The Role of Iron Overload in Systemic Iron Homeostasis, Proinflammatory Biomarkers and Obesity Etiopathogenesis

Buthaina Alkahtib*✉, Hayder Aldomi*

ABSTRACT

Obesity is associated with low-grade subclinical inflammation, systemic iron deficiency and hypoferremia. However, obesity is up-regulating iron regulatory hormone called hepcidin leading to increase iron store in liver and adipose tissue. On the other hand, iron overload in adipose tissue increases systemic insulin resistance and iron handling by macrophages, and this could lead to the development of obesity, dyslipidemia, disglycemia and non-alcoholic fatty liver disease. Given that, the importance of the complicated metabolic interference between iron and obesity has been studied and many proposed mechanisms have been placed. Hence, the objective of this critical review was to discuss the role iron overload in systemic iron homeostasis, proinflammatory biomarkers and obesity etiopathogenesis.

Keywords: Obesity, Iron Overload, Hepcidin, Anemia, Iron Homeostasis.

INTRODUCTION

Hepcidin; a 25-amino-acid hepatic antimicrobial peptide, is the central regulator of iron homeostasis (Rochette *et al*., 2014) and also known as liver-expressed antimicrobial peptide-1 (LEAP-1) (Ganz, 2013). It has been firstly isolated from plasma by Krause *et al*. (2000), then from urine by Park *et al*. 2002 and named it hepcidin. Hepcidin production is up-regulated by inflammation, iron overload, infectious stimuli (Ganz, 2015), obesity (Nikonorov *et al*., 201) and insulin (Wang *et al*., 2014), whereas; it is dow-nregulated by iron deficiency anemia, hypoxia, pregnancy (Koenig *et al*., 2014), insulin resistance (Wang *et al*., 2014) and erythropoietic activity (Ganz, 2015). Certain proinflammatory cytokines play a fundamental role in inducing hepcidin gene expression, particularly interleukin-1 (IL-1) and interleukin-6 (IL-6) (Casanovas *et al*., 2014). The primary target of hepcidin function is ferroportin which is the only known iron exporter in macrophages, hepatocytes and duodenal enterocytes from blood stream (Ganz and Nemeth, 2012). Given that obesity is a serious global health challenge with pandemic proportion resulting in significant mortality and morbidity (Lecomti *et al*., 2015), it increases adipose tissue (AT) mass accompanied by AT remodeling and macrophages infiltration (Suganami and Ogawa, 2010). Moreover, obesity has been associated with anemia of chronic disease especially systemic iron deficiency and hypoferremia (Albakri *et al*., 2014). Obesity may promote iron deficiency by inhibition of dietary iron uptake from the duodenum, and a condition termed dysmetabolic iron overload syndrome (DIOS), which is characterized by increased serum ferritin concentrations with normal or mildly elevated transferrin saturation in

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Received on 3/6/2015 and Accepted for Publication on 20/3/2016.

subjects with various components of metabolic syndrome or non alcoholic fatty liver disease, has become the most frequent differential diagnosis for elevated ferritin concentrations (Datz *et al*., 2013; Dongiovanni *et al*., 2013).

Oral iron supplementation and high-iron diet are commonly prescribed for individuals with anemia (Gisbert *et al*., 2009). High-iron diet results in decreased adiponectin production in AT leading to decrease insulin sensitivity (Wlazlo *et al*., 2013). Furthermore, iron overload leads to AT and endocrine dysfunction (Gabrielsen *et al*., 2012). This could affect adipokines secretion and\or interupt insulin signals pathway leading to obesity-related diseases. Hence, the objective of this critical review was to discuss the role iron overload in systemic iron homeostasis, proinflammatory biomarkers and obesity etiopathogenesis.

