

Metabolic Syndrome: Misleading Diagnosis or Valid Condition?

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BY CONNI BERGMANN KOURY, EDITOR-IN-CHIEF

Two major diabetes organizations – one in the United States and one in Europe – are calling for a closer examination of metabolic syndrome.

In a joint paper published in *Diabetes Care* and *Diabetologia*, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) question whether metabolic syndrome has been appropriately defined and whether it is in fact a syndrome at all.¹

Metabolic syndrome is associated with an increased risk of coronary heart disease, stroke, peripheral vascular disease and type 2 diabetes. According to the American Heart Association (AHA), metabolic syndrome has become increasingly common in the United States, with an estimated 50 million Americans who are affected. In a joint response to the diabetes groups, published in *Circulation*, an AHA and National Heart, Lung, and Blood Institute (NHLBI) panel reviewed, affirmed and reinforced their previous stance on metabolic syndrome.²

SHOULD NOT BE USING DIAGNOSIS

In breaking ranks with many cardiologists, the authors of the ADA/EASD joint paper said the syndrome is poorly defined, inconsistently used and further research is needed to help understand whether it should be treated and if so, how. They said physicians should not be diagnosing patients with this syndrome and attempting to treat it as a separate condition until the science behind it is clear.

“We shouldn’t be diagnosing people with the ‘metabolic syndrome;” said Richard Kahn, PhD, chief scientific and medical officer of the ADA. “Doing so misleads the patients into believing he or she has a unique disease. What they really have are well-known cardiovascular risk

Diagnosing patients with metabolic syndrome may mislead patients into believing he/she has a unique disease, some physicians say.

factors. The combination of risk factors does not add up to a more significant or higher cardiovascular risk than the individual components.”

According to the AHA, criteria for diagnosing metabolic syndrome are based on the recommendations of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) report made in 2001. There are some modifications. These widely used guidelines state that metabolic syndrome be identified as the presence of three or more of these components: elevated waist circumference; elevated triglycerides; reduced HDL; elevated blood pressure; or elevated fasting glucose.

INCONSISTENT CORRELATION

The World Health Organization uses different criteria to identify metabolic syndrome, including anyone who has diabetes or insulin resistance and two of the following: high hip-to-waist ratio; high triglycerides or low HDL; high blood pressure; and a high urinary albumin excretion rate. The ADA said that other organizations have yet other definitions. The authors wrote that the fact that there are conflicting definitions implies that there is no clear evidence base for what should or should not be included.

If taken individually, all of the conditions mentioned above represent a risk a factor for cardiovascular disease

(CVD) and should be treated as such. "But there is no combination of risk factors that boosts a person's cardiovascular risk beyond the sum of the parts, or constitutes a separate disease," said Ele Ferrannini, MD, president of the EASD.

Kahn and colleagues wrote that inordinate attention to metabolic syndrome in patients with diabetes or known vascular disease could impede appropriate care.¹ Treatment of individual risk factors is indicated without what they term as some arbitrary combination driving clinical decision-making.

"Metabolic syndrome requires much more study before its designation as a syndrome is truly warranted and before its clinical utility is adequately defined," the authors concluded. They recommend physicians continue to evaluate patients for the presence of other cardiovascular risk factors when one is discovered, aggressively treat individual risk factors, and avoid labeling patients with the term metabolic syndrome.

AHA, NHLBI RESPOND

An expert panel from the AHA and the NHLBI responded to the ADA and EASD statement in *Circulation*. It confirmed the recommendations on metabolic syndrome of the 2001 NCEP ATP III with some modifications. The panel also clarified several issues based on new scientific evidence.

In a statement, panel members said that metabolic syndrome, which consists of multiple interrelated risk factors, increases the risk for atherosclerotic CVD by 1.5 to threefold, and raises the risk for type 2 diabetes by three to fivefold. It affects over 26% of adults, or over 50 million Americans.

"The panel reviewed, affirmed and reinforced the previous statement. Metabolic syndrome is an important issue both for physicians and the general public," said Scott Grundy, MD, PhD, chairman of the panel and director of the Center for Human Nutrition, University of Texas Southwestern Medical Center, Dallas.²

ABDOMINAL OBESITY KEY

According to the AHA report, the dominant underlying risk factors for the syndrome appear to be abdominal obesity and insulin resistance. Physical inactivity, aging, hormonal imbalance and genetic predisposition also play a role, and certain ethnic groups such as Hispanic-Americans are at higher risk than whites.

The link between obesity and metabolic syndrome is most evident from the inclusion of waist circumference in the criteria. ATP III guidelines define a waist circumference of >40 inches in men and >35 inches in women as one of the criteria for the syndrome. The panel said

TABLE 1. THREE DEFINITIONS OF METABOLIC SYNDROME

The **American Heart Association** bases its criteria for diagnosing metabolic syndrome on the recommendations of the National Cholesterol Education Program Adult Treatment Panel III report made in 2001, with some modifications. These widely used guidelines are that metabolic syndrome be identified as the presence of three or more of these components:

- elevated waist circumference;
- elevated triglycerides;
- reduced HDL;
- elevated blood pressure; or
- elevated fasting glucose.

The **World Health Organization** uses different criteria. Anyone who has diabetes or insulin resistance and two of the following:

- high hip-to-waist ratio;
- high triglycerides or low HDL;
- high blood pressure; or
- high urinary albumin excretion rate.

