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Review Article

Mechanisms of Iron Deficiency in Obese Children

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Abstract: Obesity and iron deficiency are global public health problems. Obesity can cause nutritional disorders, such as iron deficiency. Obesity and iron deficiency during the rapid stages of growth and development in children can cause lasting and irreversible damage to the health of children and even into adulthood. Because the economy and living standards are improving, the incidence of childhood obesity increases yearly, at the same time, the incidence of iron deficiency in obese children is also higher. Obesity is closely related to the occurrence and development of iron deficiency, and the coexistence of the two can produce synergistic effects leading to serious harm, which is an urgent nutritional health problem in clinic. By impairing iron absorption, reducing iron excretion within cells, and by competing with the body for iron with the altered gut flora caused by obesity, obesity can disrupt the normal iron metabolism process and then lead to iron deficiency. The mechanism of obesity-associated iron deficiency is complex and may be related to inflammatory response, intestinal cells, anoxic microenvironment and intestinal flora. Therefore, in this review, we discuss possible mechanisms of obesity-associated iron deficiency to offer new methods and strategies for preventing and treating iron deficiency in obese children.

Keywords: Obesity, Iron Deficiency, Anoxic Microenvironment, Inflammation, Gut Microbiota

1. Introduction

Obesity and being overweight refer to abnormal or superabundant fat deposition and pose a risk to health. In the 21st century, obesity is a primary public health issue and is listed as a global epidemic by the World Health Organization. Physiologically, obesity is caused by an increase in the number and size of adipocytes. Childhood obesity can continue into adulthood, leading to a high risk of cardiovascular diseases, diabetes, and even cancer [1].

Obesity can cause nutritional disorders, such as iron deficiency. Iron is an essential participant in many physiological processes, including energy metabolism and muscle function, erythropoiesis, heme and iron-sulfur cluster synthesis, cell cycle regulation, hormone production, the immune system, DNA replication and repair, cytochrome P450 formation, and brain development [2, 3]. Iron deficiency reduces iron content in the brain of infants. The deficiency impairs the transmission of neurotransmitters and the formation of myelin [4], causing irreversible damage to the nervous system, mental retardation, cognitive and behavioral dysfunction, and emotional regulation defects, even if iron deficiency is corrected [5−7].

Because iron is prone to form insoluble oxides after contact with air, its bioavailability is significantly limited. Children are in a period of rapid growth and development. They have a substantial requirement for iron and are particularly susceptible to iron deficiency. Obesity at this stage will aggravate iron deficiency. There are many causes of childhood iron deficiency coupled with obesity. Genetic predisposition, imbalanced nutrient intake, decreased myoglobin synthesis because of too little exercise, and increased iron requirement with increased blood volume [8]. However, no difference has been found between obese and non-obese individuals in dietary iron intake or diet factors that affect iron absorption; thus, diet alone cannot explain obesity-related iron deficiency [9]. Therefore, we review possible mechanisms of obesity-associated iron deficiency to offer a theoretical foundation for prophylaxis and treatment of iron deficiency in obese children.

2. Current Status of Iron Deficiency and Childhood Obesity

As the economy and living standards improve, the prevalence of obesity in children is generally increasing. Among children and adolescents aged 5-19, obesity has increased from 4% in 1975 to 18% in 2016 [10]. About 38.2 million children aged 5 or less were overweight or obese in 2019; nearly half of these children were living in Asia [11]. In 2020, 5.7% of children under age 5 (38.9 million children) were overweight [12]. In 2017, the China Childhood Obesity report indicated that, from 1985 to 2014, among children over the age of 7, the rate of being overweight rose from 2.1% to 12.2%, and the rate of obesity rose from 0.5% to 7.3% [13]. If nothing is done, obesity is expected to reach 6% among Chinese children aged 0-7 years, and by 2030 the prevalence of being overweight and obese is expected to reach 28.0% among Chinese children aged 7 and above [5].

