



Michael J. Dunn, MD

The growing medical and scientific challenges of obesity

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Obesity places nearly one-third of American adults at higher risk for developing myriad health problems, including type 2 diabetes, heart disease and some forms of cancer.

Obese individuals have a 50% to 100% higher risk of death from all causes compared with normal weight individuals, yet this unmistakable danger signal has not slowed the mounting incidence of obesity nationally or in Wisconsin.

The obesity rate among Wisconsin adults increased by 91% between 1990 and 2002. More than 21% of adults in the state are obese, defined by a body mass index of 30 or more.

As this problem has multiplied, so have research and clinical programs grown at the Medical College of Wisconsin to offer solutions to current patients and to establish the groundwork for discoveries that will lead to future therapies and prevention measures.

Ahmed H. Kissebah, MD, PhD, Professor of Medicine (Endocrinology), has been researching obesity and its related health risks for more than 25 years. The last 10 years have yielded a number of significant findings, due largely to a truly unique relationship between Medical College researchers and Take Off Pounds Sensibly (TOPS) Club, a leading weight-loss organization based in Wisconsin.

TOPS members and their families in 10 Midwest states were ideal

volunteers for medical research into the genetics of obesity. After examining DNA samples from about 500 families, or more than 2200 people, College researchers made the landmark discovery in 2000 that an area on chromosome 3 was associated with all the fundamental features of obesity, and that a cassette of genes must control these features. Numerous other scientists have since confirmed this observation.

Doctor Kissebah's team continues to lead the scientific community in understanding the fundamental biology and genetics of obesity and its health risks. The team has identified three novel genes linked to obesity: APM1 helps body muscles burn fat. PARL helps control the body's capacity to utilize glucose in response to insulin. SELS scavenges harmful, accumulated oxygen radicals released during metabolic processes. College researchers are continuing to identify other genes and to seek complete understanding of how these genes work together to cause obesity, with a goal of developing a cure or source of prevention.

The genetics of obesity research is conducted in collaboration with the College's Human and Molecular Genetics Center, focused primarily in the labs of Michael Olivier, PhD, and Anne E. Kwitek, PhD, both Assistant Professors of Physiology.

Genes causing obesity in adults may also contribute to obesity among children, which is becoming increasingly common. Research into the genetics of pediatric obesity is being planned by Dr Kissebah and Joseph A. Skelton, MD, Instructor in Pediatrics at the Medical College and program director for NEW Kids at Children's Hospital of Wisconsin. The NEW Kids program includes nutrition, exercise, and weight management strategies for overweight children.

Genetic advances have also facilitated clinical studies, as Medical College clinical researchers—led by Gabriele E. Sonnenberg, MD, Professor of Medicine (Endocrinology)—explore the link between obesity and type 2 diabetes, which an overweight person is 10 times more likely to develop.

Adipose tissue is now known to work much like an endocrine organ, producing inflammatory factors and other hormones that have either deleterious or protective effects on the development of insulin resistance, type 2 diabetes and vascular disease. Doctor Sonnenberg and her team seek to understand the biology and genetics of the processes activated by hormones produced in fat tissues.

The team is particularly interested in the newly described hormone adiponectin, which appears to protect against insulin resistance, type 2 diabetes and atherosclerosis.

Levels of this hormone, for which the gene APM1 codes, are low in people with obesity and diabetes. Conversely, TNF-alpha, a hormone that correlates with adipose tissue content, is likely the central hormone responsible for initiating the cascade of events leading to insulin resistance and vascular disease.

Insight into the connection between obesity and diabetes is a step toward combating them both. Many patients with type 2 diabetes who undergo gastric bypass surgery to treat obesity find that their blood sugar levels return to normal after surgery, and they can stop or decrease their diabetes medications, including insulin.

For many morbidly obese patients who have failed to lose weight with other plans or prescriptions, gastric bypass surgery is the final option for a healthier life. James R. Wallace, MD, PhD, Associate Professor of Surgery

(Minimally Invasive/GI Surgery), leads the Medical College's comprehensive gastric bypass surgery program at Froedtert Hospital.

Doctor Wallace utilizes the Roux-en-Y procedure, the gold standard for gastric bypass. He also brings a rare expertise—hand-sewing (rather than stapling) the two anastomoses in the surgery. This innovative technique reduces the chance for complications, particularly from strictures, which require repair much more often when staples are used at these junctures.

Five years ago, this surgery program was just forming, but now the team performs about 400 gastric bypass surgeries annually. Eighty-five percent to 90% are performed laparoscopically.

Most patients who undergo gastric bypass can expect to lose between 60% and 80% of their excess body weight. About two-thirds of the weight is lost within the first

year, and weight loss often continues up to two years after surgery. The average person is able to keep more than 60% of their excess body weight off for 15 years after surgery.

Like diabetes, related health problems often respond well to the weight loss generated by gastric bypass. Patients regularly experience improvement in: cardiovascular problems, such as hypertension; respiratory problems, such as asthma and sleep apnea; musculoskeletal problems; and stress urinary incontinence.

Obesity's complexity and associations with other health problems require the rare collection of comprehensive resources established at the Medical College. Obesity research has fostered collaboration between our clinical departments and basic science departments in a concerted effort to find a cause and a cure for this escalating danger.

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