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Does Obesity Increase Risk for Iron Deficiency? A Review of the Literature and the Potential Mechanisms

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Abstract: Increasing obesity is a major global health concern while at the same time iron-deficiency anemia remains common worldwide. Although these two conditions represent opposite ends of the spectrum of over- and under-nutrition, they appear to be linked: overweight individuals are at higher risk of iron deficiency than normal-weight individuals. Potential explanations for this association include dilutional hypoferremia, poor dietary iron intake, increased iron requirements, and/or impaired iron absorption in obese individuals. Recent evidence suggests obesity-related inflammation may play a central role through its regulation of hepcidin. Hepcidin levels are higher in obese individuals and are linked to subclinical inflammation; this may reduce iron absorption and blunt the effects of iron fortification. Thus, low iron status in overweight individuals may result from a combination of nutritional (reduced absorption) and functional (increased sequestration) iron deficiency. In this review, we focus on subclinical inflammation in obesity, and its effect on hepcidin levels, as the most plausible explanation for the link between iron deficiency and obesity.

Key words: iron, iron deficiency, obesity, inflammation, hepcidin, transition countries

Introduction

Increasing obesity is currently a major health concern in both developed and developing countries. The World Health Organization's (WHO) latest global projections indicate that in 2005 approximately 1.6 billion adults (age 15+) were overweight and at least 400 million adults were obese [1]. At the same time, iron-deficiency anemia remains common worldwide [2]. Although these two conditions represent opposite ends of the spectrum of over- and under-nutrition, they appear to be linked: overweight individuals are at higher risk of iron deficiency than normal-weight individuals. Potential explanations for this association include dilutional hypoferremia, poor dietary iron intake, increased iron requirements, and/or impaired iron absorption in obese individuals. Recent evidence suggests obesity-related inflammation may play a central role through its regulation of hepcidin, and thereby, iron metabolism. In this review, we focus on

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subclinical inflammation in obesity, and its effect on hepcidin levels, as the most plausible explanation for the link between iron deficiency and obesity.

Epidemiological studies

Cross-sectional studies have consistently shown an association between adiposity and poor iron status, defined in most studies as hypoferremia (a low serum iron concentration). The inverse relationship between iron status and adiposity was first published in 1962, when Wenzel and colleagues [3] unexpectedly found a significantly lower serum iron concentration in obese adolescents compared with controls. One year later, Seltzer and colleagues [4] reported that serum iron levels and transferrin saturation index were significantly lower in obese male and female adolescents than in lean individuals, without differences in hemoglobin and hematocrit concentrations. Studies performed since then in children [5–10] and adults [11–18] have shown similar results. For example, in the U.S. National Health and Nutrition Examination Surveys ((NHANES) I, III, IV and 2003–2004), overweight toddlers, children, adolescents, and adults were more likely to be iron deficient than those who were not overweight in these age groups [7, 8, 10, 12, 19]. In a cross-sectional study, overweight Israeli children and adolescents had lower iron status compared with normal-weight individuals [6]. However, a study by Ozata and colleagues reported no difference in iron status between obese and normal-weight individuals [20].

All of these studies were done in industrialized countries. A recent analysis of data from the 1999 Mexican Nutrition Survey, including 1,174 children aged 5–12 years and 621 non-pregnant women aged 18–50 years, has found a similar relationship between adiposity and iron status [21]. In this study, body mass index (BMI) and BMI Z-scores were calculated, intakes of dietary iron, ascorbic acid (an enhancer of iron absorption), and calcium and fiber (inhibitors of iron absorption) were estimated, and iron deficiency (ID) was defined as either a low serum iron, or an elevated total iron-binding capacity (TIBC) and low transferrin saturation (TS). Regression analyses were done to determine relationships between hemoglobin, iron status, dietary nutrient intakes, inflammation (assessed by C-reactive protein, CRP), and BMI. The results showed that the prevalence of obesity was 3.5 % and 25.3 % in children and women, respectively. The prevalence of ID in obese women and children was significantly higher than in normal-weight subjects, (OR = 1.92 and 3.96, respectively, $p < 0.05$). Serum iron levels were lower in obese than in normal-weight women (62.57 μg/dL vs. 72.35 μg/dL, $p = 0.014$) and TIBC was higher in obese than in normal-weight children (399.76 μ/dL vs. 360.55 μ/dL, $p < 0.0001$). There were no significant associations between dietary intakes of iron or ascorbic acid and BMI. CRP concentrations were four times higher in obese women and children than in normal-weight counterparts ($p < 0.05$). Subclinical inflammation (elevated CRP), but not iron intake, was a strong negative predictor of iron status independent of BMI ($p < 0.05$). Thus, compared to normal-weight subjects, obese Mexican women and children have a two- to four-fold increased risk for ID despite comparable dietary iron intakes. Impaired iron metabolism due to obesity-related inflammation may play a role (further discussed below under 'Mechanisms').

