Obesity as protection against metabolic syndrome, not its cause

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The collection of symptoms that is the metabolic syndrome -- insulin resistance, high cholesterol, fatty liver, and a greater risk for diabetes, heart disease, and stroke -- are all related to obesity, but, according to a review in the March 9th issue of the Cell Press publication *Trends in Endocrinology and Metabolism,* not in the way you probably think they are.

In fact, says Roger Unger of the University of Texas Southwestern at Dallas, obesity is the body's way of storing lipids where they belong, in fat tissue, in an effort to protect our other organs from lipids' toxic effects. It's when the surplus of calories coming in gets to be too much for our fat tissue to handle that those lipids wind up in other places they shouldn't be, and the cascade of symptoms known as metabolic syndrome sets in.

It comes down to simple facts that all of us know on some level or another: Americans since the 1950s eat too much high-calorie food loaded with carbs and fat (what Unger calls "potent adipogenic nutrient mixtures") and, thanks to modern technology, we move far too little. Until that changes, Unger doesn't see any end to the growing epidemic of metabolic syndrome. Still, our metabolisms aren't broken; the pathways that squirrel fat away as an energy source for use in lean times are just completely overwhelmed.

"We are pushing our homeostatic capability to the maximum," says Unger, who coined the term "lipotoxicity" in 1994. "Overnutrition used to be rare—reserved for those in the castle. Today, it's just the opposite.

Bad calories are so cheap that anyone can afford to get overweight."

Unger cites plenty of evidence in support of a protective role for obesity. Genetic manipulations in mice that increase or decrease fat formation have provided evidence that adipogenesis, meaning the generation of fat cells, delays other metabolic consequences of overeating. The reverse is also true, he writes. Obesity-resistant mice have in some cases been found to develop severe diabetes upon eating too much, as a result of lipid accumulation in tissues other than fat.

There is some disagreement in the field about whether insulin resistance is a primary cause of metabolic syndrome or just one of its features, Unger notes. But on this, too, he has a clear view. Insulin resistance is not the cause of metabolic syndrome, he says, it is a "passive byproduct" of fat deposition in the liver and muscle once storage in fat cells begins to fail.

It also makes sense in Unger's estimation that cells that have already taken on too much fat would begin to exclude glucose, causing its levels in blood and urine to rise. Once in cells, glucose becomes a substrate for the production of more fat. "The body is doing what we should have done—keep excess calories out—and it may be protective," Unger says.

At the center of the transition from protective obesity to metabolic syndrome is resistance to the fat hormone leptin, well known for its appetite-suppressing effects, Unger says. The hormone is also responsible for partitioning fat in the body. The rise of leptin as fat stores grow is therefore an adaptive response, but that can only go so far before resistance sets in.

Based on the genes they carry, some people will be better able to sustain lipid storage in fat and can get away with being overweight, even obese, without the other symptoms. Eventually, though, the need to cut calories

is something all of us will face.

"Once you reach a certain age, almost everybody is leptin resistant," he says. "Nature stops protecting you once you pass the reproductive years," requiring all of us to watch our diets and do exercise.

Unger's perspective comes from the research he does at UT Southwestern's Touchstone Center for Diabetes Research and a thorough understanding of the scientific literature, but it also stems from his own memories in childhood when one only saw fat ladies at the circus. "That's how unusual it was," he says. "The younger you are, the more skewed your perception is of an epidemic that surrounds you."

Unger concludes his review article this way: "Based on evidence reviewed here, it seems that prevalent forms of metabolic syndrome and T2DM [type 2 diabetes mellitus] result from unremitting caloric surplus complicated by failure of adipocytes to maintain protection against lipotoxicity. If one imagines the USA population to be unwitting volunteers in the largest (300 million subjects) and longest (50 years) clinical research project in history, the specific aim of which was to determine if the deleterious effects of sustained caloric surplus in rodents also can occur in humans, the outcome of the project becomes clear—after 50 years of exposure to an inexpensive calorie-dense diet high in fat and carbohydrates, 200 million subjects are overweight and >50 million have metabolic syndrome. The failure of healthcare providers and pharmaceutical industries to contain the pandemic suggests that elimination of 'bargain basement' calories will be required to 'price obesity out of the market.' Unfortunately, this would have profound socioeconomic implications: How do we tax excessive calories while at the same time guaranteeing sufficient access to high-quality foods for the underprivileged?"

More information: Scherer et al.: "Gluttony, sloth and the metabolic

syndrome: a roadmap to lipotoxicity.'"

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