Metabolic Syndrome and Obesity Update

Metabolic Syndrome: The Great Debate

Is the metabolic syndrome a useful tool for clinicians or is it clinically irrelevant? Two noted diabetes experts squared off on opposite sides to debate the merits of this collection of symptoms.

George Alberti, MD of the Imperial College in London gave the "pro" side of the metabolic syndrome debate. The metabolic syndrome has historically had many sets of criteria. In 2005, the International Diabetes Federation (IDF) developed the following consensus criteria to assist clinicians: central obesity, plus two of the following four factors: elevated triglycerides (>150 mg/dL or >1.7mmol/L), low HDL cholesterol (<40 mg/dL or <1.03 mmol/L), high blood pressure (systolic ≥ 130 mmHg and diastolic ≥ 85 mmHg), or elevated fasting plasma glucose level (≥ 100 mg/dL or ≥ 5.6 mmol/L). Waist circumference was used as the measure of central obesity, with cutoffs for both gender and ethnicity.

"This is a tool for picking out people at very high relative risk" for cardiovascular disease (CVD) and diabetes, said Dr. Alberti. It should be used in conjunction with other risk markers such as family history, smoking, and LDL cholesterol. In doing this, clinicians will have an overall "cardiometabolic" risk for a patient. Dr. Alberti stressed that this is a simple thing to be used by clinicians to easily assess patients, and he feels the American Diabetes Association/European Association for the Study of Diabetes critique of the metabolic syndrome (*Diabetologia* 2005) ignored the new IDF criteria. He argued that the concept of metabolic syndrome has led to many people being evaluated and treated simply because of the attention being paid to it.

Richard Kahn PhD, the ADA Chief Scientific and Medical Officer, presented the opposing viewpoint. "The rules have virtually no scientific basis…it's an algorithm looking for a purpose," said Dr. Kahn. His argument is that there is no evidence that this diagnosis improves outcomes, and it does not change how clinicians treat patients. He does not think it is a simple tool, since new guidelines appear approximately every two years, and there are currently 7 definitions of the metabolic syndrome in existence.

He emphasized that the presence or absence of the syndrome can be misleading, and that very important risk factors for CVD such as smoking, sex, family history, inflammation, and hypercoagulation are therefore underestimated. "This only serves as a distraction," said Dr. Kahn. Instead he suggests that clinicians perform and fasting plasma glucose or possibly an oral glucose tolerance test to

predict diabetes. To predict risk of CVD, count the risk factors and use the risk calculator at www.diabetes.org. To treat obesity, measure the BMI or waist circumference and get serious about motivating patients to lose weight.

Although these two presenters did not agree on the metabolic syndrome, they did concur that the debate is an important one, bringing more attention to these issues and associated risks.

Childhood Obesity: From Epidemiology to Treatment

Obesity is a complex disease that involves multiple genes and environmental factors as well as interactions between the two. Obesity is not inherited in a strictly Mendelian manner (i.e., dominant, recessive or sex-linked) and heritability is characterized by risk to relatives of an affected individual that is greater than the incidence of the disease in the general population. Many studies have attempted to understand the impact of environment versus genetics on body weight in children in order to develop ways to curb or prevent childhood obesity.

"Much research suggests that environmental factors play an important role in shaping diet, activity and body weight, although there is little research in diverse populations, across multiple environmental settings and, particularly, minimal longitudinal research on this topic," said Penny Gordon-Larsen, PhD, University of North Carolina, Chapel Hill, NC.

She cited the National Longitudinal Study of Adolescent Health (Add Health), which collected a wide range of information on social and behavioral context health measures (Gordon-Larsen et al. *Am J Clin Nutr* 2004).

This study found that childhood and adolescent household context had a lasting effect on multiple health outcomes, including weight status and activity. The home environment appears to be particularly influential in determining phenotypic extremes, indicating potential for gene-environment reactions.

The goal of the Children's Nutrition Research Center's Viva La Familia study was to identify genetic and environmental causes of obesity in Hispanic children, explained Nancy F. Butte, PhD, Baylor College of Medicine, Dallas, TX. Three hundred and thirty-two Hispanic families participated in the study, which performed a multi-point genome scan to localize quantitative trait loci that could influence variation in adiposity and obesity-related co-morbidities. Linkage analysis was then done on these loci.

"Insulin resistance, dyslipidemia, high blood pressure, elevated liver enzymes and low physical activity were highly prevalent in the overweight Hispanic children," said Dr. Butte. "Since family members share not only genes but also diet, cultural background and many aspects of lifestyle, both genetics and environmental factors contribute to the development of childhood obesity and its co-morbidities."

New Paradigms of Obesity and Diabetes in Youth

As the prevalence of childhood obesity continues to rise in the U.S. and as healthcare costs continue to increase for overweight pediatric patients, it is important to diagnose metabolic syndrome early. Physicians and scientists debate not only whether or not metabolic syndrome exists among youth (*Arch Pediatr Adol Med* 2003), but also over the criteria for defining metabolic syndrome in obese youths.

The prevalence of metabolic syndrome among youth ages 12 to 19 ranges from 28%, using the National Cholesterol Education Program definition, modified for age (*Arch Pediatr Adol Med* 2003) to 40%, based on International Diabetes Federation criteria (*Diab Care* 2005). Metabolic syndrome has its highest prevalence among severely obese white youth (*NEJM* 2004). Study findings can have significant implications for both public health and clinical interventions directed at this high-risk (overweight) group of youths. "Double diabetes," which is an overlap between types 1 and 2 diabetes, has also become a growing concern. The emergence of double diabetes suggests that the "classic" paradigms of Types 1 and 2 no longer capture the entire clinical spectrum of diabetes.

