosphorylation of its receptor, decreased tyrosine kinase activity, and impaired phosphorylation of IRS proteins contributes to insulin resistance [36]. The persistent excess insulin levels eventually lead to impairments in renal hemodynamics contributing to an elevation of glomerular filtration rate (e.g., hyperfiltration) in experimental studies [37, 38]. The state of hyperinsulinemia in these insulin-resistant individuals also contributes to salt sensitivity and thereby increased glomerular pressure, hyperfiltration, and overtime maladaptive structural remodeling that leads to albuminuria in diabetes [39]. The contribution then of insulin excess to vascular homeostasis is a critical link to understanding the underpinning of insulin resistance to the intrarenal hemodynamic changes that lead to CKD. There is clear data regarding the impact of insulin resistance/hyperinsulinemia in vasoconstriction activity through activation of vascular sympathetic tone through catecholamine secretion [40]. Bioavailable nitric oxide (NO) is regulated, in part, by insulin through stimulation of PI3K signaling pathways in impaired vascular tissue in the insulin-resistant state. The alterations in vascular tone contribute not only to the development of vasoconstriction and hypertension but also lead to glomerular hypertension and albuminuria.

Not only does excess insulin over time contribute to the vascular abnormalities that induce endothelial dysfunction, but excess insulin contributes to vascular cell proliferation, mesangial expansion, along with extracellular matrix deposition that promotes tubulointerstitial fibrosis [41]. The actions of insulin in this capacity can occur either directly by insulin or occur in conjunction with other growth factors such as insulin-like growth factor (IGF)-1 and transforming growth factor-β (TGF-β). IGF-1 has similar

effects to insulin on the vasculature but also promotes mesangial cell and glomerular expansion [42]. Insulin has been shown to produce TGF-β in both proximal tubular and mesangial cells which in turn lead to glomerular and tubulointerstitial extracellular matrix expansion and fibrosis [43].

Inflammatory Cytokines

Increased accumulation of macrophages has been seen in adipose tissue of obese individuals. (45) Visceral adipose tissue in obesity expresses increased amounts of pro-inflammatory molecules as well as procoagulant proteins [44]. Further, increased adipocyte macrophages are thought to produce several of these pro-inflammatory molecules and have been shown to decrease insulin sensitivity and increase lipolysis and hepatic triglyceride secretion [45]. Leptin is an adipocyte-derived hormone with structure similar to the cytokine IL-2 and is thought to mediate energy balance through its actions on the hypothalamus [46]. Obese individuals with metabolic syndrome display elevations in circulating leptin and are resistant to the central neurologic effects of leptin that decrease appetite and increase energy expenditure [47]. This promotes maintenance of excess weight and helps amplify the consequences [46]. Findings in the West of Scotland Coronary Prevention Study (WOSCOPS) suggested that elevated leptin levels are independently associated with increased risk of coronary artery disease [48]. In this study higher leptin levels correlated strongly with C-reactive protein (CRP) in individuals who had a coronary event, suggesting then there exists a chronic low-grade inflammation that may increase the risk for cardiovascular disease [48].

A study of data from the third National Health and Nutrition Examination Survey (NHANES III) looked at the presence of inflammation in patients with the syndrome and varying levels of kidney function [49]. This study found that an increase in number of component conditions of metabolic syndrome increased the odds of inflammation as measured by CRP levels at various levels of kidney function [49]. While this suggests an association, direct causation has not been proved. Adiponectin is a polypeptide that is produced by adipose tissue that exhibits properties that are insulin sensitizing along with anti-inflammatory and antioxidant [50]. In this context, low adiponectin levels are associated with insulin resistance, cardiovascular disease, as well as kidney disease in obese individuals [51]. It has been shown that urine albumin excretion is inversely related to adiponectin levels in obese individuals [52] and regulates albuminuria and podocyte function in mice [53]. The MDRD study showed that each 1 μg/ml increase in adiponectin increased risk of cardiovascular mortality by 6% [54]. The cause of this paradoxical relationship in patients with CKD is unclear.

