Mechanisms Linking Glucose Homeostasis and Iron Metabolism Toward the Onset and Progression of Type 2 Diabetes

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OBJECTIVE

The bidirectional relationship between iron metabolism and glucose homeostasis is increasingly recognized. Several pathways of iron metabolism are modified according to systemic glucose levels, whereas insulin action and secretion are influenced by changes in relative iron excess. We aimed to update the possible influence of iron on insulin action and secretion and vice versa.

RESEARCH DESIGN AND METHODS

The mechanisms that link iron metabolism and glucose homeostasis in the main insulin-sensitive tissues and insulin-producing β-cells were revised according to their possible influence on the development of type 2 diabetes (T2D).

RESULTS

The mechanisms leading to dysmetabolic hyperferritinemia and hepatic overload syndrome were diverse, including diet-induced alterations in iron absorption, modulation of gluconeogenesis, heme-mediated disruption of circadian glucose rhythm, impaired hepcidin secretion and action, and reduced copper availability. Glucose metabolism in adipose tissue seems to be affected by both iron deficiency and excess through interaction with adipocyte differentiation, tissue hyperplasia and hypertrophy, release of adipokines, lipid synthesis, and lipolysis. Reduced heme synthesis and dysregulated iron uptake or export could also be contributing factors affecting glucose metabolism in the senescent muscle, whereas exercise is known to affect iron and glucose status. Finally, iron also seems to modulate β-cells and insulin secretion, although this has been scarcely studied.

CONCLUSIONS

Iron is increasingly recognized to influence glucose metabolism at multiple levels. Body iron stores should be considered as a potential target for therapy in subjects with T2D or those at risk for developing T2D. Further research is warranted.

Iron levels help to modulate the clinical manifestations of numerous systemic diseases. The importance of adequate amounts of iron for health and well-being in humans is well known. Iron is involved in binding and transporting oxygen and regulating cell growth and differentiation, as well as electron transport, DNA synthesis, and many important metabolic processes (1).

From a clinical standpoint, assessing serum ferritin concentrations is a useful measure of iron storage. Ferritin is also an acute-phase reactant and, as such, is

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REVIEW

expected to increase under conditions of low-grade inflammation. Inflammatory cytokines influence iron storage in various cell types, but different studies have shown that the link between elevated iron and metabolic abnormalities is independent of inflammation (2). Given its clinical relevance, it is surprising that the source of human serum ferritin remains to be defined (whether it is derived from damaged cells or actively secreted by a regulated mechanism). In mice, serum ferritin seems to be derived mainly from macrophages through a nonclassical secretory pathway (3). A soluble form of the extracellular transferrin receptor (TfR) can be detected in serum (serum TfR [sTfR]) as a result of the externalization of TfR during the endocytic cycle. sTfR concentration is closely related to cellular iron demands and is a marker of erythropoiesis; hence, the higher the ferritin level, the lower the sTfR concentration.

A full picture of iron metabolism is available in several excellent reviews (4–6). Here we update the mechanisms linking iron metabolism to glucose homeostasis and the possible influence of either iron excess or deficiency on the development and progression of type 2 diabetes (T2D). We mainly focus on human studies, although research in animal models is also considered when the information available in humans is scarce.

INHERITED VERSUS ACQUIRED IRON OVERLOAD SYNDROMES

The interest of clinical diabetologists in the interplay between iron metabolism and glucose homeostasis dates back to Apollinaire Bouchardat, who, in the 19th century, first described "bronze diabetes." Strikingly, the first description of "insulin resistance" might have been in patients with hereditary hemochromatosis (HH). Howard Root observed in 1929 an inadequately high need for insulin in different diseases, and he called the phenomenon "insulin resistance" (7). The title of the article referred to "bronze diabetes," the term for hemochromatosis at that time (7).

Iron deposits within hemosiderin in different cells, including β-cells, induce apoptosis in patients with HH, leading to diabetes while causing the characteristic skin pigmentation. High amounts of iron are found in hepatocytes (the liver iron concentration in patients with HH is, on average, 200–250 mmol/g). Serum levels of ferritin and transferrin, and transferrin saturation, are severely elevated.

