Genetic variant is linked to obesity and insulin resistance

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A large study in people at risk of diabetes has found a direct association between the presence of a small genetic alteration in a hormone receptor and increased body fat and insulin resistance. The results, to be presented Tuesday at The Endocrine Society's 94th Annual Meeting in Houston, suggest an adverse role for a previously described genetic variant, the BclI polymorphism.

"Our findings support the idea that even small variations in hormone receptor sensitivity can have metabolic implications, such as obesity or diabetes," said co-author Bastiaan Havekes, MD, PhD, of Maastricht University Medical Center, Maastricht, the Netherlands.

"Endocrinologists should not just focus on hormone levels themselves. Taking into account hormone receptor sensitivity could help in better understanding hormone-mediated effects on metabolism," he said.

The inherited BclI polymorphism occurs in the gene encoding for the glucocorticoid receptor, which controls the actions of glucocorticoids, steroid hormones that affect every system in the body. This small variant makes the receptor more sensitive to glucocorticoids, resulting in greater effects with similar hormone levels, Havekes said.

The effects of this change appear to be similar to, although much smaller than, the excessive glucocorticoid exposure that can occur from certain medications or diseases, Havekes said. Such excess exposure can result in weight gain, especially around the abdomen, as well as in disturbed

blood sugar metabolism. This exposure most often occurs from long-term use of prednisone or other glucocorticoid medications, which are widely used to treat inflammatory diseases or to suppress the immune system. It also can result from endocrine diseases such as Cushing's syndrome. Cushing's causes overproduction in the body of the glucocorticoid cortisol, often called the "stress hormone."

Patients in this study, however, did not have known excess exposure to glucocorticoids, according to Havekes. He and his co-investigators studied 1,228 adults who participated in one of two Dutch studies focusing on diabetes in the general population. More than half of the study participants had either prediabetes (23 percent) or Type 2 diabetes (33 percent). All subjects underwent genetic testing for the BclI polymorphism.

The researchers found that 519 subjects did not carry the alternative form of the gene, or G-allele, for the BclI polymorphism on either chromosome. Another 540 subjects were heterozygous carriers, meaning the G-allele was present on one of the two chromosomes. The remaining 169 subjects were homozygous carriers and therefore carried the G-allele on both chromosomes.

Those who had the BclI polymorphism on each chromosome had a significantly higher body mass index and larger waist and hip circumferences than did noncarriers or heterozygous carriers, the authors reported. This was reflected by greater insulin resistance, meaning that insulin is less effective at lowering blood glucose (blood sugar).

"Determining an individual's genetic risk profile for metabolic disease is of paramount importance to prevent development of cardiovascular diseases," he said. "Future studies concerning cardiovascular risk profiling should perhaps consider the BclI polymorphism."

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