Renal Manifestations in the Metabolic Syndrome

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The metabolic syndrome, which is characterized by obesity, serum lipid profile alterations, hypertension, and fasting hyperglycemia, is very common in developed countries, and its prevalence is likely to increase. Chronic kidney disease (CKD) also has become a significant public health problem because it affects a considerable proportion of the adult population and is a major risk factor for cardiovascular disease and premature death. Although it is widely known that the metabolic syndrome is a major risk factor for the development of type 2 diabetes and cardiovascular disease, its precise relationship with the risk for renal impairment only recently has been clarified: Patients with the metabolic syndrome are at significantly higher risk for microalbuminuria and/or CKD, and the level of risk is related to the number of components of the syndrome itself. Although it is difficult to discriminate the detrimental renal effects of the metabolic syndrome from those of hypertension and impaired glucose metabolism, its other aspects (particularly obesity) may favor independently the development of renal abnormalities and may be considered new modifiable risk factors for CKD. These observations provide a rationale for intervention studies that aim to verify whether treating the many components of the metabolic syndrome can effectively prevent the development and progression of renal damage.


The metabolic syndrome (also known as syndrome X or the insulin resistance syndrome) is a complex pattern of disorders that were described for the first time by Reaven in 1988 (1) and whose main features consist of abdominal obesity, hypertriglyceridemia, low HDL cholesterol levels, high BP, and high fasting blood glucose levels. Although somewhat different definitions of the syndrome have been proposed since its first description, the guidelines of the 2001 National Cholesterol Education Program—Adult Treatment Panel III (2) now are widely used to identify it (Table 1), although a recent report from the National Heart, Lung, and Blood Institute and the American Heart Association (NHLBI/AHA) (3) recommended lowering the cutoff point for fasting blood glucose levels and abdominal obesity in men and proposed diagnosing the syndrome in the presence of only two of the defined criteria (Table 1). However, it cannot be excluded that the identification of additional risk factors, such as high C-reactive protein levels (4), soon will lead to a broader definition of the syndrome. Pathogenetically, it is thought that insulin resistance plays a key role in its development, as is suggested by a number of observations linking insulin resistance (clinically defined by the detection of abnormally high plasma insulin concentrations) with each of the syndrome’s components (5).

The metabolic syndrome is very common in developed countries, and its prevalence is expected to become even higher in the near future, together with the rapidly increasing prevalence of obesity. For many years, there were few data concerning the relationship between the metabolic syndrome and the risk for developing renal abnormalities; however, recent epidemiologic analyses have found that patients with the syndrome also are at high risk for microalbuminuria and/or chronic kidney disease (CKD), thereby allowing the identification of a target population that may benefit from therapeutic strategies that aim to prevent the development of renal manifestations.

Metabolic Syndrome and CKD: Two Major Public Health Problems

The epidemiologic impact of the metabolic syndrome was evaluated in 8814 adults who were aged 20 yr or more in the United States and participated in the Third National Health and Nutrition Examination Survey (NHANES III) between 1988 and 1994 (6). The overall age-adjusted prevalence of the metabolic syndrome in this population (as defined by the 2001 National Cholesterol Education Program—Adult Treatment Panel III criteria) was approximately 24%, with a clear age-dependent increase (6.7% in those aged 20 yr and up to 42% in those aged >70 yr) (6). Applying these results to the US resident population, it can be estimated that 47 million US residents who were 20 yr or older satisfied the diagnostic criteria for the metabolic syndrome in 2000.

A number of conditions have been associated with an increased risk for the metabolic syndrome; increased body weight plays the most important role. The observed prevalence of the metabolic syndrome in NHANES III was 5% among the subjects of normal weight, 22% among the overweight, and 60% among the obese (7). A Framingham Heart Study report indicated that a weight increase of ≥2.25 kg over a period of 16 yr was associated with an up to 45% increased risk for developing the metabolic syndrome (8), and it was shown recently that each 11-cm increase in waist circumference is associated with an adjusted 80% increased risk for developing the syndrome within 5 yr (9). The rapidly increasing prevalence of obesity in the adult US population (10) suggests that the current number
of individuals who have the metabolic syndrome very probably is much higher than that estimated on the basis of the NHANES III analysis. In fact, a recent comparison of NHANES III and NHANES 1999 to 2000 data found that the overall age-adjusted prevalence of the syndrome increased from 24 to 27% (32% when using a glucose cutoff point of 100 mg/dl) of the 1677 individuals who participated in NHANES 1999 to 2000, with the percentage increase being particularly high (23.5%) among women (11). On the basis of these prevalence estimates and using the revised NHLBI/AHA definition, it is possible to estimate that at least 64 million adults in the United States were actually affected by the metabolic syndrome in 2000.

