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Review Article

Iron Overload Impacts on Glucose and Lipid Metabolism

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Abstract

Iron is essential for proper cell function, but iron in excess can exert deleterious effects on cellular homeostasis. Systemic iron overload can result from genetic mutations in Hfe gene in hereditary hemochromatosis patients, blood transfusions in β-thalassemia patients, and hyperabsorption in the gut under pathological states. Excessive iron mediates increased production of reactive oxygen species through Fenton reaction and lipid peroxidation. The resulted oxidative stress damages organelles and the expression or activity of key factors that are required for normal glucose and lipid metabolism. A line of evidence demonstrates that iron overload modulates glucose metabolism by decreasing both insulin availability and insulin receptor sensitivity. However, the underlying molecular mechanisms remain unclear. Our knowledge of the effects of iron overload on lipid metabolism is also limited. Available reports from different groups by using differential animal models and iron-feeding strategies have shown conflicting results. The potential causes of the distinct findings were here discussed. This review also summarized commonly used strategies that can combat iron overload.

Keywords: Glucose homeostasis; Iron overload; Insulin; Lipid metabolism

Introduction

Iron is an essential micronutrient for proper cell function from microbes, plants to animals [1]. In mammals, systemic iron homeostasis is mainly coordinated by four cell types: enterocytes, erythrocyte precursors, macrophages and hepatocytes, which handle intestinal absorption, utilization, recycling and storage of the iron, respectively [2,3]. In the intestine, non-heme iron absorption occurs in the duodenum that requires Divalent Metal Transporter 1 (DMT1) at the luminal membrane and ferroportin at the basolateral side of the enterocytes [4-7]. The transporter that absorbs dietary heme iron is not well defined yet. A vast majority of the absorbed iron (> 95%) is bound by transferrin [8], which delivers iron for hemoglobin synthesis in red blood cell precursors. Damaged and senescent red blood cells are then cleared by macrophages [9], and heme iron is recycled from hemoglobin via Heme-Responsive Gene 1 (HRG1) [10]. A significant fraction of plasma iron is taken up and stored in the hepatocytes through both transferrin- and ZIP14 (ZRT/IRT-like protein 14)-dependent pathways [11-13]. Ferroportin is not only crucial for dietary iron absorption but also ubiquitously expressed in many cell species responsible for iron export into circulation. The function of ferroportin is tightly controlled by hepcidin that is primarily derived from hepatocytes [14,15]. The abundance of hepcidin is usually inversely correlated with iron level in the hepatocytes [16], and hepcidin plays an essential role in systemic iron homeostasis [17]. Disruption of iron homeostasis leads to iron deficiency or overload that underlies the pathogenesis of many diseases [2]. In this review, we will focus discussing causes of iron overload, and how iron overload impairs glucose and lipid metabolism that leads to metabolic disorders.

Causes of Iron Overload

Iron overload is indicated by the presence of excess iron in the body. Iron overload is manifested as a gross elevation in serum iron and liver iron storage. A common form of inherited iron overload is found in Hereditary Hemochromatosis (HH) patients due to homozygous C282Y mutation in Hfe gene [18]. This mutation causes defective post-translational processing, accelerated degradation and failure of cell surface expression of the HFE protein. As a consequence, hepcidin production is low leading to constantly active ferroportin and uncontrolled iron absorption by the enterocytes despite of systemic iron overload. In addition, H63D mutation in Hfe gene also increases the risk of developing iron overload in human patients [19]. Non-HFE form HH has also been reported. Camaschella et al. first identified that Y250X mutation in Transferrin Receptor 2 (TFR2) gene causes progressive iron overload in humans [20]. Several other forms of mutation in TFR2 gene that causes hemochromatosis include E60X, M172K, AVAQ594-597del, and Q690P [21]. TFR2 is highly expressed in the liver and is required for hepcidin expression. Thus, the loss-of-function mutations of TFR2 results in low hepcidin [22]. It has also been reported that Q248H mutation in ferroportin gene causes genetic iron overload in native Africans [23]. Patients with β-thalassaemia develop iron overload from frequent red cell transfusions [24]. Apart from the inherited form of iron overload, excessive body iron can result from increased iron absorption in the gut [25]. It is evident that long-term intake of iron-rich diet or supplement is a potential cause. Acquired form of iron loading also occurs in pathological or disease states in general human populations who do not carry mutations in genes associated with iron absorption or metabolism [1]. A notable condition called Dysmetabolic Iron Overload Syndrome (DIOS) has recently been described [26]. DIOS is frequently associated with metabolic syndrome or Nonalcoholic Fatty Liver Diseases (NAFLD). Patients with DIOS show mild to moderate iron deposition in liver due to increased production of hepcidin [27]. A recent study further demonstrated that hepcidin resistance develops in DIOS patients [28]. Hyperglycemia is another factor that increases systemic iron loading as suggested by elevated serum iron content and iron

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deposition in the liver in both human patients and experimental murine models [29-31]. Moreover, patients with alcoholic liver disease frequently exhibit iron overload, which is likely a consequence of decreased production of hepcidin in the liver that facilitates intestinal iron absorption [32,33]. Because excessive iron further promotes the pathogenesis of diseases, it becomes important to understand the mutual regulation between pathological changes and iron metabolism in order to better control disease progression.

