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REVIEW

# Mutual interaction between iron homeostasis and obesity pathogenesis

Alexandr A. Nikonorov[a,*], Margarita G. Skalnaya[b], Alexey A. Tinkov[a], Anatoly V. Skalny[b,c]

[a] Department of Biochemistry, Orenburg State Medical Academy, Sovetskaya Street 6, Orenburg 460000, Russia
[b] Russian Society of Trace Elements in Medicine, Zemlyanoy Val Street 46, Moscow 105064, Russia
[c] Institute of Bioelementology (Russian Satellite Centre of Trace Element – Institute for UNESCO), Orenburg State University, Pobedy Avenue 13, Orenburg 460352, Russia

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ABSTRACT

Obesity is identified as an important medical problem. One of the pathologic conditions observed in obesity is systemic iron deficiency and hypoferremia. Along with a large number of studies indicating disturbed iron homeostasis in obesity, recent data indicate a cause–effect relationship between iron status and obesity-related pathologies. The primary objective of the article is to consider two aspects of the iron–obesity interplay: (1) the mechanisms leading to impaired iron balance, and (2) the pathways of iron participation in obesity-related pathogenesis. While considering disturbance of iron homeostasis in obesity, a number of potential mechanisms of hypoferremia are proposed. At the same time, the inflammation of obesity and obesity-related hepcidin and lipocalin 2 hyperproduction seem to be the most probable reasons of obesity-related hypoferremia. Oversecretion of these proteins leads to iron sequestration in reticuloendothelial system cells. The latter also leads to increased adipose tissue iron content, thus producing preconditions for adverse effects of local iron overload. Being a redox-active metal, iron is capable of inducing oxidative stress as well as endoplasmic reticulum stress, inflammation and adipose tissue endocrine dysfunction. Iron-mediated mechanisms of toxicity may influence aspects of obesity pathogenesis possibly even leading to obesity aggravation. Thus, a mutual interaction between disturbance in iron homeostasis and obesity pathogenesis is proposed. All sides of this interaction should be considered to design new therapeutic approaches to the treatment of disturbed iron homeostasis in obesity.



**Contents**



* Corresponding author. Tel.: +7 9228407320.
*E-mail address:* alalnikonorov@gmail.com (A.A. Nikonorov).

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## Introduction

Obesity is identified as an important biomedical problem, with prevalence exceeding that of infectious diseases [1]. In accordance with the classical definition, increased adipose tissue (AT) mass is supposed to be a morphological substrate of obesity [2]. At the same time, clinical and epidemiological studies widely use body mass index (BMI) as a criteria of obesity [3]. In accordance with BMI values, individuals could be identified as ones with low, normal and excessive body mass or different stages of obesity [4].

During a long period of human history, only rare indications of obesity in single persons were found archeologically. The earliest indications of obesity in hominides are presumably dated 500000 BCE and the prevalence of obesity increased slowly [5]. However, agro-industrial revolution in the XIX century led to increased food production and consumption [6]. The scientific and technical revolution in the XX century introduced a widely distributed sedentary lifestyle [7]. Taken together, these changes led to a positive energy balance that is supposed to be a principal etiological factor in obesity development [8]. During the last 100 years, the prevalence of obesity gradually increased [9] mainly in economically developed countries of Northern America and Europe [10]. In contrast to economically developed countries, the prevalence of obesity in developing countries was observed in the last decades [10,11]. At present, the number of individuals suffering from obesity and overweight in the developing countries surpasses the numbers observed in the developed ones [12]. This fact confirmed earlier projections regarding the tendencies of obesity expansion [13].

According to the World Health Organization's data in 2006 the number of overweight and obese individuals worldwide was 1.6 billion and 400 million respectively [14]. In 2008, the approximate number of overweight subjects was estimated of 1.46 billion, whereas obesity was observed in 502 million of individuals (205 in men and 297 in women) [15]. If this tendency continues, the presumptive number of overweight and obese subjects in 2015 will reach 2.3 billion and 700 million respectively [14]. At the same time, the amount of overweight subjects worldwide will raise to 3.3 billion (2.2 billion overweight and 1.1 billion obese) in 2030 [16]. Along with the increased prevalence of obesity in adults, the incidents of childhood obesity also increased [17,18].