Like the metabolic syndrome, CKD is increasingly emerging as a major public health problem, although it is still probably underestimated because widely accepted definitions of the disease only recently have been developed and only a few epidemiologic analyses have been undertaken. A recent analysis of a large nationally representative sample of US adults that was performed between 1989 and 1994 (13) found that the prevalence of moderate to severe kidney dysfunction (defined as an estimated GFR of 15 to 59 ml/min per 1.73 m²) was 4.4%, whereas the prevalence of mildly decreased kidney function (an estimated GFR of 60 to 89 ml/min per 1.73 m², corresponding to stage 2 CKD according to the Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines [12]) was 36.3%, approximtely 5% more than that found in a similar survey performed between 1989 and 1994 (13). This means that >40% of the US adult population (75 million people) can be expected to have CKD, even when patients with detectable kidney damage but without a reduced GFR are excluded.

The consequences of the increasing epidemiology of CKD are devastating, not only for the patients themselves but also in terms of the economic demands on society. CKD often is characterized by progression to ESRD, a condition that requires renal replacement treatment (RRT) if the patients are to survive and thus accounts for a disproportionate part of health care resources. The prevalence of RRT in the United States increased by 97% from 1991 to 2000, and it has been estimated that an additional 60% increase will occur between 2001 and 2010, when it is expected that 650,000 patients will require RRT (14).

Table 1. NCEP-ATP III diagnostic criteria for metabolic syndrome and revised criteria as proposed by NHLBI/AHA

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NCEP-ATP III (2)</th>
<th>NHLBI/AHA (3)</th>
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<tbody>
<tr>
<td>Waist circumference (cm)</td>
<td>&gt;102 in men</td>
<td>&gt;94 in men</td>
</tr>
<tr>
<td></td>
<td>&gt;88 in women</td>
<td>&gt;88 in women</td>
</tr>
<tr>
<td>Serum triglycerides (mg/dl)</td>
<td>≥150</td>
<td>≥150</td>
</tr>
<tr>
<td>Serum HDL cholesterol (mg/dl)</td>
<td>&lt;40 in men</td>
<td>&lt;40 in men</td>
</tr>
<tr>
<td></td>
<td>&lt;50 in women</td>
<td>&lt;50 in women</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td>≥130/85</td>
<td>≥130/85</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dl)</td>
<td>≥110</td>
<td>≥100</td>
</tr>
<tr>
<td>No. of criteria needed for diagnosis</td>
<td>3</td>
<td>2</td>
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In addition to being a precursor of ESRD, CKD is a major risk factor for cardiovascular disease, the risk for which increases with the progressive decrease in kidney function (15). In relation to this, a recent survey of almost 28,000 patients who had CKD and were followed for up to 66 mo surprisingly found that such patients are at greater risk for dying (mainly because of cardiovascular disease) than developing ESRD, regardless of the stage of CKD at the time of first evaluation (16).

**Metabolic Syndrome and Risk for Developing Renal Abnormalities**

Although the metabolic syndrome has been associated with a number of clinical conditions, including the subsequent development of type 2 diabetes, cardiovascular disease, fatty liver disease, polycystic ovary syndrome, and sleep-disordered breathing, as well as with increased all-cause and cardiovascular mortality (17–20), few data are available concerning its relationship with the risk for developing renal abnormalities, particularly CKD and microalbuminuria. Despite this, some groups have recently examined the association between the syndrome and renal impairment and found that affected individuals are at increased risk for presenting renal manifestations. A cross-sectional survey of nondiabetic native Americans that was conducted by Hoehner et al. (21) found that, after controlling for social, demographic, and comorbidity factors, the patients with one to two and those with three or more traits were, respectively, 80 and 130% more likely to have microalbuminuria than those without the syndrome. Chen et al. (22) extracted data from the NHANES III database of >6000 adults and found that the multivariate-adjusted risk for both microalbuminuria and CKD (defined as a GFR of <60 ml/min per 1.73 m²) was significantly higher in those with than in those without the metabolic syndrome and that the risk increased progressively with the number of the syndrome’s components detected in each patient.

Although the results of these studies suggest that there is a close association between the metabolic syndrome and renal dysfunction, it is difficult to draw any definitive conclusion concerning a cause-and-effect relationship because of the com-
plexity of their interrelationships. First, many patients with the metabolic syndrome are hypertensive and/or have diabetes (i.e., affected by at least one widely known risk factor for the development and progression of CKD). For example, Chen et al. (22) found that hypertension and fasting plasma glucose levels of >110 mg/dl were the individual traits of the syndrome that are associated with the greatest risk for microalbuminuria and (with the exception of hyperglycemia) a low GFR. However, some data suggest that other aspects of the metabolic syndrome may play an independent role in promoting renal damage. Chen et al. (22) found that reduced HDL cholesterol or high triglyceride levels were independently associated with a significantly increased risk for CKD, strengthening the results of a previous prospective study by Muntner et al. (23), who found that the same serum lipid abnormalities predicted the development of renal impairment in patients with normal renal function at baseline.