A negative correlation between obesity and iron status was reported by Wenzel et al. as early as 1962 [14]. The Third National Health and Nutrition Examination Survey of the United States studied 9698 children aged 2-16. The prevalence of obese or overweight children was 24% [15]. The prevalence of iron deficiency in overweight children aged 2-5 was 6.2% and 9.1% for overweight children aged 12-16 years. Nead KG et al. [15] showed by multivariate regression analysis that the probability of being overweight or obese combined with iron deficiency was about twice that of non-overweight or nonobese individuals. A cross-sectional study in Greece included ~2,500 children between the ages of 9 and 13. The prevalence of obesity or being overweight was 42%, and the prevalence of iron deficiency was 29% in obese children [16]. In Guangzhou, China, Zheng H et al. [17] showed that being overweight or obese accounted for 22.8% of all study participants, of which 8.4% of obese children had iron deficiency. Zhu Y et al. [18] reported that the prevalence of iron deficiency in children and adolescents was 4.7% in a normal weight group and 8.9% in an obese group. The study of school-age children in Shandong Province by Zhang YX et al. [19] showed that the morbidity of iron deficiency increased with the increasing severity of obesity. Sypes EE et al. [20] showed that, among children aged 1-3 years, a high risk of iron deficiency was associated with a high BMI.

It is necessary to actively prevent and treat iron deficiency in obese or overweight children to limit health damage in childhood and adulthood. Although many investigators have observed a strong correlation between obesity and iron deficiency, the mechanism of the relation is unknown [21].

3. Normal iron Metabolism

Human iron metabolism is divided into systematic and cellular iron metabolism. Systematic iron metabolism refers to source, storage, and function, whereas cellular iron metabolism pertains to absorption, utilization, and excretion. Both systemic and cellular processes involve many types of cells, including intestinal epithelial cells, red blood cells, macrophages, and hepatocytes [22]. The main source of iron is diet, followed by release from aged or damaged erythrocytes. In the process of iron metabolism, dietary iron is absorbed by duodenal epithelial cells, and iron is released from senescent or damaged red blood cells. Some of the absorbed iron and released iron binds transferrin and is used to generate new erythrocytes, some is involved in various biological processes, and excess iron is stored in the form of ferritin and hemosiderin in hepatocytes, macrophages, and intestinal epithelial cells. Then, when needed, iron is excreted by ferroportin 1 (FPN1) to enter the circulatory system. Therefore, iron homeostasis is determined by the balance between cellular iron absorption and cellular iron excretion.

3.1. Iron Absorption

Dietary iron consists of non-heme iron and heme iron. The main form of non-heme iron is Fe^{3+}; before it can be absorbed, it must be reduced to Fe^{2+}. The Fe^{3+} that enters the intestine is reduced to Fe^{2+} by the duodenal iron reductase cytochrome b (Dcytb) on the brush border cell membrane. After that, the divalent metal transporter 1 (DMT1) transports Fe^{2+} into intestinal epithelial cells [23]. The circulating Fe^{3+} can also bind to transferrin to form transferrin-bound iron, which is taken into vesicles after binding with transferrin receptor 1 (TFR1) [24]. Then, the vesicles release Fe^{3+}. The released Fe^{3+} is reduced to Fe^{2+} by the six‐transmembrane epithelial antigen of the prostate 3 (STEAP3) and transported into cells by DMT1 [25]. Heme iron is absorbed directly into cells by the action of the heme-specific carrier protein 1 (HCP1) [26]. In addition, hemoglobin (Hb) is released from aging or damaged erythrocytes, and the Hb combines with haptoglobin (Hp) to form a Hb-Hp complex, which is internalized by scavenger receptor CD163. The Hb is degraded, and heme is released and transferred to the cytoplasm [27]. Cytoplasmic heme is degraded by heme oxygenase 1 (HO-1) and Fe^{2+} is released [23]. The specific molecular mechanism involved in heme internalization is yet unknown.

