Specialists Weigh In on 'Metabolic Syndrome' Debate

BY MIRIAM E. TUCKER
Senior Writer

The American Association of Clinical Endocrinologists and the American College of Endocrinology have weighed in on the growing debate surrounding the term metabolic syndrome by reaffirming their 2003 position statement regarding what they call insulin resistance syndrome.

The new two-page document, "American College of Endocrinology/American Association of Clinical Endocrinologists Reaffirmation of the 2003 ACE Insulin Resistance Syndrome (IRS) Position Statement" (available at www.aace.com), was issued by an ad hoc committee in response to documents from several other medical organizations regarding the metabolic syndrome concept.

In September, the American Diabetes Association (ADA) and the European Society for the Study of Diabetes (EASD) issued a joint statement calling the term metabolic syndrome into question, citing a lack of data to demonstrate that the term denotes a useful marker for cardiovascular disease beyond its individual components, as well as the concern that patients might misunderstand the implications of the diagnosis (Diabetes Care 2005;28:2289-304).

Then, in mid-October, the American Heart Association (AHA) and the National Heart, Lung, and Blood Institute (NHLBI) issued a joint statement affirming the usefulness of the metabolic syndrome term, as originally stated in the 2001 National Cholesterol Education Program Adult Treatment Panel Report III.

The new AHA/NHLBI document, which was in the works before the ADA/EASD statement came out, also clarifies some issues and makes minor modifications to the Adult Treatment Panel III definition of metabolic syndrome (Circulation 2005;112:e285-90).

For their part, the American College of Endocrinology (ACE) and the American Association of Clinical Endocrinologists (AACE) still prefer the term insulin resistance syndrome, because in contrast to the poorly defined word metabolic, insulin resistance syndrome "offers a clear statement of the presumed pathogenesis of the syndrome," according to their earlier document (Endocrine Practice 2003;9:240-52).

Regardless of the term used—metabolic syndrome or insulin resistance syndrome—the ACE/AACE position differs from that of the ADA/EASD, which states that neither entity is well defined enough to qualify as a syndrome.

The ACE/AACE, however, said "the term syndrome (whether metabolic or insulin resistant) is conceptually attractive and clinically useful" and the two terms together provide "a simple construct to characterize the type of patients that clinicians see daily."

But the two endocrinologist groups do agree with the ADA/EASD statement that such syndromes should be specifically distinguished from type 2 diabetes and cardiovascular disease, because the whole idea is to identify individuals at high risk for these consequences before they occur.

Moreover, the ACE/AACE position emphasizes the importance of recognizing other associated disease consequences beyond cardiovascular disease, such as polycystic ovary syndrome and nonalcoholic fatty liver disease. ■

Are Smoking, Metabolic Syndrome Linked?

Intensity of exposure to tobacco smoke appears to be associated with the rate of metabolic syndrome in a dose-response relationship in adolescents, according to a study in the cross-sectional third National Health and Nutrition Examination Survey.

The study is the first of its kind to associate smoking with metabolic syndrome by using a biologic marker of smoking—serum levels of the nicotine metabolite cotinine—and exposure to environmental tobacco smoke in adolescents, reported Michael Weitzman, M.D., of the University of Rochester (N.Y.) and his colleagues (Circulation 2005;112:862-9).

In the 1988-1994 survey of 2,273 adolescents aged 12-19 years, exposure to environmental tobacco smoke and active smoking were independently associated with nearly fivefold and more than sixfold higher odds of developing metabolic syndrome, respectively, after adjustment for gender, age, race or ethnicity, poverty status, region, and parental history of diabetes or heart attack.

The investigators obtained similar results when they restricted their analysis to individuals with a body mass index at the 85th percentile or higher (those who are overweight and at risk for overweight).

Of 664 adolescents overweight or at risk for overweight, metabolic syndrome occurred at a rate of 5.6% in individuals who were not exposed to tobacco smoke; 19.6% in those exposed to environmental or secondhand smoke; and 23.6% in active smokers. The increase in the rate of metabolic syndrome in adolescents followed a significant trend from those who were not exposed to tobacco smoke, through the lowest to highest level of exposure to environmental tobacco smoke, up to active smokers.

The criteria for metabolic syndrome consisted of a triglyceride level of 110 mg/dL or higher, an HDL cholesterol level of 40 mg/dL or lower, a waist circumference at the 90th percentile or higher, blood pressure in the 90th percentile or higher, and a fasting plasma glucose level of 100 mg/dL or higher.

Their report cannot "conclusively establish an etiologic role for tobacco smoke in the development of the metabolic syndrome in youth," the investigators noted, adding that such a link is plausible in that "evidence in studies of children suggests that insulin resistance mediates the deleterious effects of excess adiposity on blood pressure and lipids in the metabolic syndrome" and "smoking is associated with increased insulin resistance in adults."