Interest in the topic has been growing in the almost two decades since the link between insulin resistance and serum ferritin was noticed in 1999. Some insulin-resistant patients present mild abnormalities of iron metabolism. In general they are obese; have diabetes, with stigmata of the metabolic syndrome (MetS) and/or nonalcoholic fatty liver disease (NAFLD); and have no major genetic mutations among identifiable genetic hemochromatosis-related defects. HH genetic defects involve the hepcidin gene itself (*HAMP*) or the hepcidin regulators (such as HFE, TfR2, hemojuvelin, and ferroportin-1 [FPN1]) (8). The term for this disease was "insulin resistance–hepatic iron overload syndrome" (9).

Acquired abnormalities of iron metabolism range from mild/modest to severe dysmetabolic hyperferritinemia (DHF; with normal to mildly elevated transferrin saturation and no intrahepatic iron deposition) to hyperferritinemia with mild to moderate liver iron concentration, generally higher than the normal value of 35 but below 100 mmol/g dry weight (dysmetabolic-hepatic iron overload syndrome [DIOS]). Iron deposits in hepatocytes and cells of the reticuloendothelial system).

Indeed, in 1998, iron stores, expressed as serum ferritin concentration, were proposed to be a component of the MetS (10,11), and increased prevalence of excess iron in the body was observed in subjects with the syndrome (12). Insulin resistance measured using gold-standard methodologies (euglycemic-hyperinsulinemic clamp) was associated with total body iron stores, even in the presence of normal glucose tolerance (11). Serum ferritin concentration in the apparently healthy general population was positively correlated with fasting and postload glucose (10). Iron stores have accordingly been associated with an enhanced risk of developing T2D. The first prospective (nested case-control) study demonstrating a positive association between the ratio of TfRs to ferritin and risk of T2D was reported by Salonen et al. (13). Many authors have since studied this association. The link between iron and T2D has been reviewed and updated in several articles (14,15). At least four systematic reviews and meta-analyses confirm the association of iron and increased T2D risk (16).

The initial investigations of glucose metabolism in patients with HH helped in understanding the interplay between glucose and iron metabolism. Major differences in terms of pathogenesis, liver histopathology, clinical sequelae, and potential therapeutic approaches between inherited and dysmetabolic-based iron overload syndromes clearly came to light soon after, with recognition of the role of hepcidin in such interplay. The iron regulatory feedback of hepcidin is lost in inherited forms that present inadequate or defective hepcidin production (hepcidin-deficient model), whereas it is perfectly preserved in dysmetabolic-based conditions (excess hepcidin model). This would explain most of the difference between phenotypes.

The foremost lesson from the investigation of patients with HH was that iron overload leads to diabetes by progressively reducing their β-cell function. Iron overload, on the other hand, is not so severe as to induce the rapid apoptosis of β-cells in dysmetabolic-based iron overload syndromes, but it exerts an important effect on glucose homeostasis by impairing the response to insulin in the liver, muscle, and adipose tissue.

IMPACT OF IRON ON INSULIN-SENSITIVE TISSUES

Iron and Liver "Cross Talk" Affects Glucose Metabolism

The liver is the major reservoir of iron in the body. Hepatocytes take up transferrin-bound iron from the bloodstream through TfR1, expressed on surfaces that face the sinusoids, once iron load exceeds the iron-binding capacity of ferritin (4–6). The liver can maintain iron homeostasis within a narrow physiologic range by secreting hepcidin. Hepcidin senses a number of physiological and pathophysiological stimuli that regulate iron homeostasis, and it responds by downregulating the expression of FPN1 on the enterocyte basolateral side. Hepcidin induces phosphorylation, internalization, and degradation of the iron transporter ferroportin (FPN). This factor inhibits the duodenal

absorption of the metal (17) and also inhibits the release of iron from macrophages.

Excess iron, once stored in the liver, interferes with glucose metabolism, causing hyperinsulinemia via both decreased insulin extraction and impaired insulin signaling (18). Hyperinsulinemic status, on the other hand, favors the intrahepatic deposition of iron. Insulin enhances the uptake of extracellular iron, inducing the redistribution of TfRs to the cell surface (19) while downregulating hepcidin expression (20). An editorial hypothesized that "iron and insulin are synergistic in promoting oxidative stress with release of reactive oxygen species (ROS) and inflammatory cytokines in the sub-endothelial space" (21). Such cytokines, in turn, promote ferritin synthesis in Kupffer cells and macrophages.