A number of findings also indicate obesity (a cardinal feature of the metabolic syndrome) as an independent factor for causing renal dysfunction. The multivariate analysis made by Chen et al. (22) showed that the risk for being affected by CKD was more than twice as high in patients with an increased waist circumference than in those without, suggesting that obesity may be an independent risk factor for CKD. The role of obesity as a potentially important cause of CKD also was indicated in a community-based analysis of a large sample of Japanese patients that was conducted by Iseki et al. (24), who found that the risk for developing ESRD was significantly higher in men with an increased body mass index, even after adjustments for BP and proteinuria, two overweight-related factors that may have accounted for a nonindependent detrimental effect of obesity on renal function. Moreover, since the first description of an association between massive obesity and nephrotic proteinuria in 1974 (25), a specific histopathologic pattern characterized by glomerulomegaly, in many cases accompanied by focal segmental glomerulosclerosis, has been described repeatedly in obese patients without any other defined primary or secondary glomerular diseases (including diabetic nephropathy, hypertensive nephrosclerosis, and secondary focal segmental glomerulosclerosis) and now is referred to as “obesity-related glomerulopathy” (26). At the clinical level, this glomerulopathy typically is associated with overt proteinuria (frequently within the nephrotic range) and renal insufficiency in nearly half of the patients and often is characterized by a progressive clinical course (26). It also is worth noting that a 10-fold increase in the biopsy incidence of this condition was observed over a period of 15 yr (from 0.2% of all renal biopsies in 1986 to 1990 to 2.0% in 1996 to 2000) (26), and this reflects the epidemiologic data showing an increase in the prevalence of obesity in the general population during the same period (27).

Although the exact mechanisms that link obesity and renal damage have not yet been elucidated completely, it can be speculated that at least some of the many inflammatory cytokines that are secreted by adipose tissue, including leptin, IL-6, TNF-α, and adiponectin, may be involved at least partially in promoting renal impairment (28); in particular, the high plasma leptin levels that are observed in obesity may predispose to glomerulosclerosis as a result of the intrarenal upregulation of TGF-β (29). However, it is thought that other obesity-related factors, such as altered renal hemodynamics (partially as a result of high dietary protein intake), hyperlipidemia, excess renal sodium reabsorption, activation of the renin-angiotensin and sympathetic nervous systems, and physical compression of the kidneys by adipose tissue, may lead to complex interactions between intrarenal physical forces, neurohumoral factors, and local mediators (growth factors and cytokines) that ultimately give rise to glomerular hyperfiltration, glomerular cell proliferation, matrix accumulation, and, finally, glomerulosclerosis and the loss of nephrons (30).

Potential Strategies for Preventing Renal Damage in Metabolic Syndrome

The observed association between the metabolic syndrome and the risk for renal dysfunction raises the question of whether correcting one or more of the syndrome’s many features may effectively prevent CKD. Although the aggressive treatment of all metabolic alterations in such patients may be warranted to prevent the development of extrarenal complications, it is unclear whether this may prevent renal impairment. It has been shown that intensive BP and blood glucose control effectively prevents the development of microalbuminuria and overt nephropathy in patients with diabetes (31–34), but the extent to which this is true also in patients with the metabolic syndrome needs to be confirmed by appropriate clinical trials. Furthermore, the nephroprotective superiority of angiotensin-converting enzyme inhibitors over other antihypertensive drug classes that has been suggested by a number of clinical trials involving patients with diabetes (35,36) still needs to be demonstrated in the context of the metabolic syndrome. Some recent studies, including a meta-analysis of clinical trials, have shown the effectiveness of lipid-lowering treatments in decreasing proteinuria and slowing the rate of the decline in GFR in patients with CKD (37), but whether they also are effective in preventing the onset of renal impairment in patients with normal renal function is still unclear. Finally, although there is no doubt that all obese individuals should be encouraged to undertake physical activity and change their eating habits, the significant impact of weight loss on renal outcomes suggested by preliminary observations (38) still needs to be demonstrated by properly designed clinical trials.

Consequently, because of the lack of evidence from clinical trials specifically involving patients with the metabolic syndrome, it is still unclear whether therapeutic interventions that aim to correct the various abnormalities of the metabolic syndrome (possibly using a multifactorial approach) can actually prevent the development and/or progression of renal damage. Until such trials are conducted, the only available preventive strategy consists of considering patients with the metabolic syndrome as a subset of patients who are at very high risk for developing microalbuminuria and/or CKD and who therefore require close monitoring to ensure the early recognition and treatment of subsequent renal abnormalities and their related complications.
Conclusion
A close association has been found between the metabolic syndrome and the risk for developing renal damage, clinically expressed in the form of microalbuminuria and/or CKD. This finding raises a major clinical and public health concern because both the metabolic syndrome and CKD are increasingly common disorders in all developed countries. Although it is difficult to discern the detrimental renal effects of the metabolic syndrome from those of hypertension and impaired glucose metabolism, various experimental and epidemiologic data suggest that other aspects of the syndrome (particularly obesity) may favor independently the development of renal abnormalities and thus become newly recognized (but no less important) modifiable risk factors for CKD in addition to diabetes and hypertension.

Despite the close association between the metabolic syndrome and renal damage, it is still unclear whether and to what extent treating patients with the metabolic syndrome will prevent the development and progression of CKD. Given the epidemic nature of the problem, the planning of clinical trials to prevent the development and progression of CKD is a research priority.

References
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