3.2. Iron Storage, Utilization and Discharge

Iron transported into cells forms the labile iron pool (LIP). Most of the LIP is stored in bone marrow, hepatocytes, macrophages, and intestinal cells in the form of ferritin and hemosiderin [20]; this iron enters mitochondria by way of mitochondrial ferritin (MFRN), and it is used to synthesize heme and iron-sulfur cluster (Fe-S) [28]. However, the mechanism of intracellular iron localization in mitochondria is not clear. Hamdi A et al. [29] suggested that iron targets the mitochondria directly from the uptake of vesicles without entering the cytoplasm, and then the iron is delivered into the organelle matrix by the inner mitochondrial membrane protein mitoferrin 1.

Iron is transported out of cells by FPN1 on the outside of the basement membrane. The exported iron is oxidized to Fe^{3+} by hephaestin or ceruloplasmin, then the Fe^{3+} binds to transferrin and enters the system cycle [3]. Heme synthesized in the cell can be excreted directly by the heme transporter feline

leukemia virus subgroup C1 receptor (FLVCR1). In addition, intracellular iron can control iron absorption, transport, and efflux, which is achieved by regulating the mRNA translation of ferritin, TFR1, DMT1, and FPN1 by the action of the iron regulatory protein (IRP)-iron response element (IRE) system [30]. Normal iron metabolism is summarized in Figure 1.