The question of why some obese patients develop iron excess, which can evolve into DHF or DIOS, and some others do not is still controversial, although genetics explain major biochemical, histological, and clinical differences between inherited and acquired forms. Genetics (mutations in the β-globin and α1-antitrypsin genes) (22) and dietary habits may explain some of the phenotypic variability. Different mechanisms have been hypothesized to answer the question, from alterations in diet or duodenal iron absorption to dysfunction of target molecules involved in iron metabolism (Fig. 1).

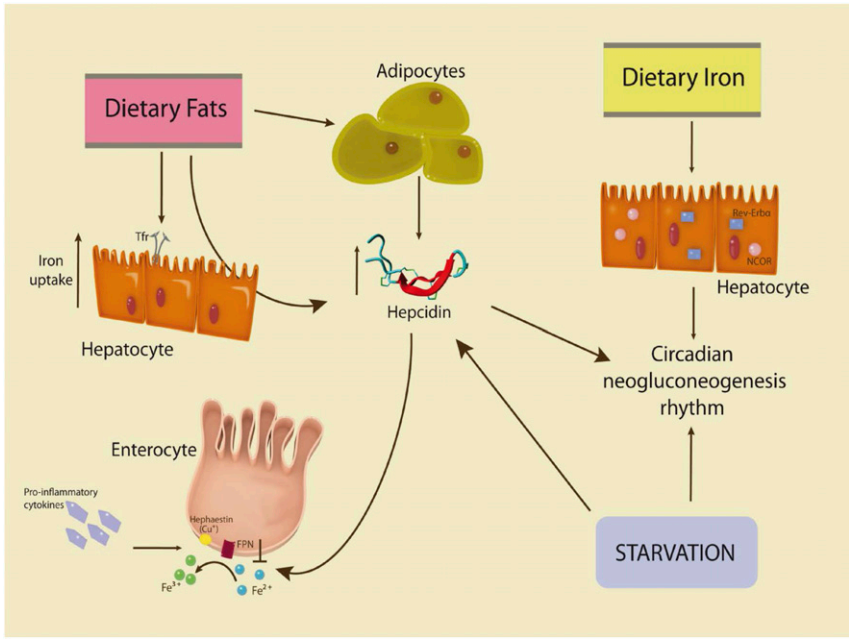

Figure 1—Postulated mechanisms promoting DIOS. Excess dietary fats favor hepatic iron uptake by enhancing the surface expression of the TfRs and secretion of hepcidin from hepatic and adipose tissue. Hepcidin senses gluconeogenesis in conditions of starvation. Dietary iron can affect the circadian rhythm of hepatic gluconeogenesis through the heme-mediated regulation of nuclear receptor subfamily 1 group d member 1 (Rev-Erbα) and its cosuppressor nuclear receptor corepressor 1. Despite being appropriately released, hepcidin might be less effective because of reduced FPN expression in the duodenum and in the liver as a result of the excess of proinflammatory adipocytokines. Copper serves mainly for enterocyte hephaestin ferroxidase activity.

A High-Fat Diet Changes Iron Metabolism

Ruivard et al. (23,24) hypothesized that the natural history of DIOS originates from a Western diet that is rich in fats and iron and is able to stimulate the compensatory release of hepcidin from the liver and adipose tissue. Animals fed a high-fat diet had increased activity of iron regulatory protein 1 in the liver and an increase in TfR1 expression (25). The high-fat diet also resulted in the increased secretion of hepcidin and the downregulation of FPN1, factors linked to increased intrahepatic deposition of iron (25).

Dietary Iron and the Circadian Clock

Feeding is one of the factors known to set the circadian clock in peripheral tissues. The circadian rhythm of the liver is known to maintain glucose homeostasis, and disruption of this rhythm is associated with the onset and progression of T2D. Dietary iron seems to affect circadian gluconeogenesis and glucose metabolism by influencing the heme-mediated regulation of two important molecules: the nuclear receptor subfamily 1 group d member 1 and its cosuppressor nuclear receptor corepressor 1. When heme synthesis was blocked by the administration of aminolevulinic acid, variations in dietary iron did not affect hepatic glucose production or expression of gluconeogenic enzymes (26).

Starvation and Persistently Activated Gluconeogenesis

Persistently activated gluconeogenesis is known to occur in patients with obesity, insulin resistance, NAFLD, and T2D. Gluconeogenesis provides fuel during starvation. Hepcidin has been shown to serve as a gluconeogenic sensor in starving mice. Starvation induced liver iron deposition by increasing the transcription of phosphoenolpyruvate carboxykinase 1 while also augmenting the levels of hepcidin and consequently the degradation of FPN1 (27). Starvation also was associated with increased levels of *Ppargc1a* and *Creb313* mRNAs, and administration of mRNAs interfering against *Ppargc1a* and *Creb313* reduced levels of the hepcidin gene.

