Metabolic Syndrome: An Emerging Threat to Renal Function

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In this issue of *CJASN*, no fewer than three articles deal with different aspects of the metabolic syndrome (MS) and its impact on the kidney—testimony to the fact that the MS is a topic of considerable current interest and of intense investigation. Obesity and the associated MS have become a scourge to the Western world. It has even been argued that the spectacular continuous increase in life expectancy and general health during the past decades may come to a halt or even be reversed by the ongoing epidemic of obesity, particularly in the young (1). The concept of risk factor clustering has a longstanding history going back to the early 20th century (2), but the idea of linking such clustering to insulin resistance was raised in the famous Banting lecture of G. Reaven (3). Among the numerous current definition(s) of the MS (World Health Organization, European Group for the Study of Insulin Resistance, American Association of Clinical Endocrinologists, and International Diabetes Federation), the one proposed by the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [NCEP-ATPIII]) (4) is most widely used. With good arguments, it has been criticized that some components in the NCEP definition are loosely, if at all, linked to insulin resistance as the assumed unifying pathomechanism (5). The "father" of the original idea, G. Reaven, even wrote a paper with the sarcastic title "The Metabolic Syndrome: Requiescat in Pace" (6). The shortcomings of the MS as defined by NCEP-ATPIII are obvious: The individual traits that compose the MS cluster have no tight relation to insulin resistance; predictive power is lost by omitting powerful predictors of cardiovascular risk, particularly age and smoking, and by adopting categorization (yes/no) for continuous variables (*e.g.*, diagnosis of hypertension instead of using BP values [7]). This may explain the following findings: In the Groningen study, the Framingham score and microalbuminuria were superior to NCEP criteria as predictors of cardiovascular events in the general population, and in the Pittsburgh study (8), microalbuminuria was more predictive of events than the MS score in patients with type 1 diabetes—an outcome not shocking to the nephrologist who is already convinced that kidney function is a most powerful indicator of cardiovascular malfunction and risk.

Despite all of these critiques, the lumping of the cluster of risk factors into one MS formula has remained popular. Although defective as a scientific tool, MS has the merit to have raised awareness of the obesity problem in the medical community and in the general population.

The concept of the MS was originally created to predict cardiovascular risk. Given the link between cardiovascular and renal risks (as we know today, this cuts both ways), it is little surprising that obesity, particularly visceral obesity (9), and MS are related to renal malfunction (*i.e.*, microalbuminuria and low estimated GFR [eGFR] [10–12]). This relationship is apparently also found in individuals with renal disease: In type 1 diabetes, the MS score was higher the more advanced the stage of diabetic nephropathy (13), and obesity (presumably also MS) is a risk factor for deterioration of renal function in primary renal disease as well (14). Part of the explanation for why obesity increases the risk for ESRD in the general population is the link between obesity and diabetes on the one hand and with hypertension on the other hand (7). Even when corrected for these two indirect pathomechanisms, the relation between obesity (15) and ESRD and between MS and chronic kidney disease (CKD) (10) persists, showing that, in addition, direct pathomechanisms are triggered by visceral (9) obesity such as increased GFR and renal blood flow, glomerulomegaly (16), podocyte damage (17), and, in extreme cases, even FSGS (18).

The relation between MS and early stages of kidney malfunction (*i.e.*, microalbuminuria and low eGFR) had first been recognized in the United States, but recent reports from Japan (19), China (20), and Thailand (21) document the same relationship. In this context, the report of Rashidi *et al.* (22) (in this issue) in a relatively small sample from Iran but with 3 yr of follow-up of eGFR is a welcome addition. The agreement of the findings in Iran with those in the United States is remarkable, given the differences of genetic backgrounds and lifestyles between these countries. Unfortunately, overcaloric nutrition and lack of physical exercise, possibly also excessive consumption of fructose (23), are certainly not restricted to the United States and Western Europe. The proportion of patients who have MS and develop CKD (*i.e.*, eGFR <60 ml/min per 1.73 m^2) was remarkably similar in the United States: 7% within 9 yr of follow-up in the ARIC study (12) and 3.4% within 3 yr in the study from Iran. Particularly in view of the differences in lifestyle, such international comparisons may be useful to identify more precisely the culprit mechanisms involved.