Transition countries like Mexico are undergoing rapid dietary and lifestyle changes that produce a "double burden" of undernutrition and overweight [22, 23]. Three transition countries in which this is occurring are Thailand, Morocco, and India [24–26]. In Bangkok, Thailand, it is estimated nearly one-third of women are overweight and 24 % are anemic [27, 28]. In Morocco, 24 % of children less than 5 years are stunted in growth and 30 % of school-age children are anemic [29]; at the same time, 9 % of school-age children are overweight [30, 31]. Similarly, in middle-class Indian school children, anemia is present in 19–88 %, while overweight affects 9–29 % [32]. In many lower income countries, the prevalence of overweight is increasing at two to four times the rate of the industrialized world [33]. The major adverse effects of iron deficiency are impaired physical and cognitive development in children [34] and poorer pregnancy outcome in women [2]. A potential interaction between the "double burden" of adiposity and iron deficiency has not been examined in transition countries.

Thus, we decided to study the association between weight status, iron deficiency, and the response to iron fortification in children from transition countries. We analyzed data from baseline (n = 1688) and intervention (n = 727) studies in children in Morocco and India to look for associations between BMI Z-scores and baseline hemoglobin, serum ferritin and transferrin receptor (TfR), whole blood zinc protoporphyrin (ZPP) and body iron stores, and changes in these measures after provision of iron. In this sample of children, 42 % were iron-deficient and 6.3 % were overweight. A higher BMI Z-score predicted poorer iron status

(as judged by body iron calculated from the serum ferritin-to-transferrin receptor ratio) [35] at baseline ($p < 0.001$) and less improvement in body iron during the interventions ($p < 0.001$) [14]. The baseline data of this study are consistent with data on iron status and adiposity in studies discussed above from industrialized countries, for example in the U.S. from NHANES III (where 14 % were at risk for overweight, 10 % were overweight, and 3 % were iron-deficient) [8], but demonstrate this same relationship exists in children in transition countries with higher rates of iron deficiency and lower rates of adiposity. In the previous studies from industrialized countries, a limitation was the use of iron status indicators, such as serum ferritin (SF) and serum transferrin, that are acute-phase proteins [2] and may be confounded by the adipose-related inflammation. In the Moroccan and Indian children, we used multiple indicators of iron status, including TfR and ZPP, two measures less likely to be confounded by inflammation [36, 37]. This study clearly demonstrates the negative impact of adiposity on response to iron fortification. It suggests the rapid increase in overweight in transition countries could impair their efforts to control iron deficiency in children. These findings need to be confirmed in other populations and settings, but imply that interactions of the "double burden" of malnutrition during the nutrition transition may have adverse consequences.

