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6,000-Calorie Diet Yields Clues to Insulin Resistance

By Ruth Kava — November 16, 2015

How obesity feeds into insulin resistance remains somewhat of a mystery. A new study, which confined normal-weight men to hospital beds while having them consume 6,000 calories per day, sheds some light onto the possible cause of insulin resistance in the obese.

[1]
Obesity ups risk of type 2 diabetes via Shutterstock [2]

A hallmark of Type 2 diabetes is insulin resistance, a condition in which the body's tissues (especially muscle and fat) no longer respond normally to insulin by increasing their uptake of glucose from the blood. The result is that blood glucose levels remain abnormally elevated after meal consumption. Insulin resistance is known to be increased among the obese, and is thus linked to the occurrence of several metabolic abnormalities that are frequently seen in such people.

But how obesity feeds into insulin resistance remains somewhat of a mystery. A new study [3], recently published in the journal *Science Translational Medicine,* sheds some light onto the possible cause of insulin resistance in the obese.

To investigate the genesis of obesity-associated insulin resistance, Dr. Guenther Boden of the Temple University Medical School in Philadelphia and colleagues confined six normal-weight men to hospital beds for a week, encouraging them to stuff themselves with food to the tune of 6,000 calories per day.

Their normal intake had been about 2,400 calories per day, so not surprisingly, they gained weight nearly eight pounds, all fat, on average. Each man was weighed daily, and their blood was sampled. In addition, at the beginning and end of the week the investigators took samples of fat tissue from the participants' thighs, and used it to examine changes in tissue metabolism.

The rapid weight gain seemed to do the trick, since the participants' insulin sensitivity began to decrease by the second day of over-eating, and by the end of the week their insulin-stimulated

glucose uptake had decreased by 50 percent.

The researchers had hypothesized that any or all of several metabolic parameters might be responsible for the changes in insulin sensitivity increased levels of fatty acids in the blood; increased stress in a sub-cellular organelle (endoplasmic reticulum); increased production of inflammatory proteins; and increases in oxidative stress. Of these possibilities, only the increased oxidative stress seemed to be related to the acute obesity onset.

Dr. Boden and colleagues found that there seemed to be increased production of reactive oxygen compounds, which are typically detoxified by anti-oxidants in body tissues. This didn't seem to be happening normally after the men had gained weight. And the researchers suggested that a protein, the GLUT4 glucose transporter, was affected by the excess of reactive oxygen species. This protein is produced by fat cells after insulin stimulation, and provides the means by which glucose is taken up from the blood. Obviously, if GLUT4 isn't functioning properly, blood glucose levels will be adversely affected.

While this research is certainly promising, it's too early to say it is definitive. For one thing, the men in the study were very inactive if they had exercised would it have delayed or changed the onset of insulin resistance in spite of overeating?

This was a very small study, and the extent to which its results would apply to women or people of other ages is, of course, unknown. Further, did the acute change in body fatness cause more oxidative stress than might occur if weight were changed more gradually? All these, and other questions, remained to be answered. That being said, this research provides some new insights into the genesis of insulin resistance, and thus to the onset of Type 2 diabetes.