The **International Diabetes Federation** consensus worldwide definition said that for a person to be defined as having the metabolic syndrome, they must have central obesity (with ethnic-specific values) plus any two of the following four factors:

- raised triglycerides;
- reduced HDL;
- raised blood pressure; or
- raised fasting plasma glucose or previously diagnosed type 2 diabetes.

while this measure still stands for the majority of individuals, it is now recognized that some persons who are not obese by traditional measures, nonetheless are insulin resistant and have other metabolic risk factors. Thus, an increased waist circumference, while providing a solid diagnostic tool, is not necessary for a diagnosis of metabolic syndrome, if other criteria are present.

"If there are three other clinical criteria present, then the diagnosis of metabolic syndrome can be made without an increased waist circumference," Dr. Grundy said.

The latest scientific statement allows for adjustment of the waist circumference to lower thresholds in individuals or ethnic groups, such as Asian-Americans, who are prone to insulin resistance. It also suggests that triglyceride and HDL plus blood pressure be

counted as abnormal, even when a person is on drug treatment for these risk factors.

The issue of waist circumference was one that the International Diabetes Federation (IDF) saw as pivotal to the diagnosis of metabolic syndrome. The IDF believes there are sufficient data for a worldwide metabolic syndrome diagnosis, prompting it to issue a new definition last April.³

IFG CRITERIA IN AGREEMENT

The latest scientific statement from the AHA and NHLBI brings the ATP III criteria for metabolic syndrome in line with the ADA lowering of the levels of fasting glucose required to be considered impaired. This adjustment reduces the threshold for elevated fasting glucose from >110 mg/dL to 100 mg/dL in accordance with the ADA's revised definition of impaired fasting glucose.

The primary goal of clinical management of metabolic syndrome is to reduce the risk for atherosclerotic CVD, and the risk of type 2 diabetes in patients who have not yet developed clinical diabetes, the panel said. If these conditions are present, treatment of metabolic syndrome must be intensified.

Grundy stressed the importance of the joint statement, saying that it provides a more in-depth discussion and justification behind the diagnosis of metabolic syndrome.² "This report strengthens the position that metabolic syndrome is important" said Grundy. "The [AHA] and the [NHLBI] strongly recommend that each of the standard cardiovascular risk factors should be treated appropriately. But this is not enough in our society where obesity and physical inactivity are becoming increasingly prevalent risk factors, in addition to well-known risk factors such as high cholesterol, high blood pressure, diabetes and tobacco abuse."

NHLBI Director Elizabeth G. Nabel, MD, said: "This statement should serve as an alert to physicians that it is vitally important to identify and treat the growing number of people with metabolic syndrome. For individuals with this syndrome, lifestyle treatment – weight control and increased physical activity – is the primary therapy for lowering their risk factors and reducing the long-term risk for heart disease."

MORE TO THE DEBATE?

Adding another angle to the debate over metabolic syndrome is a new drug being developed by Sanofi-Aventis. Rimonabant (Acomplia) has been reported in clinical trials to treat several risk factors associated with metabolic syndrome: blood glucose, waist cir-

cumference and dyslipidemia. It is believed that the company will seek regulatory approval in the United States for the treatment of metabolic syndrome.⁴

Experts say, however, that because the Food and Drug Administration does not have criteria for metabolic syndrome, it is unlikely the drug would carry such an indication on its label. Some observers speculate that this is what is behind the new interest in creating definitions of metabolic syndrome.

At the EASD annual meeting in September, Dr. Kahn said, "In America, there will not be any drug approved for the indication of metabolic syndrome in the next few years ... maybe for all time. I think there are many questions about the concept of metabolic syndrome. That does not preclude a drug being approved with many different actions – on glucose, blood pressure, and other things, such as body weight – but an indication for metabolic syndrome will not happen in the [United States]."⁵

Also speaking at the EASD meeting, Dr. Ferrannini said that a metabolic syndrome drug is not on the horizon in Europe. "It seems unlikely unless you have a unique definition in the first place that doesn't confuse people and unless you have some clear idea about pathogenesis, if not the etiology, of the problem. ... Also for economic reasons, it would be difficult and too optimistic to imagine there would be a finger snap sort of indication for that."⁵

Jeffrey Miller, MD, from the division of endocrinology, diabetes & metabolic disease in the department of medicine at Thomas Jefferson University Hospital in Philadelphia said that the battle over metabolic syndrome wages that the overall risk is not greater than the sum of individual parts.

"Obviously each additional risk factor increases CVD risk, and I do believe it is important to recognize this syndrome and treat each part (whatever it is called)," Dr. Miller told *Diabetic Microvascular Complications Today* in an e-mail interview. "We cannot put it off when the belly is bigger than the chest wall – we likely have the syndrome." He added that what is fascinating with rimonabant is that it appears to improve parameters somewhat independently of weight loss. ■

1. Kahn R, Buse J, Ferrannini E, Stern M. The Metabolic Syndrome: Time for a Critical Appraisal. *Diabetes Care*. 2005;28:2289-2304.

2. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and Management of the Metabolic Syndrome. Published online before print *Circulation* 2005. doi:10.1161/CIRCULATION-AHA.105.169405.

3. International Diabetes Federation Web site and news release. Available at: www.idf.org/home/index.cfm?unode=1120071E-AACE-41D2-9FA0-BAB6E25BA072 www.idf.org/home/index.cfm?unode=32EF2063-B966-468F-928C-A5682A4E3910. Accessed Oct 3, 2005.

4. Rimonabant treats multiple problems in type 2 diabetes. *Diabetic Microvascular Complications Today*. 2005;4:7.

5. 41st Annual Meeting of the European Association for the Study of Diabetes. September 11-14, 2005. Athens.