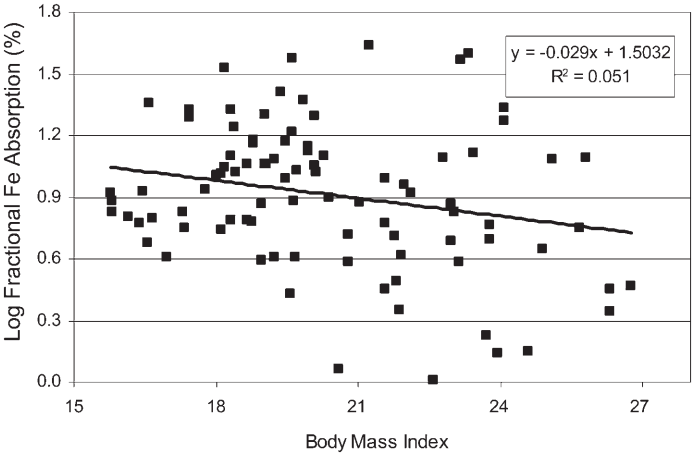

Figure 1: The relationship between log fractional iron absorption (%) and body mass index in healthy premenopausal Thai women (n = 92) who consumed meals of rice and vegetables labeled with ≈4 mg of [^{57}Fe/^{58}Fe]-ferrous sulfate. To account for differences in iron status and their effect on dietary iron absorption, iron absorption in each subject was corrected to a value corresponding to a serum ferritin of 40 μg/L [39].

Absorption studies with stable iron isotopes

To investigate if adiposity was associated with dietary iron absorption, we studied (n = 92) premenopausal Thai women (18–50 years of age) with a maximum body weight of 70 kg who were recruited in metropolitan Bangkok [14]. About 20 % were iron-deficient and 22 % were overweight. They all received the same iron isotope-labeled reference meal of steamed white rice and vegetable soup. Each meal contained 4 mg of isotopically labeled fortification iron, as [^{57}Fe/^{58}Fe]-ferrous sulfate. A second blood sample was drawn 14 days later and analyzed for isotopic composition by multicollector negative thermal ionization mass spectrometry to calculate fractional iron absorption [38].

We found that, independent of iron status, a higher BMI was associated with decreased iron absorption ($p < 0.030$). After correcting for differences in iron status among subjects using SF [39], in a multivariate regression including age, hemoglobin (Hb), CRP, and BMI, fractional iron absorption was negatively correlated with CRP (standardized $\beta = 0.422$; $p < 0.001$) and BMI (standardized $\beta = 0.106$; $P < 0.05$). The relationship between BMI and fractional iron absorption is shown in Figure 1.

Mechanisms

Several factors may explain why greater adiposity increases risk for iron deficiency. Overweight may be associated with poor quality or restricted diets low in iron, but when dietary iron intakes in overweight adults [13] and children [40] are estimated, they are not lower than in normal weight individuals. However, even if diets of overweight individuals are not lower in iron, the absorption of the iron may be reduced because increased circulating hepcidin in obesity may reduce iron absorption (see below). Iron requirements in overweight individuals may be increased due to larger blood volume and higher basal iron losses with higher body weight [41], but this has not been directly measured. In addition, overweight girls tend to mature and begin their menses at an earlier age, increasing their iron requirements [42].

The above findings in the Thai women suggest greater adiposity is associated with lower fractional

iron absorption in humans, independent of iron status. Iron absorption occurs primarily in the proximal small intestine. Transport of non-heme iron from the intestinal lumen into the enterocytes is mediated by the divalent metal transporter (DMT) 1. Efflux of iron across the basolateral membrane of the duodenal enterocytes into plasma is mainly mediated by the transport protein ferroportin [2]. Ferroportin is an iron exporter on the surface of absorptive intestinal enterocytes, hepatocytes, macrophages, and placental cells, all of which release iron into plasma [43]. Therefore, the degree of the flux is proportional to ferroportin concentration, which is determined in large part by the circulating levels of hepcidin [44]. Hepcidin, a 25-amino-acid peptide hormone with a key role in body iron regulation, is produced mainly by the liver but also, possibly, by adipose tissue [45, 46]. Circulating hepcidin acts as a negative regulator of both intestinal iron absorption and macrophage iron release. When hepcidin binds to ferroportin on the target cell membrane, this induces ferroportin internalization and degradation, thus inhibiting both gastrointestinal iron absorption and iron release from the reticuloendothelial system [47, 48].