The salient features in the genesis of microalbuminuria and loss of GFR in patients with MS are hypertension and insulin resistance/abnormal glycemia (11). In the study of Franciosi *et*

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al. (24) (in this issue), postload glycemia and insulin resistance as evaluated by the homeostasis model of insulin resistance were powerful predictors of the risk for microalbuminuria in concert with hypertension and age. Logistic regression analysis identified lipid changes (triglyceride elevation, inverse relation to statin use), hypertension, and the homeostasis model assessment of insulin resistance as contributors to the presence of microalbuminuria—all features that are potentially susceptible to intervention (*e.g.*, statins, renin-angiotensin system blockade, glitazones). As a note of hope in this population-based, cross-sectional study, the risk for microalbuminuria was significantly lower in hypertensive patients who were on renin-angiotensin system blockade than on treatment with alternative antihypertensive agents.

To the shopping list of pathologic features associated with the MS, one more addition has been made by Maalouf *et al.* (25) (in this issue): Lower acidity of the urine. Why is this of potential clinical relevance? It may explain the link of MS to uric acid stones that form in acidic urine. The underlying pathomechanism(s) remains unclear. By measuring urinary sulfate excretion, the authors excluded to some extent pedestrian explanations such as greater food (protein) intake, but after this interesting initial observation, further work to identify the pathophysiology is required.

Obesity and MS have become important targets for intervention, given the worldwide frightening "epidemic" of CKD and the resulting current quest to identify factors that contribute to the onset of CKD and promote its progression. Further investigations should be stimulated by the consideration that the better we understand the underlying mechanisms, the more effective will be our interventions: Thou should'st know thy enemy.

Disclosures

None.