Iron Homeostasis

Hepcidin is the key regulator of systemic iron homoeostasis (Hentze *et al*., 2010). While hepcidin is mainly synthesized in hepatocytes, it is also produced in intestinal cells, pancreatic cells, AT and monocytes (Zhang and Rovin 2010). The function of hepcidin is initiated by its binding to ferroportin, which is the cellular iron exporter located in the basolateral surface of duodenal enterocytes and on the cellular membrane of macrophages, leading to rapid internalization and degradation of ferroportin (Ghosh *et al*., 2013). Thus, high hepcidin levels reduces iron absorption in intestinal enterocytes and prevents the movement of dietary iron into circulation. Moreover, hepcidin prevents the movement of stored iron in macrophages and liver into circulation (Nemeth *et al*., 2004). This is mediated by the bone morphogenetic protein (BMP)-SMAD signaling cascade with BMP-6 serving as an iron related BMP-receptor ligand and its up-regulated by iron overload and inflammation (Silvestri *et al*., 2008). The rapid sequestration of iron in macrophages and the long-term of reducing enteral iron absorption lead to anemia by decreasing iron availability for erythropoiesis (Babitt *et al*., 2007). In contrast, hepcidin expression is suppressed in situations of increased erythropoietic demand, the absence of hepcidin leads to unregulated duodenal iron absorption and subsequent iron overload, which has also been reported in pathological conditions such as hereditary haemocromatosis (Fleming and Ponka, 2012) (Figure 1).

Certain proinflammatory cytokines play a fundamental role in inducing hepcidin gene expression, particularly IL-1 and IL-6 (Nemeth *et al*., 2004). Findings of studies demonstrated that elevated hepcidin levels in inflammation is mediated by increased IL-6 and play a key role in the anemia of inflammation and reticuloendothelial blockade (Park *et al*., 2006). Additionally, leptin, anti-obesity hormone, increases hepcidin expression via the Jak2/STAT3 signaling pathway in parallel with IL-6 (Chung *et al*., 2007).

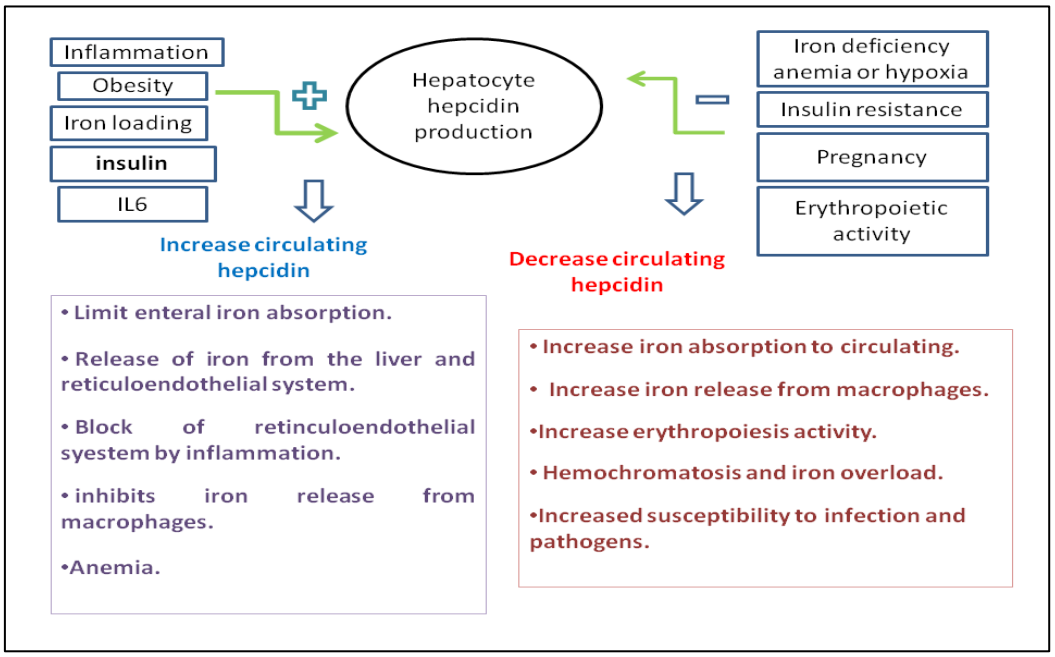

Figure 1: Hepcidin Regulation for Iron Homeostasis (Ganz, 2015; Nikonorov *et al*., 2015 and Wang *et al*., 2014)

