

## R o u n d t a b l e   D i s c u s s i o n

# The Metabolic Syndrome—What Is It and How Should It Be Managed?

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*Following a hypertension symposium in Portland, ME, in October 2005, a roundtable was convened to discuss the metabolic syndrome and its significance. Dr. Marvin Moser of the Yale University School of Medicine, New Haven, CT, moderated the discussion. Participating in the discussion were Dr. Bonita Falkner of the Jefferson Medical College of Thomas Jefferson University, Philadelphia, PA; Dr. Michael A. Weber of SUNY Downstate College of Medicine, New York, NY; and Dr. Leonard Mark Keilson of the University of Vermont College of Medicine. (J Clin Hypertens. 2006;8:44–49) ©2006 Le Jacq Ltd.*

DR. MOSER: Bonnie, what is the metabolic syndrome? Define it for us. Several different organizations have defined it in different ways. Is it real, how many people have it, and is it a disease or just a conglomeration of findings?

DR. FALKNER: You stated it correctly, there is controversy. Is the metabolic syndrome a specific disease or not? This is a syndrome of multiple risk factors that include elevated blood pressure (BP), abnormal glucose tolerance, and abnormal lipids—most specifically, a low high-density lipoprotein (HDL) cholesterol and a high triglyceride level.

DR. MOSER: Is hypertension as we define it, as BP >140/90 mm Hg, part of the syndrome, or could it be levels in the so-called high-normal or prehypertensive range, i.e., 130–135/85 mm Hg?

DR. FALKNER: The key is high BP, not necessarily hypertension, but an average BP level that is higher than ideal. A BP level that is >130/80 mm Hg is considered high BP and one of the components of the metabolic syndrome.

DR. MOSER: And what about the specific levels of HDL and triglycerides?

DR. FALKNER: The lipid criteria for the metabolic syndrome are decreased HDL cholesterol, which in men would be a level <40 mg/dL, or in women a level that is <50 mg/dL; and/or elevated triglycerides, which is a serum triglyceride level that is >150 mg/dL.

DR. MOSER: Total cholesterol and low-density lipoprotein (LDL) don't enter in the definition?

DR. FALKNER: Correct.

DR. MOSER: Okay, what are the other characteristics of the syndrome?

DR. FALKNER: The other major criterion, and possibly the leading one, is obesity—and specifically, visceral obesity. The measurement that is used in this definition is a waist circumference >40 inches in males and >35 inches in females.

DR. MOSER: Len, if you have a patient who fits these criteria, with a blood glucose of 115 mg/dL, a BP of 135/85 mm Hg, a waist measurement of 40, and an HDL of 38 mg/dL, what do you tell him? What do you do?

DR. KEILSON: Let me emphasize at the outset, that I prefer to have accurate measurement criteria to assess the metabolic syndrome. These should be obtained by myself or a well trained staff member who is not casual in assessment techniques. My pet peeve is the inaccuracy of waist size. This easily performed measurement (measuring abdominal girth over the umbilicus) should be performed as part of a baseline or initial physical exam, rather than relying on the patient self-report of belt size.

DR. MOSER: If a patient wants to know if they have a disease or just some risk factors that might contribute to getting cardiovascular disease, what do you tell them?



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DR. KEILSON: Since my work is oriented to preventive medicine, I prefer not to label the “metabolic syndrome” a disease, but a group of risk factors or conditions, that if untreated, might lead to heart or vascular disease.

DR. MOSER: Informing a patient about something you can do something about is different than telling them they have a disease or symptoms that you’re not going to be able to do anything about.

DR. KEILSON: Precisely—a “disease” label suggests the inevitable use of medications. By avoiding invoking “disease,” I can urge the patient to address components of this condition or syndrome that might “disappear” if healthy lifestyle changes are adopted, particularly weight loss.

DR. MOSER: Michael, if it’s so clear cut and we would all agree that BP elevation increases risk, that these triglyceride and HDL changes increase risk, and we all agree that obesity increases risk, then why is there any controversy? Why are some people saying that the metabolic syndrome isn’t truly a syndrome and that labeling people creates anxiety?

DR. WEBER: No one is arguing that high BP, abnormal lipids, and an elevated fasting glucose are not important risk factors. The argument has been whether or not we should use the word syndrome simply to describe the fact that these abnormalities often tend to cluster together. And even in talking about it, we shouldn’t forget that two of the major definitions currently being used, one by the National Cholesterol Education Program Adult Treatment Panel III (ATP III) in this country and the World Health Organization (WHO) used elsewhere in the world are quite different in describing the metabolic syndrome.

