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Metabolic risk factors and renal disease

JR Sowers[1]

Accumulating evidence supports that components of the metabolic syndrome coexist with both albuminuria and chronic kidney disease (CKD). The article by Tomaszewski et al. indicates that this interrelation exists in young obese men before overt renal or cardiovascular disease and also suggests that early treatment of hypertension is especially compelling to prevent the evolution of renal hyperfiltration to CKD.

In addition to the generally recognized relationship between the metabolic syndrome and the future development of type 2 diabetes and cardiovascular disease, there is emerging evidence of an important relationship among the metabolic syndrome, obesity, and both albuminuria and chronic kidney disease (CKD).[1–10] Early data suggesting this relationship[1,2] have been confirmed in large population-based studies.[3–8] For example, the relationship between body mass index and end-stage renal disease (ESRD) was observed in a Japanese population of over 100,000 people followed for 17 years. The cumulative incidence of ESRD increased significantly with rising body mass index; after adjustment for age, systolic blood pressure, and proteinuria, the odds ratio of body mass index for developing ESRD was 1.273 in men.[3] Likewise, in 10,096 nondiabetic participants in the Atherosclerosis Risk In Communities Study, the odds ratio for developing CKD in those with the metabolic syndrome compared with those without the syndrome was 1.43.[6]

Similarly, in a cohort of 320,252 adults from the United States followed up over a 15- to 35-year period, the rate of ESRD increased in a manner proportional to rising body mass index.[7] These data confirm the original observation that metabolic syndrome risk factors (elevated triglycerides and low levels of high-density lipoprotein cholesterol) accelerate progression to ESRD.[1]

Increasing components of the metabolic syndrome augment the risk for microalbuminuria[4] and proteinuria.[5] For example, the association between components of the metabolic syndrome and the risk for microalbuminuria, as well as CKD, was assessed in persons participating in the Third National Health and Nutrition Examination Survey (NHANES III).[4] In multivariate-adjusted analysis, the odds ratio for microalbuminuria and CKD was 1:89 and 2:60, respectively. Further, the risk for microalbuminuria and CKD was proportional to the number of individual components of the metabolic syndrome. Similar observations were made in a Japanese population in which the influence of the metabolic syndrome was documented in men younger than 60 years.[8]

Tomaszewski and colleagues[11] (this issue) have now advanced our understanding of these relationships between metabolic and renal disease risk factors. They carefully phenotyped 1,572 young (mean age 18.4 years), relatively healthy men for metabolic risk factors and renal function as analyzed by calculated creatinine clearance based on the Cockcroft–Gault equation. They observed that enhanced metabolic risk — clustering of at least three metabolic risk factors — was present in 8.7% of these young men and was associated with an odds ratio of 6.9 for glomerular hyperfiltration. This early renal abnormality was associated with adiposity (leptin levels and anthropometric determinants) and elevated blood pressure, each components of the metabolic syndrome.

In their discussion of the observed associations,[11] the authors propose that a major driver of hyperfiltration is probably adipose tissue — a source of inflammatory adipokines and leptin,