Pathological Effects of Iron Supplementation and Iron Overload

Pathological Effects of Iron Supplementation

Iron deficiency is the most common cause of anemia worldwide (Gisbert *et al*., 2009). Globally, iron deficiency anemia affect more than two billion people especially the children due to their heightened iron requirements (Zimmermann and Hurrell, 2007). Iron deficiency anemia is associated with a decrease in the cellular immune response, mental function, physical activity, and alterations in hormonal regulation (Viteri *et al*., 2012). Therefore oral iron supplementation is commonly prescribed for people diagnosed with anemia (Gisbert *et al*., 2009). Findings of recently reports demonstrated that iron supplementation has complex interactions between diet, the host immune system and the gut microbiome (Goldsmith and Sator, 2014). The amount of supplemental iron absorbed in the human gastrointestinal tract is low, most of the dose passes into the colon where it becomes available for the pathogenic bacteria (Sekirov *et al*., 2010), which lead to alteration in the composition of the gut microbiota in malnourished children (Monira *et al*., 2011).

Oral iron intake could alter gut function and microbial composition through direct induction of reactive oxygen species leading to increased cell stress in enterocytes and adversely affects the gut microbiome, increasing pathogen abundance and causing intestinal inflammation (Goldsmith and Sartor, 2014). Iron fortification in rural areas resulted in a significant increase of infection related mortality, mostly related to malaria and invasive bacterial infections, produce potentially pathogenic gut microbiota profile, up regulation of gut inflammation or increased morbidity due to diarrhea (Zimmermann *et al*., 2010). It has been also shown that the growth and infectivity of several enteropathogens can be promoted by iron supplementation in vitro (Weinberg, 2009).

Dongiovanni *et al.* (2013) found that iron supplementation increased hepatic iron and serum hepcidin fivefold and led to a 40% increase in fasting glucose in

mice. However, iron supplemented mice had lower visceral AT mass, associated with iron accumulation in adipocytes. Moreover, iron-enriched diet upregulated iron responsive genes and adipokines, favoring insulin resistance (Dongiovanni *et al*., 2013). Thus, weight losses in obese children and adult women were accompanied with significantly decreased hepcidin and leptin concentrations, which, in turn, increased intestinal iron absorption (Tussing-Humphreys *et al*., 2010).