Hepatic hepcidin expression is modulated in response to body iron stores, hypoxia, and inflammation, and low-grade inflammation is a characteristic of obesity. Proinflammatory cytokines, such as interleukin-6 (IL-6), affect hepcidin gene transcription through JAK (Janus kinase)–STAT (signal transducer and activator of transcription)-3 interactions [49, 50]. In addition, the adipokine leptin upregulates hepatic hepcidin expression through the JAK2–STAT3 signaling pathway [51]. Thus, increased inflammation and/or leptin levels in obese individuals could reduce iron availability. Moreover, adipose tissue itself may also produce hepcidin [45]. In severe obesity, while liver hepcidin expression is positively associated with increased body iron stores, adipose tissue hepcidin expression is positively correlated with BMI and may be negatively associated with transferrin saturation [45]. Finally, lipocalin-2 is an iron-binding protein that is upregulated by inflammation and may help sequester iron during infections [52]. It is produced by adipose tissue and its expression is increased in db/db (leptin receptor-deficient) obese mice [53]. The link between adiposity-associated inflammation and iron deficiency has been suggested in cross-sectional studies, including the large Mexican study described above. Also, in a comparison of normal-weight to overweight and obese adults in the U.S. NHANES III study, serum ferritin and CRP were progressively higher with increasing BMI category, whereas serum iron and transferrin saturation were progressively lower [16].

Thus, low iron status in overweight individuals could result from a combination of nutritional (reduced absorption) and functional (increased sequestration) iron deficiency. In normal-weight individuals, SF concentrations are decreased and directly related to transferrin saturation if body iron stores are depleted [2]. In contrast, in obese subjects, SF tends to be higher than in normal weight individuals and inversely related to transferrin saturation [17, 18, 54]. This suggests SF, an acute-phase protein that can be elevated in inflammatory conditions even in the presence of iron deficiency, may be increased by adipose-mediated inflammation. However, this hypothesis is not supported by studies in genetically obese (ob/ob) mice [55, 56]. When provided with an iron-sufficient diet, obese mice absorb twice as much iron as lean mice but have lower iron levels in the liver and small intestine [55, 56]; these studies however, predate the discovery of hepcidin and hence there is no data on hepcidin concentrations available. Further, the studies were carried out in genetically obese mice (ob/ob mice), which are leptin-deficient and this condition may differ from that of diet-induced obesity as it is usually found in humans.

To further clarify these relationships in humans, we recently compared iron status, dietary iron intake and bioavailability, as well as circulating levels of hepcidin, leptin, and IL-6 in overweight vs. normal-weight Swiss children [57]. In 6- to 14-year-old normal and overweight children ($n = 121$), we measured dietary iron intake, estimated iron bioavailability, and determined body mass index standard deviation scores (BMI-SDS). In all children, we measured fasting serum ferritin, soluble transferrin receptor (sTfR), C-reactive protein (CRP), and leptin; in a subsample, we measured IL-6 ($n = 68$) and serum hepcidin ($n = 30$). The results showed that there were no significant differences in dietary iron intake or bioavailability comparing normal and overweight children. Although total dietary iron intake did not differ between weight groups, the intake of heme iron was significantly higher in the obese children because of their higher meat intake. These data agree with a recent adult study, in which total iron consumption and iron bioavailability did not differ between obese and non-obese subjects, whereas heme iron intake and the consumption of animal protein were higher in obese adults [11].

The prevalence of iron-deficient erythropoiesis (an increased sTfR concentration) was significantly higher in the overweight than in the normal-weight children (20 vs. 6 %, $p < 0.022$, with sTfR concentrations of 4.40 ± 0.77 and 3.94 ± 0.88 mg/L, respectively; $p < 0.010$). Serum hepcidin levels were significantly

higher in the overweight children ($p < 0.001$). BMI-SDS significantly correlated with sTfR ($p < 0.009$) (Figure 2), serum hepcidin ($p < 0.005$), and the three measures of subclinical inflammation, namely CRP ($p < 0.001$), IL-6 ($p < 0.001$), and leptin ($p < 0.001$). In a multiple regression model, serum hepcidin was correlated with BMI-SDS ($p < 0.020$) and body iron ($p < 0.029$), but not with the inflammatory markers. The findings are similar to those in a recent study in obese Italian children that found lower iron and transferrin saturation and higher circulating hepcidin levels compared with normal-weight controls [58]. Thus, it appears there is reduced iron availability for erythropoiesis in overweight children and that this is unlikely due to low dietary iron supply but rather due to hepcidin-mediated reduced iron absorption and/or increased iron sequestration.