For example, WHO requires true hypertension, whereas in this country we’re willing to accept just a modest increase in BP. WHO accepts microalbuminuria as an important sign of the metabolic syndrome; we don’t.

We have been scrambling to arbitrarily define a syndrome. The American Diabetes Association and the European Association for the Study of Diabetes have recently put out a position paper saying that they’re not convinced that the syndrome actually exists in the true sense of having a single underlying etiology. That really doesn’t matter, because the important message is that if we see higher-than-normal or optimal BP, if we see abnormal lipids, if we see abnormal glucose, if we see obesity or any of the other findings that are talked about in these so-called syndromes, we ought to be taking a very aggressive approach in dealing with them.

DR. MOSER: Including the use of drugs on occasion?

DR. WEBER: There’s no question in my mind that if someone has high BP (>140/90 mm Hg), they ought to be treated, and if they have abnormal lipids, they should be treated. I’m not sure what others think about this, but it is difficult at times with or without drugs to have a meaningful impact on HDL and triglycerides. My consolation has always been that if you’re fairly aggressive with the use of statins in reducing LDL cholesterol as much as you can, that by itself seems to confer important benefits.

DR. MOSER: Bonnie, what do we know about the etiology of the metabolic syndrome or this cluster of risk factors? Is there a common denominator somewhere?

DR. FALKNER: Well, we don’t know definitively whether there is one or some combination of genes that are responsible for this cluster of risk factors. It is extremely unlikely that there is a monogenic cause or that there is a single etiology. However, this condition tracks within families, which suggests a hereditary background. Some patients have high BP plus other risk factors; but other patients may have only high BP without other risk factors. Because of the familial clustering of the metabolic syndrome, heredity probably contributes to the multifactorial cause.

DR. MOSER: Possibly a basic defect in insulin metabolism or fat metabolism that triggers the whole cluster?

DR. FALKNER: A major aspect of the syndrome is the strong relationship with obesity. However, not everybody who is obese has this syndrome.

DR. MOSER: And are there thin people who have all of the other characteristics of the syndrome except the obesity?

DR. FALKNER: It is less common, but some people who are not obese can have high BP and other metabolic abnormalities and thus have the syndrome. Individuals who are not clearly obese but have multiple risk factors tend to have central obesity, or the body fat they have is in the abdominal area.

DR. MOSER: And this fat is more active in leading to the lipid changes that we see. Is it true that you can see these other risk factors in a non-obese diabetic?

DR. FALKNER: Although there are some non-obese type 2 diabetics, more commonly the type 2 diabetics are obese—so that a large majority of diabetics with these other findings have an increased body mass index.

DR. MOSER: Len, we all know that if you have an elevated cholesterol level and a high LDL, we can use a statin, or fibrates if the statin doesn’t work

by itself, or we can use niacin, or combinations of medications to correct these abnormalities. But until very recently, we've had very few medications that can target the lipid abnormalities of the metabolic syndrome, the low HDL and elevated triglycerides, or this cluster of risk factors. Now, as Michael said, you can use a high dose of a statin and eventually you're going to increase the HDL somewhat. Eventually you're going to decrease the triglycerides somewhat, but how do you approach the specific lipid abnormalities of the metabolic syndrome?

DR. KEILSON: I think of the triglycerides as having a different role in this syndrome and actually I keep the statins reserved for the high-LDL, high-cholesterol disorders. Insulin resistance is clearly a major factor. We should pay more attention to exogenous causes like fat intake and do something about the excess of free fatty acids and triglycerides that result from enzyme systems and active adiposities in visceral tissue.

DR. MOSER: What you're saying is that in overweight people, especially in people with excess visceral fat, the adipocytes are metabolically active, and produce more fatty acids, and higher levels of triglycerides result.

DR. KEILSON: Of course, and certainly that's where the relationship to physical activity/inactivity may come in. People who are sedentary and fat tend to have insulin resistance. There's a great deal of research in molecular mechanisms now in the peroxisome proliferator-activated receptor (PPAR)- $\alpha$  and  $\gamma$  nuclear receptor families, which in many ways explain how you turn on and turn off various transcription factors that contribute to insulin resistance and diabetes.

DR. MOSER: Tell us about that.