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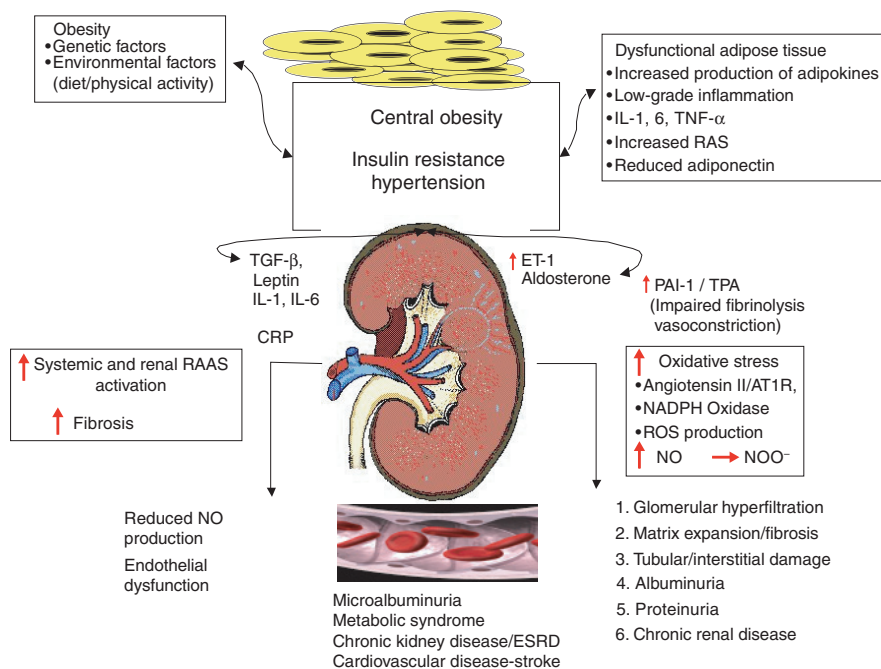
Figure 1 | Relationship between obesity and insulin resistance/compensatory hyperinsulinemia, components of the metabolic syndrome, and the development of renal injury, chronic kidney disease, end-stage renal disease, and cardiovascular disease. Insulin resistance and compensatory hyperinsulinemia are at the root of activation of the renin–angiotensin system (RAS), oxidative stress, low-chronic systemic inflammation, glomerular hypertension, microalbuminuria, matrix expansion, and fibrosis. AT1R, angiotensin II type 1 receptor; CRP, C-reactive protein; ESRD, end-stage renal disease; ET-1, endothelin-1; IL, interleukin; NADPH, ; NO, nitric oxide; PAI-1, plasminogen activator inhibitor 1; RAAS, ; ROS, reactive oxygen species; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α; tPA, tissue-type plasminogen activator.

which stimulate glomerular hypertension and remodeling (Figure 1).[9,10] Indeed, obesity — in particular, visceral-type adiposity — is characterized by dysfunctional adipose tissue and is a known source of inflammatory adipokines, including components of the renin–angiotensin system, tumor necrosis factor-α, interleukin-1, interleukin-6, leptin, and resistin, all of which have been implicated in insulin resistance.[9] The resulting decreased insulin sensitivity and hyperinsulinemia, in conjunction with hypertension, contribute to glomerular mesangial expansion, podocyte remodeling, loss of slit pore diaphragm integrity, and basement membrane thickening, all of which can lead to glomerulosclerosis and tubulointerstitial injury (Figure 1).[9,10]

Activation of the renin angiotensin aldosterone system (RAAS) also contributes to this early glomerular and tubulointerstitial remodeling/injury,

in part through generation of reactive oxygen species.[10] Whaley-Connell *et al.*[10] recently reported that angiotensin II increases NADPH oxidase/reactive oxygen species and that this is a major contributor to podocyte effacement and loss of slit pore diaphragm integrity, leading to albuminuria. Angiotensin II and aldosterone, as well as inflammatory adipokines, contribute to renal fibrosis as well as glomerular and tubulointerstitial remodeling and injury.[9] Other potential actions of an activated renal RAAS include increased tubular sodium reabsorption, renal vasoconstriction, altered tubuloglomerular feedback as well as pressure induced changes in sodium excretion (Figure 1). These renal alterations, in turn, can promote systemic vascular inflammation and endothelial dysfunction, as well as worsening hypertension, resulting in a progressive cardiovascular–renal injury feedback loop.[9]

Obesity and insulin resistance also lead to an imbalance in the endogenous fibrinolytic system, with elevation of the levels and activity of plasminogen activator inhibitor 1 and relative reductions in plasminogen activator activity.[9] In animal models, increased plasminogen activator inhibitor 1 has been demonstrated to inhibit matrix metalloproteinases, leading to impaired glomerular extracellular matrix degradation, with subsequent mesangial matrix expansion and fibrosis.[9] Indeed, elevated plasma levels of both plasminogen activator inhibitor 1 and other coagulation factors, such as factor VII, have been associated with increased urinary protein excretion. Thus, obesity, insulin resistance, and hypertension promote the progression of renal disease; and Tomaszewski *et al.*[11] emphasize the fact that this association occurs early in young persons.

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