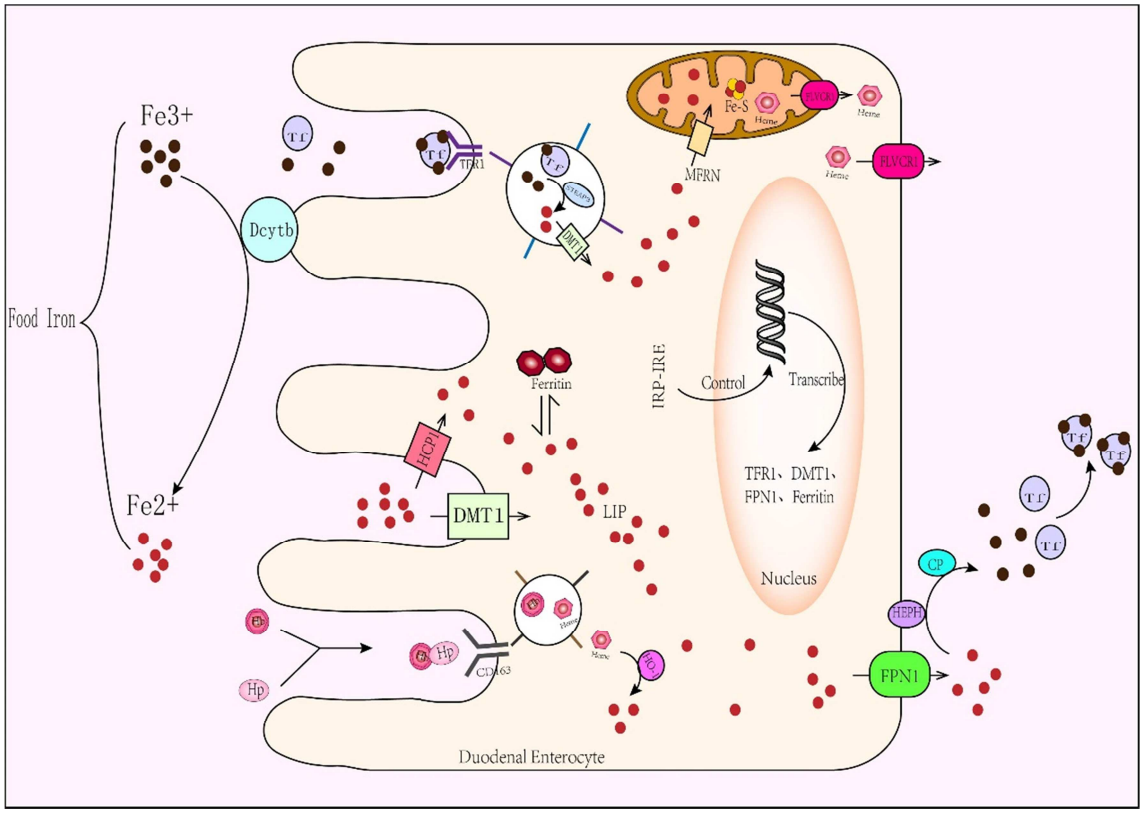

Figure 1. *Normal iron metabolism. Dcytb: duodenal cytochrome b; Tf: transferrin; TFR1: transferrin receptor 1; HCP1: heme-specific carrier protein 1; DMT1: divalent metal transporter 1; Hb: hemoglobin; Hp: haptoglobin; CD163: cluster of differentiation 163; STEAP3: six - transmembrane epithelial antigen of the prostate 3; LIP: labile iron pool; HO-1: heme oxygenase 1; MFRN: mitochondrial ferritin; Fe-S: iron-sulfur cluster; FLVCR1: feline leukemia virus subgroup C1 receptor; IRP: iron regulatory protein; IRE: iron response element; FPN1: ferroportin 1; HEPH: hephaestin; CP: ceruloplasmin.*

4. Iron Deficiency in Obesity

Hypertrophy and expansion of adipocytes can induce the surrounding tissue to form a hypoxic microenvironment, destroy intestinal epithelial tissue, and impair iron absorption. At the same time, adipose tissue releases inflammatory factors, thereby producing low-grade inflammation that induces hepcidin secretion and reduces iron excretion [31−33]. In addition, intestinal microorganisms need iron for growth and survival. The intestinal flora competes with the body for iron, which will change the structure and function of the intestinal flora, and then aggravate the iron deficiency [34]. These situations involve a variety of proteins and signaling pathways.

4.1. Iron Deficiency in Inflammation

In obese or overweight children, the number of adipocytes is increased. Expression of inflammatory mediators, such as interleukin 6 (IL-6), interleukin 1 (IL-1), tumor necrosis factor α (TNF-α), and leptin (LEP), is also increased [35, 36]. The release of inflammatory factors causes a low-grade chronic inflammatory state [31]. In such a state, hepcidin is the key hormone that regulates iron homeostasis. Hepcidin is encoded and expressed by HAMP gene, and it is a 25-amino acid peptide present in the liver [37, 38], adipocytes, macrophages, and other tissues [39, 40]. Hepcidin binds to FPN1 in hepatocytes, macrophages and intestinal cells, which promotes FPN1 internalization and degradation, thereby limiting iron output to the circulation [37, 38]. The increased concentration of inflammatory factors promotes hepcidin secretion. Interleukin 6 binds to the IL-6 α receptor to activate Janus kinase (JAK), then JAK phosphorylates signal transducer and transcriptional activator protein (STAT). Finally, SATA3 enters the nucleus and stimulates hepcidin expression. Interleukin 1β binds to bone morphogenetic protein by way of CCAAT sequence enhancer-binding protein α (CEBP-α), which phosphorylates cytosolic small-mothers-against-decapentaplegic proteins (SMAD), and SMAD enters the nucleus to activate hepcidin gene transcription [24, 38, 41]. Hepcidin can also mobilize iron reserves of liver or spleen, then indirectly regulate iron level in plasma [42]. Nemeth et al. showed that there is a binding site for nuclear factor κB (NF-κB) in the rat hepcidin gene, which suggests that hepcidin expression is regulated by NF-κB during inflammation [43]. Iron deficiency in inflammation is

shown in Figure 2.

