

Expert Panel Discussion

Microalbuminuria, Chronic Renal Disease, and the Effects of the Metabolic Syndrome on Cardiovascular Events

Marvin Moser, MD; James R. Sowers, MD; Henry R. Black, MD

In March 2007, a panel discussion was held following a hypertension symposium in New York, New York. The panel was moderated by Marvin Moser, MD, Clinical Professor of Medicine at the Yale University School of Medicine, New Haven, Connecticut. Serving on the panel were James R. Sowers, MD, Professor of Medicine and Physiology at the University of Missouri, Columbia, Missouri, and Henry R. Black, MD, Clinical Professor of Medicine at the New York University School of Medicine, New York, New York. This expert panel discussion was supported by Novartis and each author received an honorarium from Novartis for time and effort spent participating in the discussion and reviewing the transcript for important intellectual content prior to publication. The authors maintained full control of the discussion and the resulting content of this article; Novartis had no input in the choice of topic, speakers, or content. (J Clin Hypertens. 2007;9:551–556) ©2007 Le Jacq

DR MOSER: Jim, we hear a great deal about the metabolic syndrome, about microalbuminuria, and about their relationship to cardiovascular (CV) disease. Recently, there have been questions about whether the metabolic syndrome is actually a syndrome. Perhaps it doesn't make a difference whether you diagnose it or not because it is not going to affect how you treat hypertension or some of the other individual risk factors that are often included in the diagnosis. Some observers suggest that if we effectively manage hypertension, cholesterol, or blood glucose abnormalities, that is enough. It doesn't matter whether the patient has a "syndrome." How do you come down on all this? First of all, give us your definition of the metabolic syndrome. There are probably 4 or 5 different definitions at present. What should most physicians look for to diagnose this syndrome, and is it important to diagnose it?

DR SOWERS: It is important in my mind to delineate this syndrome because it represents a clustering of risk factors. In fact, even if you take people with diabetes, if they have other factors

that make up the metabolic syndrome, they are at significantly greater risk than diabetic patients without the other components.

DR MOSER: Okay, but how would you define the metabolic syndrome?

DR SOWERS: I would define it as the presence of central obesity (ie, waist measurement >40 in for men and >35 in for women), dyslipidemia characterized by elevated triglyceride levels, low high-density lipoprotein cholesterol (HDL-C), and an elevated blood pressure (BP) (ie, $\geq 130/85$ mm Hg). This is the definition that we've used in the United States.

DR MOSER: What is the cutoff for triglycerides and HDL?

DR SOWERS: The cutoff for triglycerides is >150 mg/dL and for HDL-C, I believe, it is below 35 mg/dL for men and below 45 mg/dL for women.

DR BLACK: Let me make a comment. When you talk about a syndrome, I think there are a few points that are important. Heart failure is a syndrome consisting of a whole variety of different etiologies that have a reasonably common clinical presentation. Does it really matter whether the



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metabolic syndrome has a common pathogenesis like insulin resistance, which some people believe, or is it just a clustering of risk factors in the same patient? Does this have any impact whatsoever on how we approach treatment?

DR SOWERS: Well, I don't think it's necessary to have a single cause, including insulin resistance, which is touted as a major cause. I believe the reason I view this as a clustering of CV and metabolic risk factors is that patients who have these findings are at greater risk than if they just had one of the components and perhaps even beyond the sum of several components.

DR MOSER: So, you think it is important for a physician to recognize the syndrome.

DR SOWERS: I don't think it's absolutely necessary to make a diagnosis of the metabolic syndrome, but I think it's nice as a paradigm to put these risk factors together to understand the accelerated CV risk. And let me just finish my definition by saying that I would include microalbuminuria and chronic kidney disease (CKD) as possible components of the metabolic syndrome.

DR BLACK: We had the issue in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) of the definition of the metabolic syndrome and whether diabetes should or should not be included. Some wanted to include definite diabetes, but I was not in favor of that option. My argument as a clinician who doesn't care too much about labels is that if someone already has diabetes, I don't care whether they have "the metabolic syndrome" when I am trying to understand their prognosis and risk. Knowing that an individual has the metabolic syndrome and is at higher risk as a result is important, but we can determine this based on the individual risk factors without having to invoke a syndrome. If diabetes mellitus is already present, then that patient will assume the risk of being diabetic.

DR SOWERS: Except that the presence of the metabolic syndrome increases the risk for heart attacks, strokes, and CKD.