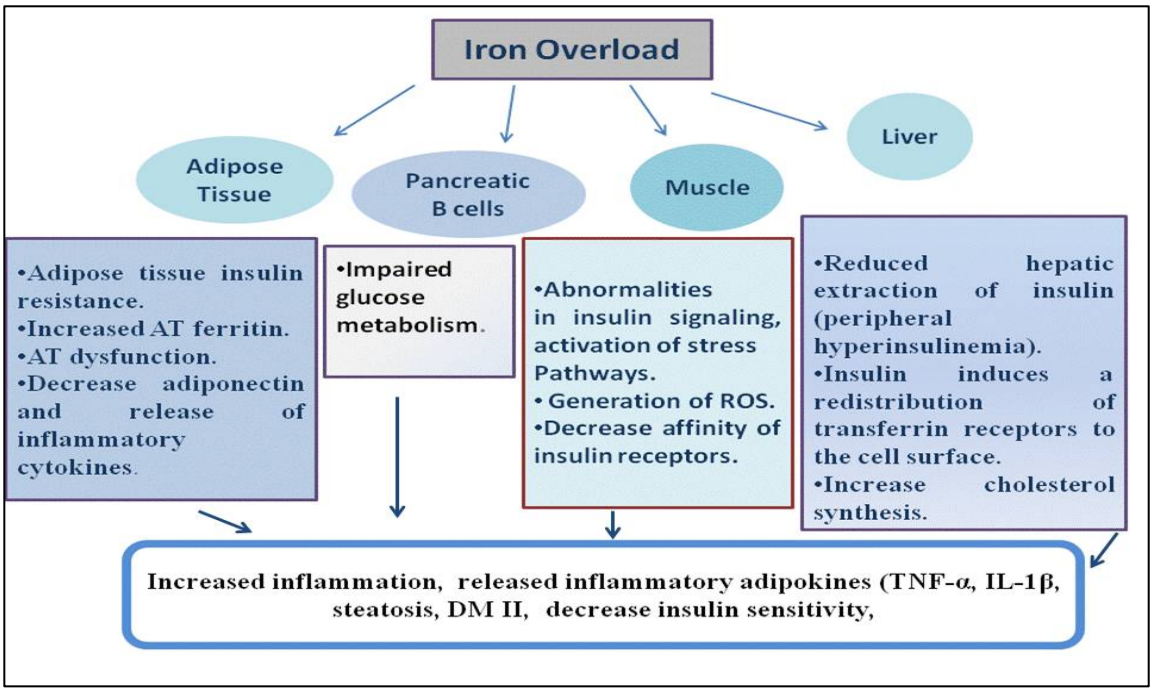

Figure 2: Effect of Iron Overload on Specific Tissues (Hubler *et al*., 2015 and Simcox and McClain, 2013).

Pathological Effects of Iron Overload

Moderately elevated iron levels are associated with chronic diseases such as atherosclerosis, type 2 diabetes mellitus (T2DM) and premature death (Fasola *et al*., 2013). DIOS is characterized by increased ferritin levels, and increased body iron stores in the presence of insulin resistance (Dongiovanni *et al*., 2013). DIOS was observed in 15% to 30% of individuals with the metabolic syndrome (Valenti *et al*., 2010). DIOS with normal or mildly elevated transferrin saturation was observed in approximately a one-third of patients with metabolic syndrome or nonalcoholic fatty liver disease (Aigner *et al*., 2014).

In order to protect against invading pathogens during prolonged chronic inflammation infectious or autoimmune disorders, the diversion of iron traffic from circulation into storage sites may limit iron for erythropoiesis even in the presence of adequate stores (local iron overload) (Wrighting and Andrews, 2006; Weinberg, 2009). The induction of hepcidin via the IL-6/STAT3 signaling pathway promotes iron retention in macrophages, which decreased dietary iron absorption and hypoferremia leading to anemia of chronic diseases (Weiss and Goodnough, 2005).

Iron overload can affect major tissues involved in glucose and lipid metabolism as well as organs affected by chronic diabetic complications (Fernandez-Real and Manco, 2014). Epidemiological studies showed an association between iron stores and the development of metabolic syndrome (Park *et al*., 2012). Zheng *et al*. (2011) noted that liver iron is increased in people with T2DM and insulin resistance. Moreover, increased body iron stores were significantly associated with risk of T2DM (Bao *et al*., 2012). Recently, it was reported that the serum concentration of prohepcidin (a precursor of the mature hepcidin) was significantly higher in males with impaired glucose tolerance or T2DM than in those with normal glucose tolerance (Derbent *et al*., 2013).

In liver, iron overload can disrupt insulin inhibition of hepatic glucose production, which together with reduced hepatic extraction of insulin lead to peripheral hyperinsulinaemia (Ferrannini., 2000) (Figure 2). Thus, insulin induces the redistribution of transferrin receptors to the cell surface where they mediate uptake of extracellular iron, activation of oxidative stress, and release of inflammatory cytokines -particularly tumor necrosis factor α (TNFα) and interleukin-1β- in the subendothelial space (Arosio *et al*., 2009). Moreover, an iron-enriched diet lead to iron accumulation and insulin resistance in visceral AT in mice (Dongiovanni *et al*., 2013). AT also seems to have an active role in the modulation of systemic iron metabolism through the production of adipokines, which, interacts with iron metabolism suggests that iron overload could contribute to obesity associated AT dysfunction (Moreno-Navarrete *et al*., 2015).

Iron overload could affect skeletal muscle (Huang *et al*., 2013), provided that skeletal muscles contain 10–15% of body iron, mainly located in myoglobin. Muscular contractions seem to stimulate transferrin receptor recruitment from a GLUT4 (SLC2A4)-containing intracellular fraction to the plasma membrane (Fernandez-Real *et al*., 2009). As such, iron overload could disrupt insulin activity in muscle possibly by activation of stress pathways with generation of ROS, which, lead to the hydroxylation of phenylalanine residues of insulin and therefore promotes insulin resistance (Huang *et al*., 2013).

