

Iron and Diabetes Revisited

Iron is the most abundant transitional metal in the body. It has long been recognized that iron overload can increase the risk of diabetes, particularly in iron-overload states such as hemochromatosis and recurrent transfusions in diseases like thalassemia. Furthermore, a large body of epidemiological evidence suggests that an increase in dietary iron (as heme, mainly from meat and meat products) is associated with an increased risk of diabetes (1). In contrast, iron deficiency (over time one of the most common nutritional deficiencies in the world) may lower the risk of diabetes. Indeed, it has been suggested that recurrent phlebotomy may protect against diabetes (2), although there are no large multicenter, randomized controlled trials to support this hypothesis. In addition, iron has been implicated in the pathogenesis of renal disease including diabetic nephropathy (1).

Two articles in this issue of *Diabetes Care* add to this evidence and report that prepregnancy dietary heme iron intake is associated with an increased risk of diabetes. The association remains significant even after adjustment for a variety of factors known to be associated with gestational diabetes mellitus (GDM). Bowers et al. (3) studied participants in the Nurses' Health Study which has a robust dataset and fairly reliable information on dietary intake. Qiu et al. (4) have prospectively studied a similar cohort of over 3,000 pregnant women and used food frequency questionnaires to assess maternal diet. Not only was heme iron intake positively associated with GDM risk, nonheme iron may have been inversely related to such risk, although it is not statistically significant. Women who reported the highest heme iron intake experienced greater than a threefold increased risk of GDM.

How might increased iron intake lead to diabetes? Multiple mechanisms that link iron with abnormal glucose metabolism have been proposed, including β -cell dysfunction and insulin resistance, possibly mediated through oxidative stress (1). Animal studies suggest that iron impairs β -cell function by inducing oxidative stress as well as impairing mitochondrial function and may also decrease glucose uptake in muscle and adipose sites. Thus

iron plays a role in several important steps in insulin action and glucose metabolism. There are very few pathophysiological studies that explore this association.

It is important to recognize that traditional methods of measuring iron may not be the best way to study the pathophysiological role of iron. For example, ferritin is often considered a marker of body iron stores but is an acute-phase protein that may be influenced by coincidental infections and, more importantly, in this setting, by the presence of low-grade inflammation associated with obesity. Moreover, ferritin itself does not participate directly in the oxidant reactions related to iron. Critical to iron's importance in biological processes is its ability to cycle reversibly between its ferrous and ferric oxidation states. This precise property, which is essential for its functions, also makes it very dangerous, because free iron can catalyze the formation of free radicals that can damage the cell. Thus, from a pathophysiological standpoint, it is important to measure iron pools that consist of chemical forms that can participate in redox cycling, often referred to as catalytic or labile iron (5–8). Baliga et al. (9) have previously demonstrated that there is a poor correlation between catalytic iron and total body iron stores. Thus measurement of catalytic iron may be important in the study of the association of iron and diabetes and its complications. Recent data suggest an increase in plasma and urinary catalytic iron in subjects with obesity without diabetes, as well as patients with diabetes-related complications and acute coronary syndromes (10–12).

The pathological effects of iron accumulation in tissue in iron-overload states are well known. What is new in the field is the recognition that iron plays an important role in the pathophysiology of disease in the absence of systemic iron overload (1). The concept of iron contributing to diabetes is supported by a few important recent animal studies. Cooksey et al. (13) have demonstrated that, in obese mice with type 2 diabetes treated with an iron-restricted diet as well as an iron chelator, there were improvements in glucose metabolism without causing overt iron deficiency. Thus, even at "normal" levels, iron exerts a detrimental effect on

β -cell function that may be reversible with removal of iron, either through phlebotomy or possibly iron chelation (2). This concept lends itself to exploring phlebotomy or iron chelation as potential treatments for diabetes. Clearly research is needed to explore this approach in states of lesser overload with iron or indeed as a potential treatment of diabetes and prediabetes, particularly in those identified (by appropriate testing) as having either excess nutritional intake or overreactive iron associated with obesity. Studies in iron-overload states demonstrate an improvement in glucose metabolism with either of these modalities (2,14).

In the context of the two papers in this issue, it is possible that menstruation is protective for diabetes in premenopausal women and cessation of menses leads to some iron accumulation. Clinical trials are needed to determine whether phlebotomy or chelation of catalytic iron in women with GDM and adequate iron stores can improve the marked abnormalities seen in insulin secretion and action associated with this condition.

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