Identifying metabolic syndrome is important because it can be a precursor to cardiovascular problems and type 2 diabetes. Sonia Caprio, MD, emphasized that a universal definition of metabolic syndrome in youth is needed to help us identify patients at risk. Dr. Caprio went on to explain that adiponectin, a collagen-like product of visceral fat, is a new biomarker of the metabolic syndrome. A study of 94 obese youth ages 9 to 21 determined that the subjects with the highest proportion of visceral fat and lower concentrations of adiponectin had the highest prevalence of metabolic syndrome (Taksali S. ADA 2006).

The changes that occur between categories of glucose tolerance in obese adolescents are marked weight gain, profound insulin resistance at baseline and reduced first phase insulin secretion at baseline. Wadden et al (*NEJM* 2005) found that the use of sibutramine in combination with intensive lifestyle intervention in obese adolescents had a great effect over 12 months, noted Michael Freemark, MD, Duke University Medical Center, Durham, NC.

Medications have varying effects on weight and metabolic function, and adverse effects are concerning in a subset of patients. Long-term risks of anorectic agents are unknown. Metformin and orlistat both can delay the development of type 2 diabetes, but the length of drug treatment required is unclear.

Some patients unfortunately have "double diabetes", and so it is now becoming necessary to study the epidemiology and establish the magnitude of the problem, as well as evaluate risk factors and temporal changes. Understanding the pathogenic mechanisms of "double diabetes" is also important for determining appropriate treatments and preventing the risks of associated conditions and complications. "Are obesity/insulin resistance ac-celerators of type 1 diabetes?" asked Ingrid Libman, MD, Children's Hospital of Pittsburgh, Pittsburgh, PA.

Children with features of type 2 diabetes but evidence of beta-cell autoimmunity have an increased risk of developing autoimmune thyroid disease, similar to that of children with typical type 1 diabetes.

Adults with a family history of type 2 diabetes who were diagnosed with type 1 diabetes as children and over time developed obesity and insulin resistance have an increased risk of developing coronary artery disease compared to those with no signs of insulin resistance or family history of T2, explained Dr. Libman.

"Treatment, prevention and management of associated comorbidities and complications are all important clinical implications of type 2 diabetes, concluded Dr. Libman. "the question is whether or not patients with double diabetes should be treated with insulin sensitizers, or if exercise and lifestyle changes should be more strongly encouraged."

Pramlintide in the Treatment of Obesity

Amylin and insulin are co-secreted in response to meals. There is evidence that amylin meets the criteria for a satiety agent because it is released after meals, has a short duration of action, decreases meal

size, decreases food intake, and antagonism of its receptor leads to increased food intake [Amylin Pharmaceuticals, internal data]. Alain Baron, MD, Senior Vice President of Amylin Pharmaceuticals, summarized clinical studies with pramlintide acetate, a synthetic analog of amylin, administered by subcutaneous (SC) injection.

In the mechanism of action study of pramlintide, 88 patients with obesity were treated for 6 weeks with 180 µg TID SC. There were statistically significant decreases in 24 hour food intake at Day 3 ($p<.001$) and binge eating score reduction at the final visit ($p<.01$).

In a dose escalation trial, 200 patients received up to 240 µg TID SC or placebo for 16 weeks. At Week 16, 31% of patients had a weight loss ($p<.001$) and the pramlintide group had a greater weight loss compared to the placebo group ($p<.001$, last observation carried forward). The observed weight loss was independent of nausea, which is the most common side effect of pramlintide.

In a dose ranging trial, 408 patients were divided into six treatment arms: 120, 240 or 360 µg pramlintide either BID or TID. Both arms showed a treatment effect when comparing baseline weight to final ($p<.01$ for BID and $p<.001$ for TID).

In summary, Dr. Baron believes that pramlintide shows promise in the treatment of obesity, and that future research will explore combining other agents with amylin.

Stress Eating and Cortisol

Stress leads to increased secretion of cortisol, a hormone that causes hyperglycemia and hypertension. Increased cortisol secretion is associated with increased abdominal fat, as seen in patients with Cushing's syndrome, major depressive disorder, and in chronically stressed animals. This has led to a popular belief that the stress of everyday life increases cortisol and this makes people fat. "There's a proliferation of products that promise to melt away stress fat, even though there's no scientific evidence that they work," commented Dr. Ellisa Epel, PhD of the University of California-San Francisco.

To further elucidate the relationship between stress, cortisol and fat, Dr. Epel studied apple-shaped women (larger amount of abdominal fat) vs. pear-shaped women (less abdominal fat) as determined by waist-hip ratios (WHR). Both groups' cortisol levels were similar at baseline, but the apple-shaped women had increased levels of cortisol in response to stress. Apple-shaped women also reported more stress in their daily lives. This finding was explored further in relationship to stress eating in a group of 57 premenopausal women. Women were given a stressor (such as a difficult math problem or giving a speech) and offered a buffet of food on stress days vs. non-stress days. Apple-shaped women had an exaggerated cortisol response to the stressors and ate more high fat/ high sugar foods compared to normal controls who were similarly stressed.

Why don't people eat healthy foods when they are stressed? One hypothesis is that stress eating is related to food-reward dependence, and that highly palatable (high fat) food stimulates the same part of the brain that opiods act upon. When women were treated with naltrexone, which blocks the action of opiods and is used to treat narcotic addiction, they ate less and their response to stress was attenuated ($p=0.03$ vs. placebo).

Although these data support the idea that stress leads to inordinate eating behaviors in some women, Dr. Epel emphasized that early environmental factors and genetics may also contribute to increased abdominal fat in women.