DR. KEILSON: The PPAR nuclear transcription factors are responsible for turning some genes "on" or "off." A number of medications and hormonal products (insulin and estrogen, for example) may inhibit PPAR activation. As a result, gene products such as lipoprotein lipase may be inhibited and triglyceride levels may rise.

DR. MOSER: So that very complicated mechanisms are involved in insulin resistance, especially in obese people, because of the activity of the adipocytes and other enzymes—and that these may all play a role in the metabolic syndrome and the high levels of triglycerides.

DR. KEILSON: That's correct. Now the question is, what can we do to correct some of these abnormalities? The fibrates, gemfibrozil and fenofibrate, which have been around for 20 years and are effective in reducing triglycerides and raising

HDL levels, are useful as initial therapy to correct the lipid abnormalities.

DR. MOSER: Why don't we use them?

DR. KEILSON: The statins are effective in reducing heart disease and have gotten a great deal of publicity, and rightfully so. There are voluminous statin trial data and little fibrate cardiovascular trial data. But we certainly shouldn't forget about the fibrates.

DR. MOSER: What do the fibrates do to HDL and triglycerides? How do they affect them?

DR. KEILSON: Well, the fibrates will turn on PPAR- $\alpha$  and  $\gamma$  and they will increase the expression of lipoprotein lipase, which is the primary enzyme responsible for the removal of triglycerides. So they will lower triglycerides. And when that occurs, you start to transfer triglycerides out of particles that may inhibit the expression of HDL. In other words, if you lower triglyceride levels, you increase HDL levels. This is one particular benefit you get either by weight loss or physical activity or with these medications.

DR. MOSER: So there is a direct effect on triglycerides and an indirect effect on HDL.

DR. KEILSON: That's right. At the same time, you have to realize that the triglyceride action is independent of the action of the statin drugs. These medications really work only on 3-hydroxy-3-methylglutaryl coenzyme A reductase to reduce cholesterol production, but the fibrates have other roles, and so do agents that we forget about, such as omega-3 oils, which also turn on lipoprotein lipase.

DR. MOSER: So in a patient with this syndrome or this cluster of risk factors, the drugs of choice in terms of lipid changes might be the fibrates.

DR. KEILSON: Well, that's correct. We still have evidence that if the patient has diabetes or heart disease, a statin drug can be chosen first and a fibrate added if triglyceride levels are very high.

DR. MOSER: The use of fibrates also decreases coronary heart disease events, doesn't it?

DR. KEILSON: Well, they do . . .

DR. MOSER: We just haven't had as many studies to confirm the original data.

DR. KEILSON: Certainly the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) and the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial, which was presented at the AHA in Dallas, TX, and has been published in *Lancet* (2005;366:1849–1861), indicate that the use of fibrates will reduce CV events. We know that statins work. Organizations like the American Diabetes Association have strongly encouraged physicians to lower LDL cholesterol to

70 mg/dL or less in very high-risk patients. But since most people with diabetes have elevated triglycerides, the next add-on therapy should be a fibrate. It could be niacin or the omega-3s.

DR. MOSER: What are the side effects of the omega-3 preparations?

DR. KEILSON: Of fish oil?

DR. MOSER: Of fish oil in quantities that are necessary to reduce triglyceride levels.

DR. KEILSON: You'll get a 45% lowering of triglycerides from about 1 or 2 g of fish oil per day, and if you take it after a meal you don't usually have fish burps which people tend to complain about. It really is quite tolerable.

DR. MOSER: What kind of dosages are we talking about with the fibrates? Give us two examples. I know that there are three or four on the market.

DR. KEILSON: The nice thing about one particular product, fenofibrate, is that it can be taken as one dose of 145 mg a day with or without a meal. That would be how one would use a fibrate. The other, gemfibrozil, is given at 600 mg b.i.d. It appears to cause more side effects than fenofibrate, which has less muscle-related side effects.

DR. MOSER: Okay, Michael, if you had someone with this syndrome, if they just had triglyceride and HDL abnormalities, you might use one of the fibrates or nicotinic acid. You would certainly lower the BP if it were >140/90 mm Hg. But what if the patient had BPs of 130/85 mm Hg with the other constellations of this syndrome: would you attempt to lower the BP with specific medication? In a prehypertensive or high-normal subject without other risk factors, we might just try nonpharmacologic approaches. Would you try something more vigorous in these people?

DR. WEBER: Not at first. If the BP was in the prehypertensive range and there were other risk factors present, i.e., lipid abnormalities or obesity, I would try very hard at first with lifestyle modification, because there's a good chance that all of those abnormalities would improve.