DR BLACK: If someone had diabetes and dyslipidemia but wasn't hypertensive yet and didn't have proteinuria or microalbuminuria or other components compared with someone who had the metabolic syndrome . . . wouldn't you treat them just as aggressively?

DR SOWERS: Studies in Finland, the United States, and other countries indicate that having 3 components of the metabolic syndrome in addition to diabetes puts the diabetic patient at greater risk for stroke and heart attack. So, therapeutic approaches, including lowering BP to <130/80 mm Hg should, in my view, be more aggressive for

patients with the syndrome plus diabetes than for those with just diabetes mellitus.

DR BLACK: Do you really believe that treatment would be different for a patient with diabetes and the metabolic syndrome as opposed to someone with just the metabolic syndrome or someone with just diabetes?

DR SOWERS: I would treat lipid and BP abnormalities as aggressively in a person with the cardiometabolic syndrome without diabetes as in someone with diabetes without the requisite components of the syndrome.

DR MOSER: I tend to agree with Henry, but basically what Jim is saying is that he is not too concerned with different definitions or about whether we call it a syndrome or not but is concerned that the cluster of risk factors that we label as a syndrome dramatically increases risk and that it should be identified because recognition of it will change therapy.

DR SOWERS: I'm not hung up on the definition, but I believe that, if recognized, more aggressive treatment will be undertaken.

DR MOSER: Now, can a person have the metabolic syndrome without evidence of CKD?

DR SOWERS: Absolutely. It's just that microalbuminuria and evidence of CKD are predictors of other components of the metabolic syndrome, just as components of the metabolic syndrome are predictors of albuminuria and CKD.

DR MOSER: Henry, what is microalbuminuria and how do you test for it in the real world?

DR BLACK: There are several different definitions. The one that I'm most comfortable with is a permanent elevation of albumin in the urine of >30 to <300 mg/d or about >20 to <200 µg/min.

DR MOSER: So do you have to measure 24-hour urine values?

DR BLACK: No, that isn't necessary. But currently used dipsticks are not generally accurate enough to detect microalbuminuria and will only be positive if >300 mg/d is being excreted. So, you do need a special test.

DR SOWERS: You ideally would measure this in an early morning spot collection in which albumin and creatinine are measured. The albuminuria ratio (in mg) per grams of creatinine is the criterion used by most experts. A ratio of about 0.03 to 0.30 mg/g of albumin to creatinine is considered positive for microalbuminuria.

DR MOSER: What about the Micral-Test as a dipstick for microalbuminuria?

DR SOWERS: This is okay but not quite as accurate as an urinary albumin/creatinine ratio.