Alterations in Duodenal Absorption of Iron

Increased duodenal absorption of iron is a possibility that has been studied as a potential primary defect causing DIOS. However, patients with DIOS had significantly less intestinal iron absorption (evaluated using stable isotopes) than subjects without hepatic siderosis or control subjects (23).

Hepcidin

Hepcidin is primarily secreted by hepatocytes and, to a minor extent, by adipocytes and macrophages. α2-Macroglobulin is the specific high-affinity, hepcidin-binding molecule that carries hepcidin into the bloodstream. Enlarged adipose tissue overreleases hepcidin (excess hepcidin model), and inflammatory molecules, including interleukin-6, tumor necrosis factor-α, and leptin, stimulate further production of hepcidin mRNA. The hepcidin-induced downregulation of intestinal iron absorption was physiologically preserved in patients with DIOS (23). They

overexpress and release hepcidin in concordance with the increased levels of circulating ferritin to counterbalance intrahepatic iron deposition (28). Hepcidin, however, might be less effective since the expression of FPN1, the physiological target of hepcidin, was reduced in the duodenum and liver of these patients (29). The reduced expression of FPN1 is the consequence of an increased proinflammatory milieu with particularly elevated levels of tumor necrosis factor-α (30). Normal or overexpressed levels of hepcidin result in macrophage retention and redistribution of iron toward Kupffer cells despite FPN1 downregulation (Fig. 2). Iron deposition in hepatocytes is usually moderate (31).

TfR1

An impaired hepatic expression of TfR1 in patients with DIOS is also a possibility. TfR1 expression was, however, physiologically reduced in response to iron accumulation in these patients, showing a preserved compensatory response to iron overload (30).

Alterations in Copper Metabolism

Copper serves a role in hephaestin ferroxidase activity in duodenal enterocytes, where it promotes the loading of iron to apo-transferrin. Copper is implicated in ceruloplasmin ferroxidase activity to mobilize iron from hepatocytes and macrophages. As such, copper is also involved in cell surface stability of FPN1 (32). Patients with DIOS have low levels of hepatic and serum copper in parallel to reduced activity of serum ferroxidase ceruloplasmin (33), and consequently reduced iron mobilization in hepatic cells (30).

Enhanced Phagocytosis of Fragile Erythrocytes

Enhanced phagocytosis of fragile erythrocytes might favor the development of DIOS. It is interesting that aggregates of erythrocytes were documented in microscopic areas of inflammation from liver biopsies of patients with NAFLD (34). Excess iron and erythrocytes engulfed by Kupffer cells were also reported in a rabbit model of familial hypercholesterolemia that exhibits steatohepatitis and fibrosis (34).

Most of the evidence of the association of hepatic iron overload and impaired glucose homeostasis has been collected in patients referred for hepatic steatosis. Some of them presented with overt T2D. It will, however, be important to investigate the prevalence of hepatic siderosis among patients with T2D. In this regard, MRI is a reliable tool for noninvasive assessment of the iron concentration in specific tissues (liver, brain, spleen). The MRI techniques used for iron assessment are based on the changes of relaxation times produced by local magnetic field inhomogeneities and intrinsic tissue properties. Microscopic field gradients induced by paramagnetic ferritin-loaded cells produce a random phase shift of the hydrogen protons, affecting their relaxation. The relaxation signals of tissues are therefore affected by diffusion-mediated contributions of iron. Transverse relaxation rates of the MRI parameter R2* show a strong linear correlation with liver iron concentration (35). Iron depletion is effective in ameliorating parameters of glucose metabolism in patients with DHF, as discussed elsewhere (16). Based on the available evidence, iron depletion should also be tested in patients with DIOS and T2D, and MRI is of potentially extreme utility in their follow up to evaluate its effectiveness. Although only liver biopsy visualizes iron-associated liver damage and provides significant information on the degree of simple steatosis, steatohepatitis, and fibrosis, further research on liver iron using MRI is needed.