DR. MOSER: Just with weight loss.

DR. WEBER: Just with weight loss and an exercise program, for example. I think we all recognize that once we start with antihypertensive drugs, we forever label those patients, and at least in theory, they should be taking a BP medication for the rest of their lives. So I'm reluctant to take that step, even in patients such as you described with multiple risk factors, until I've given them a chance to use lifestyle modification.

DR. MOSER: Okay, sounds reasonable. Let's get back to another topic. Why haven't we paid as

much attention to HDL as we should? Remember, the Framingham data kept telling us all that the total cholesterol-to-HDL ratio is probably as important an indicator of risk as anything else. If the ratio is <4.0, risk is not increased. But in the last 15–20 years, LDL levels have been repeatedly highlighted. All of the guidelines say LDL is the criterion for treatment, for benefit, and for outcome.

DR. WEBER: The truth is pretty clear. We don't have a good easy treatment for low HDL. And we have great treatments for high LDL. I think it's as simple as that.

DR. MOSER: Well, we have fibrates and we have nicotinic acid, which will lower LDL and cholesterol levels too, as well as having a favorable effect on HDL and triglycerides. Why aren't they being used?

DR. WEBER: Because they're not familiar to many physicians; they're not as easy to use as a statin. Perhaps the most interesting recent data we've had on reducing cardiovascular risk are the data from the lipid-lowering part of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT). If you recall, they took high-risk patients . . .

DR. MOSER: About 10,000 of them.

DR. WEBER: About 10,000 patients who had hypertension and at least a few other parts of this clustering of abnormalities as well. They had so-called usual levels of LDL cholesterol, such that it was ethical to compare a statin with placebo, and they went ahead and showed that giving a low-dose statin dramatically improved prognosis. In fact, the question I asked after reading that study was whether every person with high BP and other components of the so-called metabolic syndrome should automatically go on a statin—despite its lack of specific direct effects on HDL or triglycerides. In fact, I even asked the question whether we should even bother to measure the lipid profile—or should we just simply say if anyone's got high BP and these other abnormalities, go directly onto a statin.

DR. MOSER: That's like someone years ago saying just put diuretics in the water in high risk for hypertension areas. Len, would you put everybody on a statin with high normal BP and these other components of the metabolic syndrome?

DR. KEILSON: Well I was sitting here listening to Michael's comments. My first observation relates to the mechanisms of heart disease. Hypertensives die of a vascular event and, in fact, the organs involved are simply bystanders for the disease itself. We should consider lipid deposition and all of the proinflammatory activities that take place in the artery wall. Events themselves,

whether a stroke or a heart attack, are results of plaque rupture and clot formation. If you had no plaques to rupture, would you ever have coronary events in the hypertension-treated population? This leads to the question, if statins might help to prevent plaques, then why not use them?

DR. MOSER: The answer is you probably would use statins.

DR. KEILSON: Well, the answer is yes. I think that the aggressive use of statins has been shown to reduce plaque burden in the artery wall itself and dramatically reduce further risk of cardiovascular disease—this applies to hypertensive patients with metabolic syndrome findings.

DR. MOSER: How do we know that fibrates don't do this? No one has carefully done specific outcome studies with these agents in this type of patient.

DR. KEILSON: Well, this remains to be seen. There is a hint that fibrates will do positive things; for example, the fibrates will lower C-reactive protein, an inflammatory marker for cardiac disease. In both VA-HIT and in some of the fenofibrate studies, C-reactive protein levels were reduced with fibric acid derivatives. So that suggests that perhaps these medications are influencing all of the other cytokines that might be related to atherosclerosis.

DR. MOSER: Alright, what happens tomorrow morning if someone markets a really good HDL enhancer that elevates HDL and decreases triglycerides? Do we change directions and pay attention to what Framingham told us years ago? Do we now begin to pay more attention to the total cholesterol/HDL ratio, especially in the millions of people with the metabolic syndrome?

DR. FALKNER: What needs to be determined is whether treatment to raise HDL cholesterol, particularly in young people, has benefit which is in addition to the benefit of managing the other risk factors. Or is there benefit in and of itself that outweighs the benefit of dealing with other risk factors? It is well known that controlling BP reduces cardiovascular events. There is benefit in weight reduction, and benefit in measures to prevent progression of diabetes. It is important to develop evidence that shifting the HDL upward provides additional benefit in risk reduction.