The adverse health effects of obesity are not only caused by increased adipose tissue mass itself, but rather by its comorbidities. Evidence suggests a strong association between obesity and hypertension [19], cardiovascular diseases [20], atherosclerosis [21], renal pathology [22], allergopathology [23], oncology [24] and others. A close relationship between obesity and diabetes mellitus was observed, coining the new term "diabesity" [14,25]. Moreover, a complex of pathologies including obesity, hyperglycemia, arterial hypertension and dyslipoproteinemia was clustered and termed "metabolic syndrome" [26].

One pathologic condition frequently observed in obesity is systemic iron deficiency and hypoferremia. The first evidence of these conditions was obtained in 1960s in obese children. The serum iron decrease was as frequent as 36% in males and 18% in females [27]. This observation was later confirmed in adolescents [28,29] and adults [30,31] suffering from obesity. However, the intimate mechanism(s) of obesity-related hypoferremia is (are) still unknown. In light of these discoveries, the possibility of obesity-induced iron-deficient anemia was discussed for a long time, but was not confirmed by experimental data [32,33]. Recent experimental data showed a cause–effect relationship between iron content and development of obesity. Thus, preliminary studies on iron chelation with deferoxamine in KKAy were effective to reduce obesity [34]. It was also proposed that iron supplementation in addition to a high-fat diet can possibly increase adiposity in rats and adipose tissue iron content [35]. However, these phenomena were demonstrated only in rodents and its contribution to human obesity still remains unknown.

The role of iron in obesity became a "hot topic". To contribute to this discussion, the primary objective of the review is to consider the two sides of iron–obesity relationship: (1) the mechanism(s) leading to impaired iron balance, and (2) the pathway(s) of iron participation in obesity-related pathogenesis. This review does not address the role of iron and mechanisms of its effect on pathogenesis of dysmetabolic iron overload syndrome (DIOS) as it was discussed earlier [36].

## Disturbance of iron homeostasis in obesity

As discussed above, obesity is accompanied by iron deficiency. The intimate pathways of this comorbidity are still unknown. At least three potential mechanisms of hypoferremia of obesity have been proposed by Yanoff et al. [37]:

(1) Nutritional iron deficiency;
(2) Elevated blood volume as a function of increased adipose tissue mass leading to enhanced iron requirements;
(3) Systemic inflammation of obesity.

In view of the contradictory data on the relationship between nutritional iron deficiency and hypoferremia of obesity [38,39], the contribution of the diet to these disturbances remains debatable. At the same time, the impact of a poor-iron diet on obesity-related hypoferremia in developing countries cannot be excluded. The role of increased blood volume in obese patients in development of hypoferremia was confirmed by experimental data [40]. At the same time, the most probable reason of obesity-related hypoferremia is obesity-induced inflammation. The presumable mechanism of inflammation-induced hypoferremia is increased hepcidin and lipocalin 2 production in obesity [37].

### *Hepcidin*

Hepcidin is a peptide hormone secreted in inactive form as 84-amino acid preprohepcidin. N-terminal cleavage of preprohepcidin results in prohepcidin formation. Further proteolysis of prohepcidin leads to generation of active hepcidin containing 25 amino acid residues [41]. The primary site of hepcidin secretion is liver [42]. However, hepcidin is also produced in a number of tissues such as heart, spinal marrow, adipose tissue, myeloid cells, macrophages, monocytes and other cells, though the contribution of extrahepatic hepcidin production to total hecidin level is still under discussion [43]. A special emphasis is given to adipose tissue hepcidin production. Adipose tissue expression of hepcidin mRNA is increased in obesity, whereas liver hepcidin expression is not [44]. Taking into account the increased adipose tissue content and increased adipocyte hepcidin expression, it is assumed that adipose tissue significantly contributes to circulating hepcidin levels [45].