In clinics, the commonly used measurements that determine body iron storage include the analysis of ferritin level in serum and Magnetic Resonance Imaging (MRI)-based analysis of tissue iron level. Serum ferritin is a commonly checked parameter to indicate systemic iron storage [34], but this test has a low sensitivity and specificity because the expression of ferritin is also affected by many other factors, such as inflammation and alcohol abuse [35,36]. It is therefore more important to monitor the trend of changes over time than individual measurements. However, ferritin trends are not recommended to reflect total body iron in patients with transfusional iron overload [37]. MRI is by far the best noninvasive method that can reflect total body iron content by measuring the level of iron in the liver [38,39], despite that certain conditions like hepatic steatosis can reduce the sensitivity. Besides, hepatic biopsy is sometimes taken to quantify iron overload, but biopsy is an invasive procedure and is susceptible to sampling error because of the tiny size of tissue [39,40].

Effects of Iron Overload on Glucose Homeostasis

The first evidence linking iron overload to the regulation of glucose homeostasis was initially observed in HH patients. Iron overload impacts glucose metabolism through two mechanisms by modulating insulin availability and insulin receptor sensitivity. It has been shown that excessive iron deposition causes apoptosis of insulin-secreting β cells in the pancreas [41,42]. The first study on the effects of iron on insulin generation was performed in $Hfe^{-/-}$ mice. It was found that insulin secretory capacity is decreased because of reduced number of β-cells in the islet due to oxidative stress-induced apoptosis [43]. Increase in the production of Reactive Oxidative Species (ROS) is partially resulted from iron-mediated Fenton reaction with hydrogen peroxide [44]. The study also showed that increased intracellular iron interferes with the trafficking of other metals causing decreased mitochondrial uptake of manganese, an important metal required for the activity of antioxidant enzyme Superoxide Dismutase (SOD) [45]. Although oxidative stress is considered as the pivotal factor that attenuates β-cell viability, strategies combating iron-induced ROS generation are not available.

Increased iron deposition also impairs insulin action in many tissues, including the liver, adipose tissue and skeletal muscle, which are the major tissues that dispose glucose. Therefore, iron overload causes both insulin-dependent (type 1) and-independent (type 2) diabetes mellitus [46]. Increased incidence of diabetes is found in patients with inherited iron overload, such as in HH patients, as well as in patients with acquired form [47]. Accumulating evidence shows positive correlation between serum iron content and the prevalence of diabetes in general human populations [48-52]. It was initially thought that excess iron impairs insulin sensitivity delaying glucose disposal based on clinical observation. However, early studies by the McClain group demonstrates $Hfe^{-/-}$ mice show a better tolerance to glucose challenge suggesting improved insulin sensitivity [43]. They found that the expression of adiponectin, an adipose-derived insulin sensitizer, is increased in in $Hfe^{-/-}$ mice [43]. In contrast, the same group observed that mice fed a high-iron diet, which represent dietary iron overload, elicit less adiponectin expression than chow-fed control mice [53]. The differential response of adiponectin expression in $Hfe^{-/-}$ vs nongenetic iron loaded mice was suspected owing to distinct expression of hepcidin (low in $Hfe^{-/-}$ mice, high in iron-fed mice). However, it remains controversial about the regulation of adiponectin by iron as another study reported that the expression of adiponectin is not altered in mice fed with iron-rich diet [54]. Moreover, this study showed that mice develop insulin resistance after 16-week feeding with a diet containing 3% carbonyl-iron [54]. AMP-Activated Protein Kinase (AMPK) is another important protein that regulates glucose metabolism in many tissues [55]. A well- known AMPK agonist, metformin, is currently widely used for glycemic control especially in type 2 diabetic patients [56]. Surprisingly, it was shown that high-iron diet-fed mice elicit enhanced AMPK activity and, as a consequence, glucose tolerance is improved [43]. The above findings from experimental models are contradictory to the clinical observation of increased prevalence of diabetes in iron-loaded patients. Thus, our understanding of iron loading-mediated effects on insulin sensitivity and glucose homeostasis remains very preliminary. Evidence supports that the prevalence of diabetes in iron-loaded patients is often observed in aged and obese human patients [57]; however, many of the animal experiments used young mice (3-6 months old) that were given iron-rich diet only for 4-8 weeks. It is tempting to propose that, at early stage of iron loading in young mice, glucose metabolism or insulin sensitivity is promoted through compensatory mechanisms, such as increased expression of adiponectin or AMPK activity. In contrast, a long-term exposure to excessive iron damages the cellular homeostasis system that eventually leads to insulin resistance state. It would be interesting to examine how adiponectin expression and AMPK activity are altered in aged mice with a prolonged duration of iron loading. It is high likely that iron alone is not sufficient to impair insulin sensitivity, whereas iron combining high fat intake causes the problem. Future research using experimental models should be designed to better mimic the conditions in human patients.