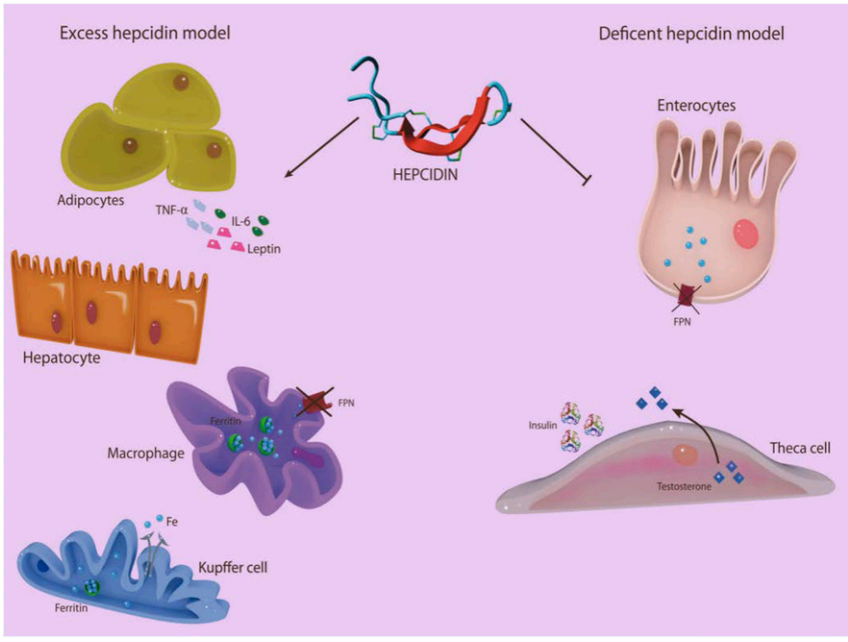

Figure 2—Iron (Fe) overload in hepcidin-excess vs. hepcidin-deficient disease models. Increased hepcidin downregulates cellular FPN expression and promotes macrophage retention of excess iron, resulting in iron redistribution toward Kupffer cells, with prevalent sinusoidal distribution of iron. Conversely, insulin downregulates hepcidin expression in hepatocytes and adipocytes. IL-6, interleukin-6; TNF-α, tumor necrosis factor-α.

Iron and Muscle Relationships With Glucose Homeostasis

There is some evidence that iron overload also affects skeletal muscle (36), the main effector of insulin action. Skeletal muscle represents about 40% of body mass and contains 10–15% of body iron, which is mainly located in myoglobin. Muscular contraction, but not insulin, is known to stimulate TfR recruitment from a GLUT4-containing intracellular fraction to the plasma membrane (Fig. 3). Exercise affects iron status, but this is usually underrecognized. When obese subjects were submitted to a diet and exercise program resulting in weight loss, circulating sTfR significantly decreased, and this decrease was proportional to changes in muscle volume and leg and arm force. Weight loss induced by diet alone did not affect circulating sTfR (37).

The iron status of skeletal muscle also changes dramatically with aging. Iron-induced free radical production seems to be a pivotal factor in the progression