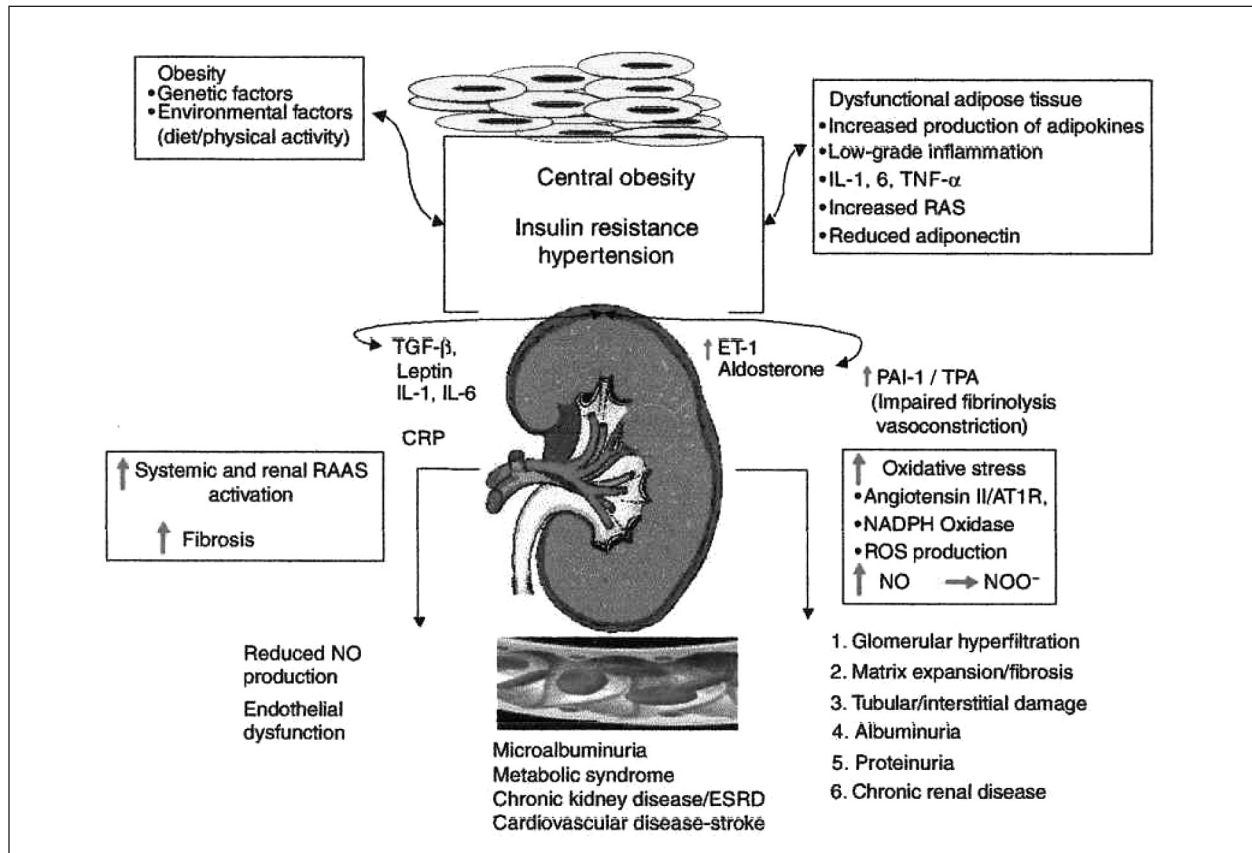


Figure. Relationship between obesity and insulin resistance/compensatory hyperinsulinemia, components of the metabolic syndrome, and the development of renal injury, chronic kidney disease, end-stage renal disease (ESRD), and cardiovascular disease. Insulin resistance and compensatory hyperinsulinemia 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 indicates angiotensin II type I receptor; CRP, C-reactive protein; ET-1, endothelin 1; IL, interleukin; NADPH, nicotinamide adenine dinucleotide phosphate oxidase; NO, nitric oxide; PAI-1, plasminogen activator inhibitor 1; RAAS, renin-angiotensin-aldosterone system; ROS, reactive oxygen species; TGF- β , transforming growth factor β ; TNF- α , tumor necrosis factor α ; TPA, tissue-type plasminogen activator.

DR MOSER: So, you should send off a spot urine test, and the laboratory does the calculation.

DR SOWERS: Yes, and expresses the ratio. Which, as we noted, should be 0.03 to 0.30 mg/g to make the diagnosis.

DR MOSER: Do you think that everyone with some CV risk factors should be tested for microalbuminuria, or is testing for high levels of protein in the urine with a regular dipstick still acceptable?

DR SOWERS: Persons with the metabolic syndrome or diabetes most certainly should be tested for microalbuminuria because the prevalence is probably between 10% and 25% and it is also more prevalent in people with hypertension.

DR BLACK: I think it is important to see whether microalbuminuria is present. There are therapeutic implications. If a patient has microalbuminuria or frank proteinuria, you might take a different approach to therapy.

DR MOSER: Is microalbuminuria related to CV risk?

DR SOWERS: It certainly is. Microalbuminuria is very clearly related to stroke, heart attacks, and coronary artery disease. The more albumin you have in the urine, the more graduated the risk and the greater likelihood you are to have CV events.

DR MOSER: Let's go back a little bit. What's the mechanism of microalbuminuria? Is it related to insulin resistance or just glomerular permeability or something else?

DR SOWERS: Glomerular permeability is increased. What happens is you lose the integrity of something called the (slit pore) diaphragm in the glomerulus, which is anchored by what we call foot processes or podocytes. So, in early damage to the glomerulus, you get a fusion of and then a sloughing off of podocytes, which are little foot processes, and you get a loss of your filtering membrane integrity.

DR MOSER: Why do you have increased glomerular permeability? Is that just part of the metabolic syndrome, a part of early diabetes, just insulin resistance, or what?

DR SOWERS: In diabetes, there are direct abnormalities associated with hyperglycemia. Anything that increases the generation of reactive oxygen species can contribute to hyperfiltration and subsequent increase in membrane permeability. Reactive oxygen species generation and inflammation are similar processes. They're defined a little differently, but, in general, I think diabetes and other diseases associated with albuminuria are associated with increased inflammation, oxidative stress, and injury, whatever causes that, whether hyperglycemia, dyslipidemia, or an increase in filtration pressure. For example, early on in diabetes or obesity there is hyperfiltration with increased pressure in the glomerulus. So, it's a multifaceted causality (Figure).

