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Metabolic Syndrome: Don't Blame the Belly Fat

Abdominal fat, the spare tire that many of us carry, has long been implicated as a primary suspect in causing the metabolic syndrome, a cluster of conditions that includes the most dangerous heart attack risk factors: prediabetes, diabetes, high blood pressure, and changes in cholesterol.

But with the help of powerful new imaging technologies, a team of Howard Hughes Medical Institute (HHMI) researchers at Yale University School of Medicine has found that insulin resistance in skeletal muscle leads to alterations in energy storage that set the stage for the metabolic syndrome.

"Knowing how insulin resistance alters energy storage before it leads to more serious problems can help those susceptible prevent the onset of the metabolic syndrome."

— **Gerald I. Shulman**

Insulin resistance is a condition in which the body's cells become resistant to insulin, a hormone secreted by the pancreas that plays an essential role in regulating the carbohydrates, lipids, and proteins obtained from food.

The new study, published July 16, 2007, in the *Proceedings of the National Academy of Sciences (PNAS)*, demonstrates that insulin resistance in skeletal muscle — caused by decreased ability of muscle to make glycogen, the stored form of carbohydrate from food energy — can promote an elevated pattern of lipids or fats in the bloodstream that underpins the metabolic syndrome.

The study was led by HHMI investigator Gerald I. Shulman and Kitt Falk Petersen, both of the Yale University School of Medicine. Coauthors of the paper were from Yale and Harvard Medical School.

The metabolic syndrome is a very common metabolic abnormality and the prevalence is growing. However, the underlying factors that cause it are poorly understood. The syndrome afflicts more than 50 million Americans and roughly half of all Americans are predisposed to it, making it one of the nation's most serious human health issues.

To begin to shed light on the earliest molecular events that lead to the metabolic syndrome, Shulman and his colleagues used powerful new magnetic resonance imaging techniques to observe how nutrients are channeled in the body in both insulin resistant and insulin sensitive human subjects.

The subjects for the study were all young, lean, non-smoking, healthy individuals who were sedentary and matched for physical activity. Aside from insulin resistance in one cohort, these volunteers had none of the other confounding factors typically associated with obesity and type 2 diabetes, which have been thought to play a key role in the pathogenesis of the metabolic syndrome.

"Our hypothesis was that the metabolic syndrome is really a problem with how we store energy from food, Shulman explained. "The idea is that insulin resistance in muscle changes the pattern of energy storage."

After providing the study's subjects with two meals high in carbohydrates, Shulman and his colleagues turned to magnetic resonance spectroscopy to measure the production of liver and muscle triglyceride, the storage form of fat, and of glycogen, the storage form of carbohydrate. □ "What we found is that (insulin) sensitive individuals took the energy from carbohydrate in the meals and stored it away as glycogen in both liver and muscle," said Shulman.

In the insulin resistant subjects, the energy obtained from their carbohydrate rich meals was rerouted to liver triglyceride production, elevating triglycerides in the blood by as much as 60 percent and lowering HDL cholesterol (the good cholesterol) by 20 percent. "In contrast to the young, lean, insulin-sensitive subjects, who stored most of their ingested energy as liver and muscle glycogen, the young, lean, insulin-resistant subjects had a marked defect in muscle glycogen synthesis and diverted much more of their ingested carbohydrate into liver fat production, Shulman and his colleagues reported.

"What we see," he noted, "is alterations in patterns of energy storage. An additional key point is that the insulin resistance, in these young, lean, insulin resistant individuals, was independent of abdominal obesity and circulating plasma adipocytokines, suggesting that these abnormalities develop later in the development of the metabolic syndrome."

The new findings promise to help untangle the early molecular events of a syndrome at the root of one of the world's most significant health issues. Knowing how insulin resistance alters energy storage before it leads to more serious problems can help those susceptible prevent the onset of the metabolic syndrome, Shulman said.

Another key observation was that skeletal muscle insulin resistance precedes the development of insulin resistance in liver cells, and that fat production in the liver is increased. These findings also have important implications for understanding the pathogenesis of nonalcoholic fatty liver disease, one of the

most prevalent liver diseases in both adults and children Shulman said.

The good news, according to Shulman, is that insulin resistance in skeletal muscle can be countered through a simple intervention: exercise.