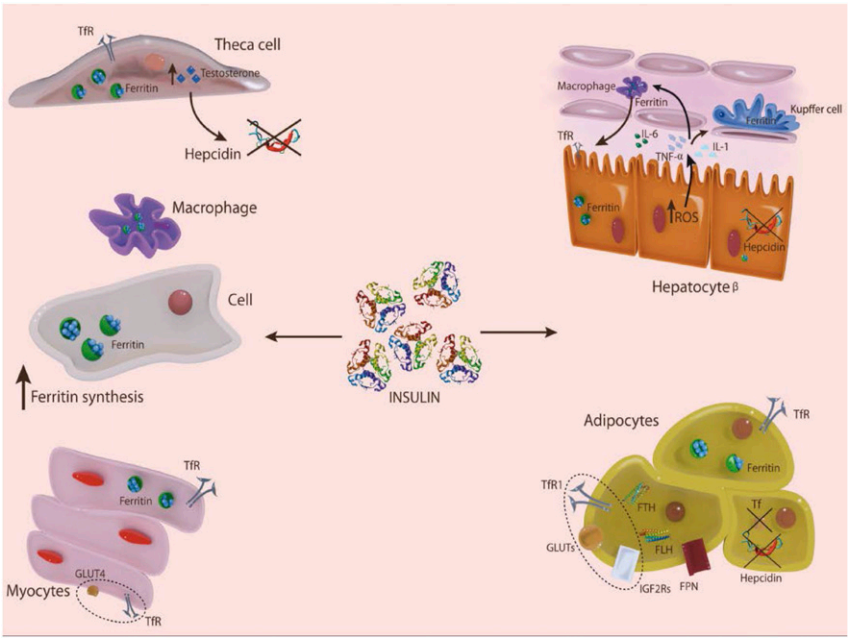

Figure 3—Effects of insulin on body iron trafficking. Insulin causes increased ferritin synthesis and redistribution of TfRs to the cell surface, thereby facilitating iron uptake by different tissues and cells. Insulin downregulates hepcidin expression in adipocytes and hepatocytes; stimulates expression of FPN, ferritin heavy chains (FTH), and ferritin light chains (FTL); and reduces expression of transferrin (Tf) in adipocytes. It promotes the release of ROS in hepatocytes. In myocytes, the muscular contraction stimulates TfR recruitment from a GLUT4-containing intracellular fraction to the plasma membrane. IGF2R, insulin-like growth factor-2 receptor; IL, interleukin; TNF-α, tumor necrosis factor-α.

of oxidative injury and dysfunction observed in senescent skeletal muscle (38). Declines in heme synthesis and dysregulation of iron uptake or export pathways have been suggested to constitute contributing factors (39). Increased iron uptake through the iron transporter DMT1 and intracellular iron retention as a result of decreased FPN both contribute to iron status elevation in senescent muscle (38,40). The increase of muscle iron content is not paralleled by increased ferritin expression, suggesting an expansion of iron in the nonferritin compartment (40). Whether these alterations in aging muscle result in impaired glucose metabolism should be studied in more depth.

In vitro studies have shown that reductions in iron availability induced by iron chelators resulted in increased glucose utilization owing to the enhanced expression of GLUT-1 in the muscle cell line L6 (41). Paradoxical effects have been observed in animal models. Iron-rich diets led to elevated AMP-activated protein kinase activity and impaired insulin signaling in skeletal muscle and liver of C57BL/6J male mice. Consistent with the increased AMP-activated protein kinase activity, glucose uptake was enhanced (42).

Iron and Adipose Tissue

Obesity is a crucial component of peripheral insulin resistance. A recent study revealed that ferritin light chain (*FTL*) mRNA and protein levels, and FPN transcripts, were significantly increased, whereas transferrin mRNA decreased in adipose tissue from obese subjects in association with insulin action (43). Bariatric surgery–induced weight loss resulted in increased transferrin mRNA and decreased *FTL* and FPN in subcutaneous adipose tissue in association with improved insulin action (43). Why were these iron-related genes altered in adipose tissue from obese subjects? Iron may affect insulin action by modulating the degree of adiposity with different mechanisms.

Iron Affects Adipocyte Differentiation and Adipose Tissue Hyperplasia and Hypertrophy

Disruption of iron homeostasis, either in excess or in defect, results in impaired adipocyte differentiation and decreased adipogenic capacity. Adipocytes accumulate fat during differentiation, and stored iron and the expression of several iron-related genes change at the same time (44).

Iron-enriched diets affect adipocyte size, which is significantly reduced, along with decreased adipocyte insulin sensitivity, in murine models. This iron-enriched diet was associated at the same time with visceral adipose tissue hyperplasia and hypertrophy (45). An iron-restricted diet led to the opposite results, with low amounts of circulating free fatty acids and triglycerides (46). The reduction of iron levels by deferoxamine, an iron chelator, inhibited the development of adipocyte hypertrophy in mice and decreased macrophage infiltration (47). A parallel reduction in oxidative stress and inflammatory cytokine production, and improved glucose metabolism and insulin signaling, were observed in adipose tissue and skeletal muscle (47). The importance of iron in adipocyte differentiation and insulin action was confirmed by in vitro models: Incubation of rat adipocytes with excess iron resulted in decreased insulin-stimulated glucose transport and increased lipolysis (48), whereas silencing of the iron-related genes transferrin and lactoferrin in murine cell lines resulted in impaired adipocyte differentiation and reduced insulin signaling (49). Immune cells that are resident in adipose tissue may have a pivotal role since polarized macrophages have increased iron-handling capabilities, promoting local and systemic insulin resistance, and contributing significantly to the overall metabolic derangement and progression toward T2D (50).

The Paradox of Iron Deficiency

A paradox exists about the relationship of iron status with glucose metabolism in obese patients and/or patients with T2D, which is important to keep in mind since ferropenic anemia is prevalent among these patients.