Morover, serum ferritin is considered an indicator of systemic iron overload (Chang *et al*., 2013), yet it is not a sufficient biomarker for tissue iron overload determination, because there are many different metabolic tissues, including pancreas, liver, and AT that could be relevant to the metabolic disturbances associated with iron overload (Hubler *et al*., 2015; Simcox and McClain, 2013).

Association between Obesity and Inflammation

Obesity is a pandemic health problem associated with low-grade chronic inflammation, (Albakri *et al*, 2014). In 2014, more than 1.9 billion adults worldwide were overweight; of these over 600 million were diagnosed with obesity (WHO, 2015).

Obesity increased adipose AT mass (hypertrophy) and cells number (hyperplasia) accompanied by AT remodeling and macrophages infiltration leading to adverse health effects and obesity comorbidities including insulin resistance and T2DM (Suganami and Ogawa, 2010). Adipose tissue produces many cytokines and adipokines such as IL-6, interleukin-1β, interleukin-8, TNF-α, leptin, adiponectin, resistin, lipocalin-2, C-reactive protein (CRP), monocyte chemoattractant protein 1, complement components, plasminogen activator inhibitor-1 (Arslan *et al*., 2010). Moreover, AT of obese individuals expressed up regulation of pro-inflammatory cytokines and down-regulation of anti-inflammatory cytokines (Albakri *et al*., 2014). Thus, leading to macrophages infiltration, ectopic fat accumulation, hypoxia and death of AT (Suganami *et*

al., 2012). Furthermore, the increase in adipocyte death in obese individuals has been attributed to local hypoxia, adipocyte hypertrophy and AT stress (Fujisaka *et al*., 2013). The inflammatory response of AT is associated with a rise in cytotoxic T cells, B cells, mast cells, neutrophils and macrophages (Winner *et al*., 2011). Adipose tissue macrophages function as antigen-presenting cells and stimulate the expansion of respective CD4 T cells (Morris *et al*., 2013). Thus, the infiltrated macrophages cells surrounding the adipocytes and form a crown-like structures (Albakri *et al*., 2014). In mice, the AT macrophages in obesity has been demonstrated to phenotype switching from a more alternatively activated (M2) to a classically activated (M1) phenotype (Luming *et al*., 2007). The increase in macrophages during obesity was attributed to an enhanced recruitment of chemo-attractant factors, such as monocyte chemo-attractant protein 1 (MCP-1), chemerin or progranulin, are upregulated in AT of obese rodents and humans (Youn *et al*., 2009).

Role of Obesity in Iron Homeostasis

Obesity has been associated with anemia of chronic disease especially systemic iron deficiency and hypoferremia (Ghadiri-Anari *et al*., 2014) and it is well documented to increase hepcidin production and inflammation; this may, in part at least, lead to iron dis-metabolism. Table 1 summarizes the association between body weight, inflammation and iron status in human (Table 1).

Additionally, obesity could increase iron deficiency by inhibition of dietary iron uptake from the duodenum leading to DIOS which has become the most frequent differential diagnosis for elevated ferritin levels (Datz *et al*., 2013). Obesity-related hypoferremia could be attributed to obesity-induced inflammatory state produced from the increased hepcidin and lipocalin 2 levels in obese individuals (Nairz *et al*., 2015). The coexistence of both lipocalin-2 and hepcidin limit iron availability for bacterial growth; this, increases iron import into the storage cells leading to elevated intracellular iron in obese individuals (Xu *et al*., 2012). Obese individuals are characterized by increased AT hemojuvelin mRNA expression, a co-receptor of bone morphogenic protein which mainly produced by liver, and is significantly positive correlated with hepcidin mRNA expression (Luciani *et al*., 2011). Furthermore, there is an important role of endoplasmic stress (ESR) in adipocyte dysfunction and metabolic abnormalities of obesity; iron overload is capable of inducing ERS in a number of tissues and inducing hepcidin synthesis (Tan *et al*., 2013). In obese AT, macrophages are activated forming M1 phenotype and down-regulated M2 phenotype by which M1 macrophages are able to sequester iron while M2 macrophages are capable of regulating intracellular iron content, therefore, transferrin1 and ferroportin1 are both upregulated in M2 macrophages, while ferritin is down-regulated (Recalcati *et al*., 2010). MFe^{hi} cells is a unique population of macrophages that regulate iron homeostasis, they have even greater expression of M2 genes, and a reduction in M1 genes as compared to MFe^{lo} cells (remaining ATMs) (Martinez *et al*., 2008).