References

1. Olshansky SJ, Passaro DJ, Hershow RC, Layden J, Carnes BA, Brody J, Hayflick L, Butler RN, Allison DB, Ludwig DS: A potential decline in life expectancy in the United States in the 21st century. *N Engl J Med* 352: 1138–1145, 2005
2. Hitzenberger K: R-QM: A contribution to the (deranged) metabolism (in patients with) vascular hypertension [in German]. *Wiener Arch Innere Med* 2: 189, 1921
3. Reaven GM: Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes* 37: 1595–1607, 1988
4. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 285: 2486–2497, 2001
5. Kahn R, Buse J, Ferrannini E, Stern M: The metabolic syndrome: Time for a critical appraisal—Joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 28: 2289–2304, 2005
6. Reaven GM: The metabolic syndrome: Requiescat in pace. *Clin Chem* 51: 931–938, 2005
7. Bakker SJ, Gansevoort RT, de Zeeuw D: Metabolic syndrome: A fata morgana? *Nephrol Dial Transplant* 22: 15–20, 2007
8. Pambianco G, Costacou T, Orchard TJ: The prediction of major outcomes of type 1 diabetes: A 12-year prospective evaluation of three separate definitions of the metabolic syndrome and their components and estimated glucose disposal rate—The Pittsburgh Epidemiology of Diabetes Complications Study Experience. *Diabetes Care* 30: 1248–1254, 2007
9. Pinto-Sietsma SJ, Navis G, Janssen WM, de Zeeuw D, Gans RO, de Jong PE: A central body fat distribution is related to renal function impairment, even in lean subjects. *Am J Kidney Dis* 41: 733–741, 2003
10. Chen J, Muntner P, Hamm LL, Jones DW, Batuman V, Fonseca V, Whelton PK, He J: The metabolic syndrome and chronic kidney disease in US adults. *Ann Intern Med* 140: 167–174, 2004
11. Chen J, Muntner P, Hamm LL, Fonseca V, Batuman V, Whelton PK, He J: Insulin resistance and risk of chronic kidney disease in nondiabetic US adults. *J Am Soc Nephrol* 14: 469–477, 2003
12. Kurella M, Lo JC, Chertow GM: Metabolic syndrome and the risk for chronic kidney disease among nondiabetic adults. *J Am Soc Nephrol* 16: 2134–2140, 2005
13. Thorn LM, Forsblom C, Fagerudd J, Thomas MC, Pettersson-Fernholm K, Saraheimo M, Waden J, Ronnback M, Rosengard-Barlund M, Bjorkesten CG, Taskinen MR, Groop PH: Metabolic syndrome in type 1 diabetes: Association with diabetic nephropathy and glycemic control (the FinnDiane study). *Diabetes Care* 28: 2019–2024, 2005
14. Bonnet F, Deprele C, Sassolas A, Moulin P, Alamartine E, Berthezene F, Berthoux F: Excessive body weight as a new independent risk factor for clinical and pathological progression in primary IgA nephritis. *Am J Kidney Dis* 37: 720–727, 2001
15. Hsu CY, McCulloch CE, Iribarren C, Darbinian J, Go AS: Body mass index and risk for end-stage renal disease. *Ann Intern Med* 144: 21–28, 2006
16. Hall JE, Kuo JJ, da Silva AA, de Paula RB, Liu J, Tallam L: Obesity-associated hypertension and kidney disease. *Curr Opin Nephrol Hypertens* 12: 195–200, 2003
17. Nagase M, Yoshida S, Shibata S, Nagase T, Gotoda T, Ando K, Fujita T: Enhanced aldosterone signaling in the early nephropathy of rats with metabolic syndrome: Possible contribution of fat-derived factors. *J Am Soc Nephrol* 17: 3438–3446, 2006
18. Kambham N, Markowitz GS, Valeri AM, Lin J, D'Agati VD: Obesity-related glomerulopathy: An emerging epidemic. *Kidney Int* 59: 1498–1509, 2001
19. Ninomiya T, Kiyohara Y, Kubo M, Yonemoto K, Tanizaki Y, Doi Y, Hirakata H, Iida M: Metabolic syndrome and CKD in a general Japanese population: The Hisayama Study. *Am J Kidney Dis* 48: 383–391, 2006
20. Chen J, Gu D, Chen CS, Wu X, Hamm LL, Muntner P, Batuman V, Lee CH, Whelton PK, He J: Association between the metabolic syndrome and chronic kidney disease in Chinese adults. *Nephrol Dial Transplant* 22: 1100–1106, 2007
21. Kitiyakara C, Yamwong S, Cheepudomwit S, Domrongkitchaiporn S, Unkurapinun N, Pakpeankitvatana V, Sritara P: The metabolic syndrome and chronic kidney disease in a Southeast Asian cohort. *Kidney Int* 71: 693–700, 2007
22. Rashidi A, Ghanbarian A, Azizi F: Are patients who have

metabolic syndrome without diabetes at risk for developing chronic kidney disease? Evidence based on data from a large cohort screening population. *Clin J Am Soc Nephrol* 2: 976–983, 2007

23. Heinig M, Johnson RJ: Role of uric acid in hypertension, renal disease, and metabolic syndrome. *Cleve Clin J Med* 73: 1059–1064, 2006
24. Franciosi M, Pellegrini F, Sacco M, De Berardis G, Rossi MCE, Strippoli GFM, Belfiglio M, Tognoni G, Valentini M, Nicolucci A; on behalf of the IGLOO (Impaired Glucose tolerance, and Long-term Outcomes Observational Study) Study Group: Identifying patients at risk for microalbuminuria via interaction of the components of the metabolic syndrome: A cross-sectional analytic study. *Clin J Am Soc Nephrol* 2: 984–991, 2007
25. Maalouf NM, Cameron MA, Moe OW, Adams-Huet B, Sakhaee K: Low urine pH: A novel feature of the metabolic syndrome. *Clin J Am Soc Nephrol* 2: 883–888, 2007

See the related articles, "Are Patients Who Have Metobolic Syndrome without Diabetes at Risk for Developing Chronic Kidney Disease? Evidence Based on Data from a Large Cohort Screening Population," on pages 976–983, "Identifying Patients at Risk for Microalbuminuria *via* Interaction of the Components of the Metabolic Syndrome," on pages 984–991, and "Low Urine pH: A Novel Feature of the Metabolic Syndrome," on pages 883–888.