Old studies found out that iron deficiency induced increased lipid synthesis in white adipose tissue from rats, as well as hyperglycemia despite enhanced insulin sensitivity (51). An independent study recently confirmed these findings, showing enhanced expression of lipogenic genes and alterations in levels of plasma lipids in response to dietary iron

deficiency (52). The precise mechanisms responsible for the relative hyperglycemia associated with ferropenic anemia remain unclear (53,54). A more pronounced increase in fasting blood glucose was associated with more severe anemia (53,54).

Iron Status May Influence the Release of Adipokines From Adipose Tissue

Adipose tissue releases a number of proinflammatory adipokines that might interfere with iron homeostasis. Secretion of several adipokines may be influenced by iron levels. Research shows that leptin and adiponectin are actively involved in iron homeostasis (55). Bloodletting of patients with impaired glucose tolerance and increased ferritin values led to increased adiponectin and improved glucose tolerance, showing an interplay between iron status and adiponectin secretion (55). Serum ferritin has also been linked to adipocyte insulin resistance (defined by the product of fasting insulin and nonesterified fatty acids) and negatively correlated with circulating adiponectin. Mice fed a high-iron diet, and cultured adipocytes treated with iron, exhibited decreased adiponectin mRNA and protein (55). Iron seems to negatively regulate adiponectin transcription via FOXO1-mediated repression. Loss of the adipocyte iron export channel, FPN, in mice resulted in adipocyte iron loading, decreased adiponectin, and insulin resistance. Body iron overload and increased adipocyte FPN expression in the context of hemochromatosis were associated with decreased adipocyte iron, increased adiponectin, and improved glucose tolerance and insulin sensitivity (55).

We speculated that the sexually dimorphic behavior of some adipokines, not completely explained on the basis of different fat amounts and the influences of sex hormones (56), might relate to iron metabolism as well (56–58). For instance, leptin (57) has, remarkably, been shown to stimulate hepcidin mRNA production in a similar manner as interleukin-6 (59). In obese children following a 6-month weight loss program, weight loss was associated with lower hepcidin concentrations. The extent of leptin reduction paralleled hepcidin reduction, and this association was independent of BMI (60).

Retinol binding protein-4 (RBP4) is a fat-derived lipocalin belonging to a family of proteins that bind small hydrophobic molecules, such as retinol (RBP4) and iron (lipocalin-2, another adipokine linked to iron and insulin resistance [56]), that constitute appropriate transporters for transferring biologically hazardous molecules between cells in a safe and controlled manner. RBP4 expression in adipose tissue was increased in obesity and insulin resistance in association with iron stores, being higher in men than women, in parallel to increased serum ferritin in men (58). Excess iron led to increased plasma retinol and RBP4, whereas iron depletion resulted in decreased serum RBP4 concentration (58).

Associations between levels of serum visfatin, an adipokine secreted prevalently by the visceral adipose tissue, and different parameters of iron metabolism (serum prohepcidin and sTfR) were observed in obese patients and patients with T2D; these associations differed according to obesity and glucose tolerance status (61). The meaning of such associations remains unclear, even though visfatin mRNA is enriched in iron-rich tissues (liver, muscle, bone marrow) (61).

Iron and β-Cell Relationships

An increase in β-cell mass, with increased basal and stimulated C-peptide secretion, was suggested in a small number of patients with T2D with increased serum ferritin levels (62). C-peptide secretion decreased after phlebotomy-induced iron depletion, suggesting increased β-cell insulin sensitivity (62).

HH is, conversely, diabetogenic mainly because of decreased insulin secretion, and diabetes usually results when insulin resistance develops (such as with increasing body weight). Patients with HH cannot respond with increased insulin secretion because of the primary impairment of β-cells. Insulin-secretory abnormalities improve with phlebotomy in this context (63).

Experimental studies have also shown the importance of iron in β-cell physiology. *Ob/ob* mice administered low-iron diets exhibited significant increases in insulin sensitivity and β-cell function, consistent with the phenotype in mouse