A recent report showed that 25% of macrophages (MFe^{hi}) in lean AT have a twofold increase in intracellular iron stores allowing them to be isolated based upon their ferromagnetic properties (Orr *et al*., 2013). Furthermore, in obese individuals, newly recruited macrophages do not take on a role in iron handling. As such, the MFe^{hi} cells become more inflammatory and appear to lose their ability to handle iron properly (Martinez *et al*., 2008). Importantly, this change in MFe^{hi} cells occurs along with adipocyte iron overload and reduced adipocyte adiponectin expression (Hubler *et al*., 2015). Interleukin-4 (IL-4) has been shown to induce M2-like macrophage polarization, thereby

decreasing the labile iron pool (Kim and Ponka, 2000). Thus, IL-4 enhances production of transferrin1 mRNA through a non-iron response proteins dependent pathway and it may serve as a control for both macrophage polarization and iron handling (Hubler *et al*., 2015). Moreover, the expression of heme oxygenase-1, which is an enzyme that metabolizes heme into iron and it is a part of the cellular defense against oxidative stress, has been reduced in MFe^{hi} cells in obese mice (Kovtunovych *et al*., 2010). However, heme oxygenase-1 is downregulated by the inflammatory cytokine interferon-γ and upregulated by IL-4 (Sierra-Filardi *et al*., 2010).

CONCLUSION

The complex interaction between obesity induced inflammatory state, hypoxia and high iron intake could up-regulate hepcidin and other inflammatory cytokines in adipose tissue, leading to increase oxidative stress and tissue iron overload, which, could affect the pathogenesis of several chronic metabolic diseases. However, this necessities further studies to understand the possible mechanisms that may explain the role of iron status in the pathogenesis of obesity taking in consideration the impact of hepcidin and other inflammatory cytokines effect in different specific tissues.

Table 1 : The Association between body weight, inflammation and iron status in human

Author and year	Study Design	Study Sample	Objectives	Main Outcomes
Phinas-Hamiel *et al*., (2003)	Cross-sectional	321 children and adolescents (aged years old)	To examine the association between body weight and iron status	A significantly higher proportion of obese children have iron deficiency anemia than that in normal-weight children.
Nead *et al*., (2004)	National Health and Nutrition Survey III (1988-1994)	9698 children (aged 2 to 16 years old)	To investigate the association between weight status, as measured by body mass index (BMI), and iron deficiency.	Increased prevalence of iron deficiency between overweight children.
Chambers *et al*., (2006)	Cohort study	670 adult participants (aged 17-54 years old)	To examine the relationship between serum iron levels and body composition determined by BMI	An inverse association of measures of body fat distribution and total fat mass with serum iron level in Hispanic women was established.
Ynoff *et al*., (2007)	Cross-sectional	234 obese and 172 non-obese adults (aged 18-64 years old).	To examine the relationships between obesity, serum iron, measures of iron intake, iron stores and inflammation.	Obese subjects had a higher prevalence of iron deficiency. The hypoferremia of obesity appears to be explained both by true iron deficiency and by inflammatory-mediated functional iron deficiency.