Inappropriate Activation of the RAAS

The RAAS is a complex and widely studied topic well known for its central role in the regulation of blood pressure, kidney blood flow, and sodium and water regulation. The RAAS pathway encompasses several peptides and enzymes. Angiotensin II has long been considered to be the predominant effector peptide of the RAAS to exert its maladaptive effects via the angiotensin II receptor type I. However, recently several other effector molecules have been identified at the tissue level establishing the existence of both circulatory and tissue-based RAAS in several non-kidney tissues including the brain, heart, adipose tissue, and pancreas [55]. Additionally, there have been a number of observations that highlight the tissue level RAAS functions independent of the systemic RAAS.

Angiotensin II levels in the kidneys are several fold higher than the systemic levels [56], and angiotensin receptor blockade contributes to a disproportionately higher vasodilation despite low plasma renin activity [57]. Further, in the obese, insulin-resistant individual, persistently elevated insulin levels lead to activation of SNS and RAAS along with obesity-induced physical compression of kidneys that collectively contribute to increased renal tubular sodium reabsorption, volume expansion, and hypertension [58].

When considering the salt retention and hyperfiltration and the systemic activation of the RAAS, this is then inappropriate.

It is well known angiotensin II increases glomerular pressure and induces intrarenal inflammatory cytokines and growth factors that contribute to development of albuminuria [59, 60]. Angiotensin II is also shown to stimulate proliferation of mesangial cells, glomerular endothelial cells, and fibroblasts [60]. Additionally, there has recent interest in excess aldosterone in promotion of altered insulin signaling and its contribution to hypertension and kidney structural and functional abnormalities independent to that of angiotensin II [61, 62].

Inappropriate activation of the RAAS is associated with cardiovascular and kidney diseases. Recently, an abnormally hyperactive RAAS has also been implicated in pathogenesis of metabolic syndrome [63–66]. Hyperactive systemic RAAS and adipose tissue RAAS has been associated with human obesity and various other animal obesity models [67]. The common link also extends to hyperglycemia, hypertension, and cortisol that are associated with activation of RAAS and also are risk factors for metabolic syndrome [68]. Recently, specific polymorphisms in RAAS have been linked to the development of the syndrome [69].

Patients with diabetes demonstrate hyperglycemia either secondary to impaired secretion of insulin or decreased sensitivity to insulin. The resultant hyperglycemia is associated with activation of RAAS at the tissue level. In rodent models, Singh et al. demonstrated that hyperglycemia is associated with an increase in angiotensinogen and angiotensin I ultimately resulting in an increased mesangial angiotensin II. They also demonstrated other angiotensin-related peptides (angiotensin 1–9, angiotensin 1–7, and angiotensin 3–8) and also that hyperglycemia facilitates the conversion of mesangial angiotensin 1–9 to angiotensin II [70]. Zhang et al. proved that these are mediated through the stimulatory effect of hyperglycemia on angiotensinogen gene expression in the renal proximal tubular cells and on a molecular level at least partly through the activation of protein kinase C independent, p38 mitogen-activated protein kinase signal transduction pathway [71]. There is also a role for succinate stimulating the novel metabolic receptor GPR91 behind the mechanism of RAAS activation in hyperglycemia [72]. Similar observations of increased angiotensin II levels in the cardiac myocytes leading to cardiomyocyte apoptosis and fibrosis have been made [73].

Both animal and human experiments have proven the ability of RAAS inhibition to improve hyperglycemia. In human studies, angiotensin receptor blockade improves beta-cell function and insulin sensitivity and reduces the progression to overt diabetes [74, 75]. In another study, although angiotensin-converting enzyme (ACE) inhibition did not reduce the incidence of diabetes, it demonstrated increased regression to normoglycemia [76]. These observations elucidate the causal link of RAAS in causing hyperglycemia and the ability to regress toward normoglycemia with its inhibition [77].

Increased adipose tissue is the hallmark of obesity, and it is an integral part of metabolic syndrome, impaired glucose tolerance, and diabetes [78]. The decreased insulin sensitivity of obesity has been well known for its association with hyperglycemia, and RAAS inhibition results in decreased incidence of hyperglycemia. There is also strong evidence that obesity activates both systemic and tissue RAAS emphasizing it as a unifying mechanism in the cardiorenal metabolic syndrome. Adipose tissue is regarded as an autocrine organ with presence of all the components of RAAS [79]. Typically angiotensinogen is synthesized by the liver in lean individuals, but in obese individuals adipose tissue is an important source [80]. After the above described cascade of reactions, the final effector molecule angiotensin II acts locally to mediate fat mass expansion via angiotensin II receptor (AT_1R) types 1 and 2, by decreasing lipolysis and increasing lipogenesis, respectively. About one-third of the circulating angiotensinogen is contributed by adipose tissue and is to be considered as an autocrine and more recently an endocrine organ [81].

