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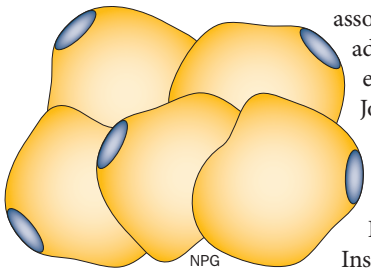
METABOLISM

Iron metabolism, adiponectin and T2DM—the link with adipocyte insulin resistance

Two new studies shed light on the important role of adipose tissue in the relationship between iron, adiponectin and type 2 diabetes mellitus (T2DM).

In epidemiological studies, high levels of serum ferritin (a biomarker for iron stores) are associated with an increased risk of T2DM. However, many factors contribute to elevations of serum ferritin levels, including inflammation, which raises the question of whether iron has a causal role in the development of T2DM. Some research suggests that the role of iron in the pathogenesis of T2DM is related to induction of insulin resistance, although where in the body this effect might occur is unclear. Wlazlo *et al.* and Gabrielsen and co-investigators took the search for iron's effect on insulin resistance to the adipose tissue.

"Both increased ferritin levels and low concentrations of adiponectin (an adipose-tissue-derived hormone) are known to be associated with insulin resistance. It was also known that ferritin is negatively associated with adiponectin," explains José Manuel Fernández-Real of the Biomedical Research Institute of Girona, who was not involved in these two studies. "This research demonstrates that the association is causally related. Iron leads to increased ferritin synthesis in parallel to repressing adiponectin production. In addition, this mechanism could be an important mediator of the association between iron and risk of T2DM."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> "...high dietary iron downregulated adiponectin and caused insulin resistance..."

In the first study, Wlazlo *et al.* investigated the association of several markers of iron metabolism with plasma adiponectin levels and adipocyte insulin resistance in 492 individuals with or at increased risk of T2DM or cardiovascular disease. Adipocyte insulin resistance is thought to be an early event in the pathogenesis of T2DM and is defined as the product of fasting insulin and nonesterified free fatty acid levels. The researchers show associations of several markers of iron metabolism with adipocyte insulin resistance, after adjustment for several covariants. Markers of iron metabolism were also associated with nonesterified free fatty acid levels. Two markers of iron metabolism, ferritin and transferrin, were also inversely associated with adiponectin levels.

In the second study, Gabrielsen and co-workers show in humans that serum levels of ferritin and adiponectin are inversely associated independently of inflammation. In tissue culture, mouse model and human studies they demonstrate a causal relationship between iron and adiponectin level, in which iron regulates adiponectin at the transcriptional level. They also report that adipocytes express ferroportin, an iron exporter, which is consistent with a role of adipocytes as an iron sensor. "The most significant finding, that high dietary iron downregulated adiponectin and caused insulin resistance, is important in that it suggests that decreasing iron will improve the diabetes phenotype," explains senior author Don McClain.

Body iron stores can be altered by interventions such as phlebotomy; therefore, McClain's team will now conduct a clinical trial of 'blood letting' (donating blood to the Red Cross) for patients with a short duration of T2DM.

Carol Wilson

Original articles Wlazlo, N. *et al.* Iron metabolism is associated with adipocyte insulin resistance and plasma adiponectin: the Cohort on Diabetes and Atherosclerosis Maastricht (CODAM) study. *Diabetes Care* doi:10.2337/dc12-0505 | Gabrielsen, J. S. *et al.* Adipocyte iron regulates adiponectin and insulin sensitivity. *J. Clin. Invest.* doi:10.1172/JCI44421