Author and year	Study Design	Study Sample	Objectives	Main Outcomes
Zimmermann *et al*., (2008)	Intervention study	92 Thai women ,1688 and 727 in Morocco and India (aged 18-50 years old)	To investigate the association between BMI and iron absorption, iron status and the response to iron fortification in various populations.	Adiposity in young women predicts lower iron absorption, and pediatric adiposity predicts iron deficiency and a reduced response to iron fortification.
Richardson *et al*., (2009)	Prospective	106 obese children (aged 2-19 years old).	To determine the association between the low iron state described in obese children with the chronic inflammatory state seen in obesity.	The chronic inflammation of obesity results in the low iron state reported in obese children, similar to what is seen in other inflammatory diseases.
Del Giudice *et al*., (2009)	Case- control	60 obese children and 50 controls (mean age 11.5 years old).	To assess the association between poor iron status and obesity. To investigate whether iron homeostasis of obese children may be modulated by variations in serum hepcidin levels. To assess the potential correlation between leptin and serum hepcidin variations.	Hepcidin production was increased in obese patients, at least partly leptin mediated, represents the missing link between obesity and disrupted iron metabolism.
Aeberli *et al*., (2009)	Case- control	121 normal and overweight children aged (6-14 years old).	To compare iron status, dietary iron intake and bioavailability, as well as circulating levels of hepcidin, leptin and IL-6.	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.

Author and year	Study Design	Study Sample	Objectives	Main Outcomes
Cepeda-Lopez *et al*., (2011)	Data from the 1999 Mexican Nutrition Survey	1174 children (aged 5–12 years old) and 621 women (aged 18-50 years old).	To examine the relations between BMI, dietary iron, and dietary factors affecting iron bioavailability, iron status, and inflammation.	The risk of iron deficiency in obese Mexican women and children was 2–4 times that of normal-weight individuals. This may be due to the effects of obesity-related inflammation on dietary iron absorption.
Bouglé and Brouard (2013)	Cross-sectional	obese youth (502 patients; 57% girls) (mean age 11.4 years old)	To study the effect of inflammation parameters in obese subjects with Fe status	Fe storage is associated with risk of metabolic syndrome and non alcoholic fatty liver disease
Ghadiri-Anari *et al*., (2014)	Cross-sectional	406 adult (aged 18–65 years old).	To examine the association of BMI with hemoglobin concentration and iron parameters.	There is no difference in hemoglobin concentrations, serum iron, transferrin saturation index, and ferritin between normal weight, overweight, and obese persons.
Mujica-Coopman *et al*., (2015)	Cross-sectional	318 Chilean childbearing age women (aged 15-49 years old).	To assess the association of BMI with both Fe absorption and Fe status	There was no relationship between BMI and Fe status, but obese women displayed lower Fe absorption compared with overweight and normal weight women, possibly due to inflammation associated with obesity.

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دور الحديد الفائض في توازن الحديد في الجسم و المؤشرات الحيوية للالتهاب والسمنة: مراجعة نقدية

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ملخص

تهدف هذه المراجعة النقدية إلى البحث في توازن الحديد في الجسم، ودور هرمون الهيبسيدين في تنظيمه ، ودراسة تأثير فائض الحديد على مستوى الخلية الموضعي ومستوى أجهزة الجسم وكذلك التداخل بين تنظيم الحديد والسمنة. يعتبر هرمون الهيبسيدين وسيطا جديدا لجهاز المناعة الفطري وله دور مهم في تنظيم مستوى الحديد في الجسم. يتأثر إفراز هرمون الهيبسيدين بعدة عوامل؛ إذ يزداد افرازه في حالات الالتهاب، والسمنة، وعند ارتفاع الحديد في الجسم سواء كان من الغذاء أو من المكملات. بينما يقل إفرازه في حالات فقر الدم الناجم عن عوز الحديد و الحمل ونقص الأكسجين. تؤدي زيادة افراز الهيبسيدين إلى ارتفاع مستوى سكر الدم نظرا لزيادة مقاومة الانسولين. تعتبر السمنة مشكلة التهابية تؤدي إلى عوز الحديد في الدم بينما تزداد نسبته المخزنة في الأنسجة خصوصا في النسيج الدهني، مما يؤدي إلى تنشيط السيتوكينات المحفزة للالتهاب والتي تؤدي بدورها إلى اختلالات وظيفية بدءا من مقاومة الانسولين وصولا إلى ارتفاع القابلية للإصابة بأمراض متلازمة الأيض.

الكلمات الدالة: السمنة، الهيبسيدين، توازن الحديد، فائض الحديد، عوز الحديد.

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تاريخ استلام البحث 2015/6/3 وتاريخ قبوله 2016/3/20.