COMMENT ON PODMORE ET AL.

Association of Multiple Biomarkers of Iron Metabolism and Type 2 Diabetes: The EPIC-InterAct Study. Diabetes Care 2016;39:572–581

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Podmore et al. (1) reported the largest and most comprehensive study to date implicating iron excess in the pathogenesis of type 2 diabetes (T2D). Dose-related statistical associations existed between levels of body iron (ferritin levels) and increased T2D risk in men and women. By contrast, increasing percent transferrin saturation (%TSAT) levels predicted reduced risk in women. Similar trends for %TSAT levels were shown for men that did not reach statistical significance. Rising ferritin likely represented increased potentially damaging levels of redox active iron, whereas rising %TSAT levels likely represented protective effects of transferrin scavenging of redox active iron. The authors cautioned that iron-T2D risk associations could represent reverse causation or confounding by multiple potential confounding variables. However, ferritin effects were found prior to clinical diabetes as observed in previous studies. Effects of elevated ferritin levels remained on multivariate analyses in lean individuals and after exclusion of individuals with extreme ferritin elevation. Importantly, elevated ferritin predicted T2D risk in individuals with no signs of overt inflammation, liver disease, high alcohol consumption, or obesity.

In fact, prospective effects of elevated ferritin levels, low risk of T2D in Mediterranean populations having limited dietary iron consumption, and increased risk in the absence of "overt inflammation" point to forward causation of T2D by unphysiological levels of body iron. Furthermore, exploration of the mechanisms of iron toxicity, particularly to the β-cells of the pancreas, should consider aberrant hepcidin expression in diabetes risk.

Hepcidin blocks iron absorption in the gut and iron release from macrophages by binding ferroportin, the sole known iron exporter, on cell membranes, causing its internalization and degradation (2). Hepcidin levels are upregulated by iron intake and inflammation and downregulated by iron deficiency. Multiple variables may contribute to abnormal hepcidin expression in diabetes, including insulin resistance associated with gluconeogenic signaling shown to regulate hepcidin transcriptionally (3). Induction of hepcidin leads to tissue iron retention while reducing iron absorption and levels of serum iron and %TSAT. This function of hepcidin is presumably intended to preserve tissue iron to maintain cellular respiration. Food excess may activate gluconeogenesis persistently resulting in the overstimulation of hepcidin, causing cellular iron accumulation and damage. The apparent "laboratory paradox" of tissue iron excess with high levels of ferritin, inflammatory markers, and hepcidin but relatively low serum iron and %TSAT has been described with metabolic abnormalities, including obesity, insulin resistance, and inflammation, apart from diabetes per se (4,5). For example, this pattern exists in dysmetabolic/nonalcoholic fatty liver disease, having mixed mesenchymal/parenchymal hepatic iron overload, insulin resistance, and hepcidin induction due to activation of gluconeogenesis (3). Iron depletion by phlebotomy lowered hyperinsulinemia and transaminase levels, indicating a detrimental effect of iron in this condition (6).

Substantial incentive exists for further investigation of hepcidin regulation of iron homeostasis in diabetes. Effects of iron unloading on clinical outcomes in T2D are unknown. Current evidence suggests that primary avoidance of iron excess with maintenance of physiological levels of body iron may ameliorate the current diabetes pandemic.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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The authors of the cited article did not respond.

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