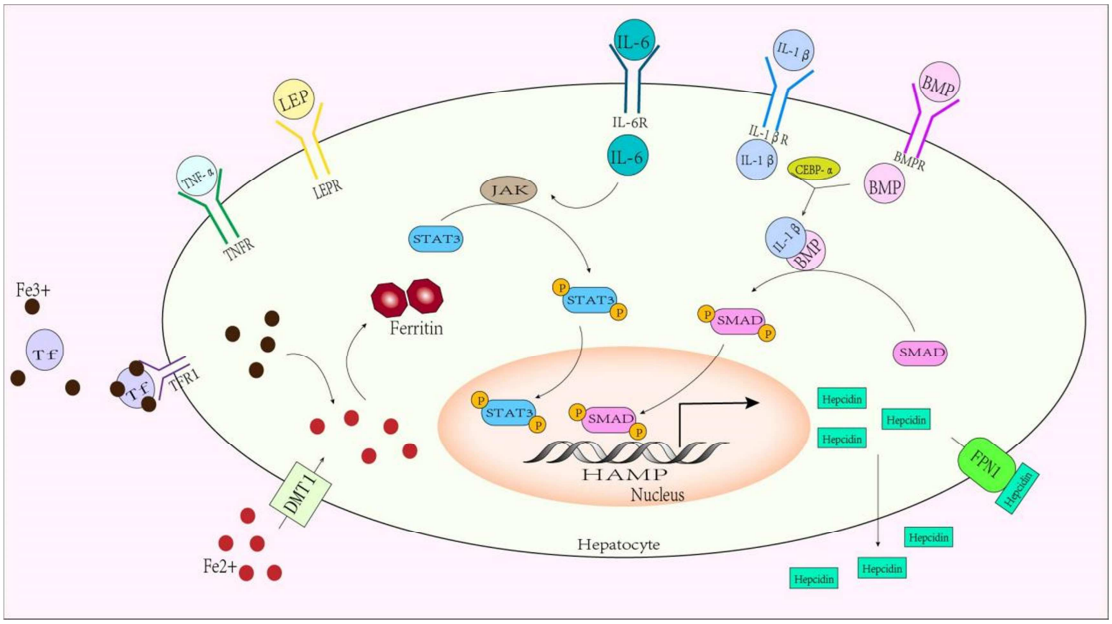

Figure 2. *Iron deficiency in inflammation. Tf: transferrin; TFR1: transferrin receptor 1; TNF-α: tumor necrosis factor α; TNFR: tumor necrosis factor receptor; LEP: leptin; LEPR: leptin receptor; DMT1: divalent metal transporter 1; IL-6: interleukin 6; IL-6R: interleukin 6 receptor; IL-1β: interleukin 1β; IL-1βR: IL-1β receptor; JAK: Janus kinase; STAT3: signal transducer and transcriptional activator protein 3; P: phosphorylation; CEBP-α: CCAAT sequence enhancer-binding protein α; BMP: bone morphogenetic protein; BMPR: bone morphogenetic protein receptor; SMAD: small - mothers - against - decapentaplegic protein; FPN1: ferroportin 1.*

4.2. Iron Deficiency in Intestinal Epithelium

Intestinal epithelial tissue is the primary location for absorption of nutrients, water, and ionic salts. The intestinal epithelium is also a barrier that protects against pathogens, bacteria, and toxins in the intestines. Iron absorption occurs mainly in the duodenum. Osbak PS et al. [32] reported that, in mice made obese by a high-fat diet (HFD), expression of tight junction protein between intestinal epithelial cells was decreased, myosin light chain phosphorylation was increased, intestinal permeability was increased, and intestinal epithelial function was impaired. In addition, in obese mice, Sonnweber T et al. [44] found that the mRNA level of Dcytb was depressed, and the reduction of Fe^{3+} was decreased; however, these decreases were compensated by increases in the protein and mRNA levels of TFR1 and DMT1. Mishra J et al. [45] reported that loss of breast cancer - resistant protein (BCRP) phosphorylation mediated by JAK3 causes dysfunction of FLVCR1 in the intestinal tract and leads to a decrease in heme output in obese people.