DR MOSER: Back up a little bit. We're talking about the metabolic syndrome. Did we decide that someone had to have diabetes to fall into this category?

DR SOWERS: What you do have very often in the metabolic syndrome is dysglycemia, a fasting blood glucose level of 100 mg/dL to 126 mg/dL. That in itself may be injurious. And slightly elevated BP and obesity also contribute to glomerular damage. There have been many animal studies to show that obesity is associated with increased filtration of protein in the urine.

DR MOSER: Jim, again, is there a common denominator in all this? Is hyperfiltration related to insulin resistance?

DR SOWERS: The cardiometabolic syndrome is probably caused by insulin resistance but the problem, and one of the criticisms of the definition, is that we don't measure insulin resistance in the majority of people. Different people measure it in different ways and have different definitions. Generally, insulin resistance is one of the major underlying abnormalities in the metabolic syndrome and type II diabetes. But we don't usually measure insulin resistance in clinical practice.

DR BLACK: I recall just reading a paper by Mancia's group that looked at the 5 or so definitions of the metabolic syndrome and the 5 components that make up those definitions. Elevated BP and glucose intolerance were the most predictive of outcome, much more so than the others. Insulin resistance is certainly related to these factors.

DR MOSER: A comment—insulin in a person without a disease process is a vasodilator, but in

a person with any kind of metabolic perturbation, it is a vasoconstrictor. This can effect glomerular function. In addition to that, elevated levels of insulin have an effect on growth factor and numerous other hormonal reactions that may result in renal injury.

DR SOWERS: Absolutely. You explained it very well; I'll just add a little bit. Basically, we know that insulin resistance can occur in metabolic tissues such as skeletal muscle and fat and that this is related to a reduced metabolic signaling by insulin. The insulin signaling pathway that moves glucose into cells is what we call the metabolic pathway and that involves phosphoinositol phosphate and protein kinase B. If insulin is inhibited from working through the metabolic pathway, it affects other systems.

The other signaling pathway for insulin, as you stated, involves growth and remodeling. So, insulin resistance may contribute to left ventricular hypertrophy, hyperfiltration in the kidney, or vascular remodeling. Excess insulin is inhibited from working through the metabolic pathway but continues to signal through the growth pathway. Animal studies have shown that in hypertension, insulin's 2 pathways are disparate in the sense that the metabolic pathway becomes less and less effective, whereas the growth pathway that interacts with angiotensin II, catecholamines, and growth factors continues to be activated.

DR MOSER: In insulin resistance, is angiotensin II activity increased?

DR SOWERS: Yes, there is a fair amount of evidence that the tissue renin-angiotensin-aldosterone system is turned on in insulin resistance states and that the loss of activity through the insulin metabolic pathway leads to an increase in the angiotensin II type I receptor expression and generation of tissue angiotensin II. So it does look like there is linkage between angiotensin 2 activation in tissues such as those of the heart, which, in turn, is enhanced by insulin signaling through the growth pathway.

DR MOSER: So, how does angiotensin II affect glomerular function?

DR SOWERS: It promotes hyperfiltration via a constriction of efferent arterioles. Further, elevated insulin levels promote hyperfiltration by vasodilating the afferent arteriole. So, there are several interacting factors. If albuminuria or CKD is present, the risk is further increased.

DR MOSER: Now, Jim, you mentioned oxidative stress as a factor in vascular injury. This is a term that everybody uses. Would you explain exactly what oxidative stress is? What actually are we talking about? Insulin resistance increases oxidative stress; does this

Table. Definitions of the Cardiometabolic Syndrome	
NCEP DEFINITION ^a	WHO DEFINITION ^b
Fasting glycemia ≥ 110 mg/dL	Hyperinsulinemia ($\geq 75\%$ of normal) or insulin resistance (clamp) Fasting glycemia ≥ 110 mg/dL or oral glucose tolerance test (2-hour) ≥ 140 mg/dL
Waist circumference ≥ 102 cm (men) and ≥ 88 cm (women)	Waist-to-hip ratio ≥ 0.90 (men) and ≥ 0.88 (women) or body mass index ≥ 30 kg/m ²
Triglycerides ≥ 150 mg/dL	Triglycerides ≥ 150 mg/dL
High-density lipoprotein cholesterol < 40 mg/dL (men) and < 50 mg/dL (women)	High-density lipoprotein cholesterol < 35 (men) and < 39 (women)
Blood pressure $\geq 130/80$ mm Hg	Blood pressure $\geq 140/90$ mm Hg Microalbuminuria ≥ 20 mg/min or urinary albumin/creatinine ratio ≥ 30 mg/g