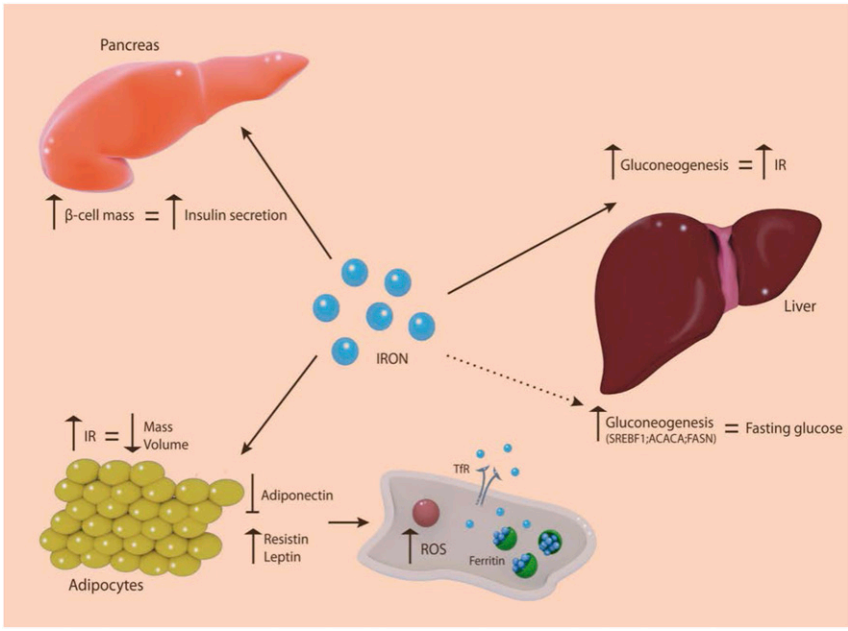

Figure 4—Effects of iron deprivation vs. acquired iron overload on glucose metabolism. Excess iron (solid lines) causes insulin resistance (IR) in hepatic (reduced insulin extraction and inappropriate gluconeogenesis) and adipose tissue (reduced adipose tissue mass and cell volume). It affects expression of adiponectin, resistin, and leptin, which enhances oxidative stress and causes the redistribution of TfRs on the cell surface. In the pancreas, it causes increased β-cell mass. Iron deficiency (dashed lines) is associated with enhanced hepatic glucose production as a result of the increased expression of sterol regulatory element binding factor (SREBF1), acetyl-CoA carboxylase α (ACACA), and fatty acid synthase (FASN), as well as higher glucose disappearance.

models of hereditary iron overload. The effects were not accounted for by changes in weight or feeding behavior. Treatment with iron chelation had a dramatic effect, allowing the *ob/ob* mice to maintain normal glucose tolerance for at least 10.5 weeks (46). The effects on overall glucose levels were less apparent because of a loss of the beneficial effects of iron on insulin sensitivity, although dietary iron restriction preserved β-cell function in *ob/ob* mice fed a high-fat diet. Beneficial effects of iron restriction were minimal in wild-type mice on a control diet but were apparent in mice on a high-fat diet (63).

In vitro studies have shown that H-ferritin mRNA is four- to eightfold higher in rat islets treated with 20 mmol/L glucose than in islets treated with 1 mmol/L glucose. The potential reason for the increased ferritin in the β-cells is that ferritin exhibits antioxidant properties, and β-cells are particularly sensitive to oxygen radicals. The large amount of ferritin can explain why iron is preferentially retained in β-cells. In fact, iron deposition in islets, although variable, is restricted to β-cells. Moreover, β-cells may be especially sensitive to iron because of the high expression of the iron importer DMT1 (needed to import zinc for secretory packaging, but can also transport free serum iron) and low or absent expression of the iron exporter FPN (64). An integrative vision of iron effects in different tissues is proposed in Fig. 4.

FUTURE DIRECTIONS AND CONCLUSIONS

Iron status at both extremes of the spectrum is associated with premature death. Increased transferrin saturation showed a dose-dependent association with an increased total mortality (65). A moderate to marked increase of ferritin concentrations also predicted early death in a dose-dependent linear manner among the general population (65) and among patients with T2D (66). Clinicians must be aware of the importance of preventing, diagnosing in a timely manner, and treating disturbances of iron metabolism in patients with MetS and T2D.

The possibility that excess iron stores contribute to the pathogenesis of MetS and T2D deserves further investigation given the association between elevated iron stores and MetS in people with mild hyperferritinemia (ferritin between 100 and 300 mg/dL).

Further research is needed regarding the target serum ferritin concentration in patients with T2D. The focus of the research should move toward investigation of body iron stores affecting solid measures such as insulin sensitivity, vascular resistance, viscosity, and oxidative damage (11). An in-depth study of iron metabolism in T2D may uncover unsuspected relationships. The search for an ideal iron status in T2D may result in unexpected benefits.

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