Given that obesity is associated with subclinical inflammation, and that SF is an acute-phase protein, sTfR is likely to be the best clinical measure of iron status in overweight individuals [14]. In iron deficiency, sTfR is increased because cell expression of the transferrin receptor is upregulated to increase the uptake of circulating iron, primarily into marrow red cell precursors. sTfR concentrations are not significantly affected by inflammation, and are therefore useful in differentiating iron deficiency from inflammatory hypoferremia [2]. Thus, in iron-deficient overweight children, sTfR and SF may be discrepant because of the confounding effect of obesity-associated inflammation on SF. In the study of Aeberli *et al.* [57], all three inflammatory markers (CRP, IL-6, and leptin) significantly increased with increasing adiposity, and CRP was a significant predictor of SF, but not TfR, independent of adiposity. These data emphasize the limitations of SF as an iron status indicator in overweight individuals.

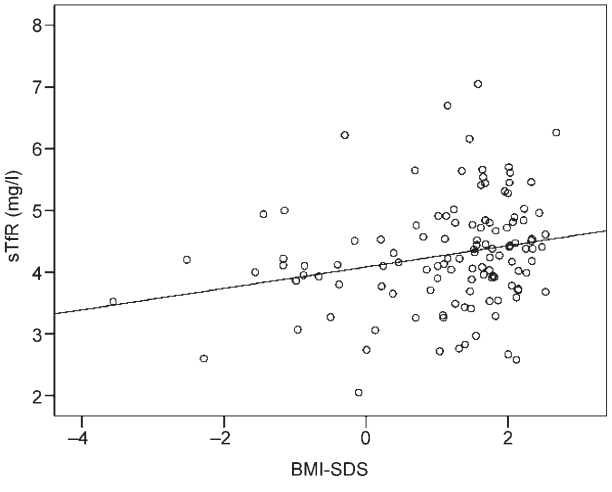

Figure 2: Associations between body mass index standard deviation scores (BMI-SDS) and soluble transferrin receptor (sTfR) in 6- to 14-year-old children in Switzerland ($n = 118$; $r^2 = 0.058$).

Prospective studies

The hypothesis that iron deficiency in obesity is due to hepcidin-mediated reduced iron absorption and/or increased iron sequestration needs confirmation by intervention studies that show that weight loss reduces circulating hepcidin levels, increases iron absorption, and improves iron status. An Italian study of fifteen obese children found that weight loss was associated with a significant decrease in circulating hepcidin levels and an increased response to iron supplementation [59]. Two studies have been reported in bariatric surgery patients. In women who underwent bariatric surgery for morbid obesity ($n = 178$), iron depletion was significantly correlated with increased markers of inflammation (CRP, orosomucoid, and haptoglobin) at baseline. Following significant weight loss six months after bariatric surgery, markers of inflammation decreased and were inversely correlated with an increase in transferrin saturation [60]. In another study performed in premenopausal women, significant weight loss following restrictive bariatric surgery was associated with decreased serum hepcidin and improved iron status (sTfR, Hb, and Hct) [61].

Conclusions

The data discussed here suggest that increasing obesity may contribute to iron deficiency in high-risk populations. This is a cause for public health concern as both iron deficiency and obesity have adverse short- and long-term health effects. Overweight and obesity are major risk factors for chronic illnesses such as cardiovascular diseases. Iron deficiency affects growth and development during early life. Both are associated with impaired cognitive ability. Further research is needed to identify the specific mechanisms involved in the development of iron deficiency in obese children and reproductive-age women, and to clarify the adverse health effects. More studies on the modulation of obesity-related inflammation and the resulting effects on iron status would be welcome. Results from such studies may provide valuable information to ensure sufficient bioavailable iron for obese individuals.

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