^aThe National Cholesterol Education Program (NCEP) definition requires presence of at least 3 of the above diagnostic criteria.
^bThe World Health Organization (WHO) definition requires presence of hyperinsulinemia (fasting insulin in the upper quartiles of normal) of fasting glycemia ≥ 100 mg/dL and at least 2 of the above diagnostic criteria. Adapted from Manrique C, Lastra G, Whaley-Connell A, et al. Hypertension and the cardiometabolic syndrome. *J Clin Hypertens (Greenwich)*. 2005;7(8):471–476.

affect the endothelium, does it relate to inflammatory reactions, or plaque formation, etc?

DR SOWERS: Well, basically we have the generation of charged particles reactive oxygen species (ROS) all the time as a result of normal breathing and metabolism. There is a balance between production of these charged particles and their consumption. We have protective mechanisms in the body that destroy free radical particles very quickly. So when people have an excess level of charged particles at any time, it's either because they produce too many or they don't produce enough of the substances that scavenge them.

DR MOSER: And factors that produce too many might be insulin resistance, hypertension, smoking . . .

DR SOWERS: Factors that produce too many charged particles include smoking and hypertension. There is also evidence that angiotensin II itself, insulin resistance, and obesity are involved in inflammatory and oxidative stress reactions that result in vascular and renal injury. Fat tissue and macrophages in fat tissue produce charged particles and inflammatory molecules. If you lose weight, levels of all the markers of inflammation such as interleukin 1 and C-reactive protein are reduced.

DR MOSER: But is it true that in patients with insulin resistance, those systems that reduce charged particles and inflammation are not functioning very well?

DR SOWERS: People with insulin resistance and diabetes have increased production and reduced ability to utilize the dismutase/catalase systems that break down charged particles.

In diabetes for instance, just to give you an example, the ability to make nitric oxide, a major

vasodilator and moderator of endothelial function, is actually increased. If you add sugar to endothelial cells, it increases nitric oxide production. However, the nitric oxide is destroyed much more rapidly because of charged particles (ROS) that are not removed. The bottom line is that there is less nitric oxide available in diabetics.

DR BLACK: And peroxynitrite is increased.

DR SOWERS: Peroxynitrite is increased. That's another charged particle that damages the endothelium and the glomerular membrane further. It is produced when nitric oxide reacts with ROS.

DR BLACK: What do you think are the therapeutic implications for a patient who has the metabolic syndrome with or without microalbuminuria, however you wish to define it.

DR SOWERS: First of all, I think the treatment of BP should be more aggressive.

DR MOSER: So should we have a lower goal?

DR SOWERS: I think people with the cardiometabolic syndrome should have a goal of 130/80 mm Hg just as in diabetic patients even without evidence of microalbuminuria or diminished glomerular filtration rate. I also believe that the aggressiveness with which we treat dyslipidemia should be greater. There should be lower goals for cholesterol and low-density lipoprotein levels in persons with the cardiometabolic syndrome.

DR BLACK: Should we shoot for a low-density lipoprotein < 70 mg/dL in these patients?

DR SOWERS: Perhaps. But, in my view, they should be on a statin at an early age once they are diagnosed.

DR BLACK: Is the metabolic syndrome a coronary risk factor to the same degree as diabetes?

DR SOWERS: It's not exactly equivalent in an epidemiologic sense.

DR MOSER: But you would treat a patient with the metabolic syndrome like you would a diabetic or a patient with coronary heart disease.

DR SOWERS: Yes. Or like a patient with CKD. I would impose the same BP and lipid goals as in these very high-risk patients. Let me just add that at one time, Europeans actually included microalbuminuria and CKD as part of the metabolic syndrome (Table).

DR MOSER: To summarize, the presence of a cluster of CV risk factors with or without clinical

diabetes or evidence of chronic renal disease suggests that therapy should be aggressively pursued. BP and lipid abnormalities should be managed in the same way that they might be in a diabetic or a patient with evidence of coronary heart disease. A diabetic who is obese or has dyslipidemia (a majority of them do) is at even greater risk for a CV event than a diabetic without the features of the metabolic syndrome; therapy should be especially targeted. Finally, the presence of microalbuminuria, even without specific chemical evidence of chronic renal disease is associated with increased CV risk and should be considered in any treatment plan.