Patients with obesity demonstrate several abnormalities including increased circulating levels of angiotensinogen, renin, ACE, and angio-

tensin II and increased adipose tissue levels of renin, ACE, and angiotensin II expression [67, 82]. These abnormalities tend to improve or resolve with weight loss [83]. There is some discrepancy from animal models of obesity that revealed that these relationships could be strain specific. There is also evidence that systemic RAAS stimulation results in weight loss in contrast to the stimulation of the adipose tissue RAAS that causes weight gain [81, 84]. These facts highlight the complexity of the pathology behind the syndrome. Overall, the consensus is that both systemic and tissue RAAS are overactive in humans with obesity. RAAS inhibition has been demonstrated to have reduced obesity in hypertensive obese humans [85].

Endothelial Dysfunction

The endothelium is composed of a single layer of cells lining the luminal surface of the vasculature and plays a central role in vascular tone. This is primarily mediated by the local production of nitric oxide (NO). Endothelial NO synthase, an enzyme, and tetrahydrobiopterin, a cofactor, facilitate the reaction that leads to synthesis of NO from L-arginine. Mechanical shear stress is the most important stimulus for eNOS [86]. Several other chemical mediators like bradykinin and adenosine mediate nonmechanical stimulation of eNOS [87]. NO diffuses into the vascular smooth muscle activating guanylate cyclase and resulting in a c-GMP-mediated vasodilation. Beyond vasomotor regulation, a normal endothelium is important in prevention of atherosclerosis through regulation of smooth muscle cell proliferation and vessel wall inflammation, cellular adhesion, and even resistance to thrombus formation [88]. Endothelial function is assessed by endothelium-dependent vasodilation, markers of activation, and damage [89]. Assessment of endothelium-dependent vasodilation is done by the degree of vasodilation in response to nitric oxide, the local levels of which can be increased pharmacologically or mechanically. Endothelial activation and damage occur with the inflammation of the endothelium with excess circulating levels of factors such as soluble intercellular adhesion molecule, von Willebrand factor, plasminogen activator inhibitor-1 (PAI-1), and CRP [88, 90–93].

The hallmark of a diseased endothelium is decreased NO and impaired vasodilation. This can result from reduced NO production or increased destruction of NO by reactive oxygen species [88]. Diabetes or impaired glucose intolerance, dyslipidemia, and hypertension are independent risk factors for endothelial dysfunction [94–97]. This is explained by the presence of impaired endothelium-dependent vasodilation [94, 98, 99] and increased levels of various markers in circulation as described above [100–102]. Metabolic syndrome is a clinical entity that is a result of clustering of several of the above risk factors. This translates to a proportionally greater magnitude of the biochemical abnormality [103] and greater cardiovascular risk [98]. The overall endothelial dysfunction leads to leaky capillaries in the kidneys giving rise to microalbuminuria that has elevated microalbuminuria as a diagnostic criterion to define metabolic syndrome [13]. In patients with metabolic syndrome, several interventions including dietary alterations, physical exercise, and treatment of diabetes, dyslipidemia, and hypertension are associated with improvement in the markers of endothelial dysfunction [89, 100, 104].

Conclusions and Perspectives

The relationship between diabetes and CKD and CKD-related outcomes is well established. However, the impact that insulin resistance and hyperinsulinemia has on cardiorenal risk and progressive kidney dysfunction is emerging and as important as the effects of hyperglycemia derived from overt diabetes. There is strong population level data to support this association and equally strong experimental data to support this relationship. The various mechanisms that excess insulin has on fat-derived adipokines, inflammation, oxidative stress, and inappropriate activation of the RAAS and SNS collectively lead to impaired renal hemodynamics and downstream vascular

proliferation, extracellular matrix deposition, and fibrosis. There is further need to understand the impact of insulin resistance and hyperinsulinemia on kidney disease. While the impact that interruption of the RAAS has on CKD is clear, the effect of non-pharmacological measures such as physical activity and weight reduction, along with pharmacological interventions such as insulin-sensitizing agents, is less clear.

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