Effects of Iron Overload on Lipid Metabolism

Iron in excess increases lipid peroxidation that modifies fatty acid profile of the cellular membranes leading to damages of organelles and mitochondrial dysfunction [58,59]. It is thus conceivable that lipid metabolism is impaired with dysfunctional mitochondria. Iron overload can also exert direct effects on lipid metabolism, but conflicting data have been reported. It was shown that carbonyl-iron and iron dextran feeding for 8 months causes elevated enzymatic activity of Stearoyl-Coa Desaturase (SCD) [60], an endoplasmic reticulum enzyme that catalyzes the formation of monounsaturated fatty acids [61]. In contrast, mice fed with ferric citrate for 3 months showed no changes in hepatic fatty acid composition [62]. A recent study showed that $Hfe^{-/-}$ mice show up-regulated expression of Carnitine palmitoyl transferase b (Cpt1b) in skeletal muscles and increased fatty acid oxidation [63]. Silva et al., reported that rats received intraperitoneal injection of iron dextran (4 weeks) increases cholesterol and Triacylglycerol (TAG) content in the serum [64], which is likely due to decreased expression of Sterol Regulatory Element-Binding Protein 2 (SREBP2), a transcription factor that controls the expression of enzymes involved in endogenous cholesterol, fatty acid and TAG synthesis. Moreover, the same group observed that iron overload attenuates PPARα expression in the liver. PPARα is an important

transcription factor that promotes lipid and lipoprotein metabolism [65], and therefore decrease in PPARα expression might be an important mechanism underlying iron overload-mediated disruption of lipid metabolism. It remains to be defined what signaling cascade (s) triggered by iron regulates the expression of PPARα and possibly other members of the PPAR family. Moreover, it was shown that dietary iron overload causes decreased expression of leptin [66], a hormone that is primarily synthesized in adipocytes and decreases appetite. Leptin is also known to promote lipolysis and fatty acid oxidation [67]. Therefore, iron overload can inhibit lipid metabolism by attenuating leptin expression. Decreases in the expression of PPARα and leptin potentially promotes weight gain, while it was shown that mice fed with iron-rich diet gain less weight than standard chow-fed controls [54]. We have also found that weigh gain is slower in a novel mouse stain which shows moderate iron overload because of transgenic expression of DMT1 in intestinal epithelial cells (Peijian He, unpublished data). The above distinct findings might result from using animals of different ages or from the exposure of animals to iron overload for different lengths. A majority of the absorbed iron enters the mitochondria facilitating the synthesis of heme and iron sulfur cluster and acting as an essential component for enzymes that participate in metabolism. DMT1 was reported to localize in mitochondria [68], but its function in mitochondria is unknown. It is possible that DMT1, as a mitochondrial structural protein, interacts with and regulates the activity of certain catalyzing enzymes that are required for fatty acid β-oxidation.

Management of Iron Overload

It is undoubtable that iron loading alters glucose and lipid metabolism despite of the conflicting results. Further research is needed to demonstrate whether and how the magnitude and duration of iron overload as well as other factors like aging and high fat diet intake differentially regulate nutrient metabolism and the pathogenesis of metabolic diseases. Regardless, a large body of clinical evidence has clearly shown a close relationship between body iron content and the prevalence of diabetes. It is therefore important to tightly monitor the iron level especially for populations at high risk, e.g., hereditary hemochromatosis patients and persons with metabolic disorders. Phlebotomy that reduces free iron store through an increase in erythropoiesis is a frequently used strategy in relieving high blood sugar level in diabetic patients. However, phlebotomy potentially triggers the system to absorb more iron in the gut. Iron chelation by using agents like desferoxamine can efficiently reduce iron storage, but it causes severe side effects. In the circumstance of dietary iron overload, dietary iron restriction or suppression of intestinal iron absorption may be considered. Scientists are trying to develop strategies that can specifically inhibit intestinal DMT1 to limit iron acquirement, yet no drug is currently available. Moreover, treatment with hepcidin blocks dietary iron absorption, whereas intracellular iron retention as a consequence of the inhibition of ferroportin exerts deleterious effects in many cell species. Above all, the degree of iron loading and progression of metabolic diseases should be precisely assessed before measures are taken to manage iron storage. It is also very important to define the beneficial zone of iron content, which may vary in individuals with different genetic background, in order to better control iron overload and its detrimental effects on glucose and lipid metabolism.

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