—Jeff Evans

Tesaglitazar Reduces Metabolic Syndrome in Early Trial

BY BRUCE JANCIN
Denver Bureau

STOCKHOLM — Tesaglitazar markedly reduces the prevalence of both metabolic syndrome and impaired fasting glucose in hypertriglyceridemic, insulin-resistant nondiabetic patients, Steen Stender, M.D., reported at the annual congress of the European Society of Cardiology.

Tesaglitazar (Galida) is a novel oral dual α and γ peroxisome proliferator-activated receptor (PPAR) agonist. Both animal and clinical studies indicate the investigational drug simultaneously improves both lipid profiles and glucose metabolism, said Dr. Stender of Gentofte University Hospital, Hellerup, Denmark.

He presented a post hoc analysis of data from the Study in Insulin Resistance (SIR), a seven-country randomized, double-blind, phase II, dose-finding study in which 397 nondiabetic patients with hypertriglyceridemia, increased waist-to-hip ratio, and insulin resistance were randomized to 12 weeks of placebo or tesaglitazar at 0.1, 0.25, 0.5, or 1.0 mg/day.

The trial's primary end point was a change in fasting triglyceride levels, which dropped in dose-dependent fashion by a maximum of 37% with the 1.0-mg dose of tesaglitazar.

The 1.0-mg regimen also boosted HDL cholesterol levels by 16%, reduced non–HDL cholesterol levels by 15%, lowered fasting insulin concentrations by 35%, and more than doubled the prevalence of the favorable LDL cholesterol pattern-A particle diameter.

Dr. Stender reported on tesaglitazar's effect on two key secondary end points—metabolic syndrome and impaired fasting glucose—that are recognized as major risk factors for the development of cardiovascular disease and diabetes, respectively.

In the trial, tesaglitazar reduced the prevalence of metabolic syndrome (as diagnosed under National Cholesterol Education Program criteria) and impaired fasting glucose in dose-dependent fashion. (See box below.)

"Simultaneous improvements in several risk factors have the potential to delay development of type 2 diabetes and reduce cardiovascular risk. This of course has to be shown in prospective studies, but the rationale for doing these [ongoing] phase III studies is present," Dr. Stender said.

The drug was well tolerated. The most common side effect was dose-dependent weight gain, which averaged 0.8 kg in 12 weeks at 1.0 mg/day. Small reductions in hemoglobin and leukocyte count and a nonsignificant rise in creatinine were also seen. "Whether these small changes in laboratory parameters have clinical significance, we don't yet know," Dr. Stender said.

Luc Van Gaal, M.D., voiced concern regarding the weight gain, which stems from tesaglitazar's PPAR-γ effect. If this weight gain comes mainly as abdominal fat, it will increase the waist-to-hip ratio, a known cardiovascular risk factor, noted Dr. Van Gaal, professor of diabetology, metabolism, and clinical nutrition at the University Hospital Antwerp, Belgium.

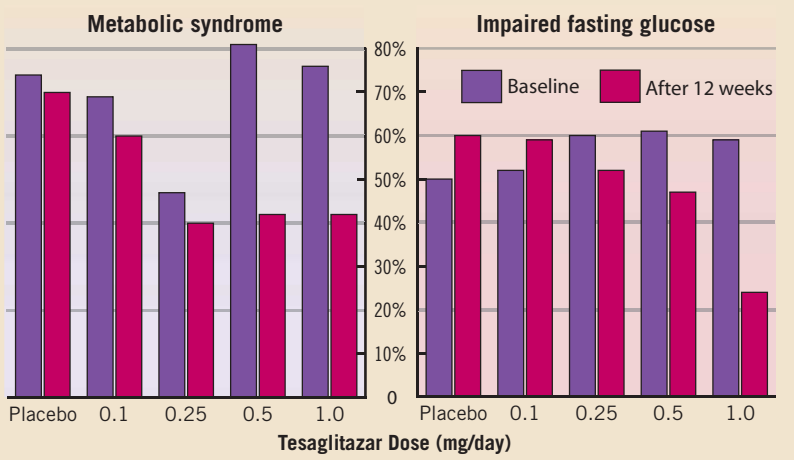
Dr. Stender replied that no change in waist-to-hip ratio was seen in SIR; however, that wouldn't be expected in a relatively short 12-week study. "That might take a couple of years."

When asked how he envisions tesaglitazar's use in clinical practice if it eventually receives marketing approval, Dr. Stender said the drug's multiple effects make it very attractive at a time when patients are on so many medications for chronic conditions that compliance becomes a major consideration.

"Usually you have several drugs to treat one risk factor, as in hypertension. Here you have one drug treating several risk factors. So I expect it might be lifelong therapy, if it turns out tesaglitazar has an effect on the hard end points," Dr. Stender said.

SIR was sponsored by AstraZeneca Pharmaceuticals LP. ■

Prevalence Drops for Secondary SIR End Points



Note: Based on data from 397 patients in the Study on Insulin Resistance.
Source: Dr. Stender