DR. MOSER: Well we won't know that until we have a medication and someone is willing to commit to an outcome study—we'll have to wait and see.

DR. WEBER: Dr. Falkner, I recall that a few years ago you published some very compelling information on young African-American adolescents showing a high prevalence of insulin resistance

even at a young age. Do you see the abnormalities that we're talking about and what we're now calling the metabolic syndrome in those children, or is that something that only comes later?

DR. FALKNER: Yes, you can see multiple risk factors in young individuals. In terms of outcome, people who have high BP with insulin resistance continue to have high BP. They go from having elevated BP to hypertension and concurrently they have a deterioration in glucose tolerance, and a certain number develop diabetes. There are some people who you can predict are going to have the full-blown syndrome of metabolic deterioration.

DR. MOSER: Before summarizing, would all of you put patients with the metabolic syndrome on aspirin? We now recommend that men over the age of 40 years and woman over 50 years should probably be on low-dose aspirin, unless there is a contraindication. Why not patients with the metabolic syndrome, whatever their age, if we're worried about clotting and plaques?

DR. KEILSON: I like evidence-based medicine, and even your comment about putting women on aspirin now becomes problematic because of some recent trials that suggest an absence of benefit. So I'm not sure.

DR. MOSER: Bonnie, would you go on an aspirin, 81 mg a day, if you had the cluster of metabolic symptoms? Obesity, high-normal BP or prehypertension, and glucose levels >100 mg/dL but <126 mg/dL?

DR. FALKNER: Yes, I think I would. Stroke prevention is a high priority. In addition to controlling BP, reducing excess body weight (or fat) and controlling blood glucose concentration, the addition of aspirin should be considered, especially if the other metabolic and BP numbers are not optimal.

DR. MOSER: Michael, let's say that you were 32 years old with this syndrome. There are no guidelines for this.

DR. WEBER: No, I don't think I would take an aspirin at 32. I do take one now. I have never been a great follower of guidelines, which I think very typically are a consensus statement or compromise that really doesn't satisfy everyone.

There are guidelines, however, that I've tended to take a bit more seriously. The US Food and Drug Administration labeling for antiplatelet drugs, and particularly for aspirin, does not indicate it for people who have not yet had an event. What has held them back, and what scares me a little as well, is that there is a small but real possibility of aspirin promoting a hemorrhagic stroke. If the risk of that happening is as high as or even higher

than the risk of another event, then clearly I don't want to be taking aspirin. So I believe that we still need further information about the relatively low-to-medium-risk cardiovascular patient taking prophylactic aspirin as compared with the person who's already had events and clearly will benefit from antiplatelet treatment.

DR. MOSER: Another difference of opinion. So to summarize—the metabolic syndrome perhaps should not be called a syndrome; perhaps it shouldn't be labeled a disease. But it is a real entity and there are people who cluster with obesity, BP above the normal or ideal level, blood glucose levels not >126 mg/dL but between 100 and 126 mg/dL, with abdominal waist measurements >40 inches for men or >35 inches for women. This cluster of findings exists. What do you do about it? Etiology probably is related most specifically to obesity, insulin resistance, and some of the changes that Len described in terms of free fatty acids being mobilized with elevated triglyceride levels and low HDL levels. Obesity control probably is the first intervention. Exercise and diet obviously will help.

In terms of BP, I think the consensus was that we probably would not treat levels of 130 mm Hg or thereabouts with specific medication unless the

other concomitant risk factors were very significant and we couldn't achieve weight loss with diet and exercise. But if we couldn't reduce weight, we might be tempted to use a small dose of an antihypertensive drug in the patients in the higher-risk groups.

In terms of the specific lipid abnormalities in the metabolic syndrome, these are difficult to correct with the available drugs, i.e., raising HDL and lowering triglycerides are difficult to do with statins, but we do have the fibrates, nicotinic acid, and omega-3 oils that are effective. If the omega-3s become available in a more palatable form and are easier to take, it might be something we'd consider. Hopefully, in the near future, other medications that raise HDL and lower triglycerides will be available. Perhaps all people with this cluster of metabolic abnormalities should not be on a statin. But, at the moment, the use of statins has been shown to protect against cardiovascular diseases in both high- and lower-risk subjects. So, even if they do not impact the specific effects of the metabolic syndrome, we should use them.

And finally, there is some concern about putting people at low risk on aspirin even though it may be effective in reducing cardiovascular risk, although there clearly is a difference of opinion about this.

Thank you.