



Michael J. Dunn, MD

## Dean's Corner

# Complexity of metabolic syndrome necessitates diverse research efforts

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**H**eat disease, stroke, diabetes—these are the grim promises of metabolic syndrome, an epidemic growing in step with waistlines, cholesterol levels, and blood pressures in the United States, affecting an estimated quarter of the US adult population. Since metabolic syndrome comprises a constellation of health risks, we must hunt in multiple areas for new diagnostic and therapeutic tools to increase our odds of successfully combating this ubiquitous problem. The insights gained by Medical College of Wisconsin researchers in recent months give me confidence that our multifaceted approach will bear fruit.

Through his NIH-funded research of sitosterolemia, Shailesh B. Patel, MD, DPhil, professor of Medicine and chief of Endocrinology, Metabolism, and Clinical Nutrition, identified 2 genes—ABCG5 and ABCG8—that control cholesterol balance, providing an avenue for reducing 1 of metabolic syndrome's risk factors. These genes play a critical role in controlling serum cholesterol and keeping non-cholesterol sterols out of the human body. Mice that lack either ABCG5 or ABCG8 seem to have less fat and are resistant to weight gain. These genes may therefore provide a link between

cholesterol, fat metabolism, and the metabolic syndrome. The research helps confirm that, over and above the calories in food, the quality of the dietary pathway in some way manipulates fat gain.

Scientists now know some of the genes that regulate inflammation, with implications for diabetes, obesity, cardiovascular disease, and many other health problems. Internationally recognized obesity researcher Ahmed H. Kissebah, MD, PhD, professor of Medicine, and a team of multi-national researchers identified the SEPS1 gene's role in inflammation, a response that can initiate the hardening of arterial walls and the onset of type 2 diabetes.

The finding builds on Dr Kissebah's genetics of obesity research, in which he was the first to link SEPS1 and the health complications of obesity. SEPS1 normally cleans out the faulty proteins that can build up when a cell is under stress. A variation in SEPS1 impairs its ability to purify cells, leading to an accumulation of defective proteins, which induces inflammation. With this new knowledge, scientists may be able to develop medications that could restore the normal function of SEPS1 or even enhance its activity. These drugs could reduce inflammation, potentially prevent-

ing heart disease and diabetes in some obese patients.

Kee-Hong Kim, PhD, assistant professor of Medicine (Endocrinology, Metabolism, and Clinical Nutrition), who was involved with Dr Kissebah's earlier obesity gene mapping work, is exploring additional aspects of SEPS1 and the role of inflammation in fat tissue. Adipose tissue is known to secrete various inflammatory proteins and enzymes, so in the case of metabolic syndrome, the body can become a hostile environment for cells.

Using animal models, Dr Kim is studying the function of SEPS1 in endoplasmic reticulum stress (caused by protein accumulation) in macrophages and pancreatic beta-cells. The ensuing inflammatory response can cause cell death, which, in the case of these 2 cell types, contributes to the incidence of atherosclerosis and diabetes.

Research at the Medical College is also generating concepts for caring for patients with metabolic syndrome. Obesity researchers led by E.B. Safek Guven, MD, assistant professor of Medicine (Endocrinology, Metabolism, and Clinical Nutrition), recently found that a multidisciplinary clinical approach to caring for patients with metabolic syndrome could swiftly

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and significantly lower their risk for heart disease.

After 6 months of treatment at the newly established Froedtert & The Medical College of Wisconsin Obesity/Metabolic Syndrome Clinic, study participants' body mass index, waist size, and triglycerides dropped 4.4%, 4.3%, and 13.1% respectively; HDL cholesterol levels rose 6.2%, thus reducing participants' 10-year risk of developing cardiovascular disease by 19.5%, based on NIH criteria. The research could be a step toward establishing national clinical standards of care for metabolic syndrome and accreditation for clinics treating it.

Medical College faculty are

conducting pediatric-specific research related to metabolic syndrome as well. A recent study by Ramin Alemzadeh, MD, professor of Pediatric Endocrinology, and Wendi G. Ehrman, MD, assistant professor of Pediatrics (Adolescent Medicine), found that simple and inexpensive tests adequately identified diabetes in obese children and youth but did not reliably identify those with prediabetes. Early identification of impaired glucose tolerance is critical to prevent the progression to type 2 diabetes.

In the study of 227 children, a Hemoglobin A1c test, a reflection of average glucose levels over about 2.5 months, identified 80% of those with diabetes but only 50% of

those with impaired glucose tolerance. A more cumbersome and expensive test—a 2-hour oral glucose tolerance test—was needed to identify children with prediabetes. This test identified 75% of those with impaired glucose tolerance. The results were not surprising, but they highlight the challenge of identifying children at risk for developing diabetes.

With metabolic syndrome growing in prevalence, results in this field can't come fast enough. There are not many success stories in obesity and metabolic syndrome research, but through our ambitious efforts, we can establish the momentum needed to reverse these unhealthy trends.

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