Intestinal crypt cells are in charge of iron absorption in duodenum. They absorb iron as transferrin-bound iron that binds the TFR1 [46]. Hepcidin in intestinal epithelial cells may inhibit the production of DMT1 by repressing transcription, which results in a decrease in Fe^{2+} absorption in the duodenum. Hepcidin can also control the LIP in duodenal crypt cells by regulating the function of the β2 microglobulin/hemochromatosis protein/transferrin receptor 1 complex in intestinal crypt cells [47]. Hepcidin can reduce the release of iron from duodenal crypt cells, thereby increasing the iron content in the LIP. The iron content in the LIP decrease the activity of IRP, and the combination of IRP and IRE reduce the expression of iron transport-related proteins such as DMT1, Dcytb, FPN1, and HEPH. When intestinal crypt cells differentiate into mature mucosal epithelial cells, the proteins used for iron absorption are reduced in abundance, and duodenal iron absorption is inhibited [48].

Human visceral fat bank is mainly omentum and mesenteric adipose tissue that exists in direct contact with the intestinal mucosa. Although obesity or being overweight can lead to systemic circulating iron deficiency and damage to various tissues and organs, iron deficiency in specific tissues and cells may have a positive influence on the health of adipose tissue. Zhang Z et al. [49] found that iron transport mediated by TFR1 was essential for the growth and maturation of white and brown adipose tissue. Moreover, adipocytes regulated intestinal lipid absorption by the iron-dependent fat-gut signal axis. Zhang Z et al. used mice whose TFR1 on adipocytes was knocked out. Compared with the control group, under the induction of HFD, the iron level in adipocytes of the knockout mice was lower, the absorption and transport of intestinal lipids were inhibited, body weight gain and body fat level were significantly lower, blood triglyceride and cholesterol levels were significantly lower, and there was less liver steatosis. These findings indicated that low iron levels in adipocytes could improve adipose function, reduce intestinal absorption of lipids, and improve obesity induced by HFD.

4.3. Iron Deficiency in an Anoxic Microenvironment

In the early stage of obesity or being overweight, the

neovascularization do not keep up with the hypertrophy and dilatation of adipocytes. This condition causes adipose tissue hypoxia and surrounding tissue ischemia and hypoxia due to the compression of the surrounding tissue, thus generating a local anoxic microenvironment [33]. Hypoxia activates the hypoxia inducible factor (HIF)-hypoxia response element (HRE) system and up-regulates hypoxia inducible factor 2 (HIF-2) [33]. In the kidney, HIF-2 promotes expression of erythropoietin, thereby increasing the production of erythrocytes and redistributing iron in tissues for erythropoiesis. This process increases the consumption of iron by red blood cells. At the same time, HIF-2α in intestinal cells increases transcription of DMT1 and Dcytb, thereby increasing iron absorption [50].

As an important cofactor of prolyl hydroxylase, iron participates in the regulation of the HIF-HRE system, which affects transcription of TFR1 and DMT1 by regulating IRP1. There is mutual inhibition between the IRP-IRE and HIF-HRE systems, i.e., IRP1 inhibits translation of HIF-2α and transcription of IRP1 is inhibited by HIF [2]. Muckenthaler MU et al. [51] showed that the 5' non-coding region of HIF-2α mRNA contains an IRE, which binds the IRP when the intracellular iron concentration decreases. This interaction inhibits HIF-2 translation, reduces iron absorption, reduces erythropoietin level, restricts production of red blood cell, and reduces iron consumption [51]. The 5' regulatory region of IRP-1 contains an HRE. In transient hypoxia, HIF binds to the HRE and reduces the level of IRP-1 mRNA and protein. However, Luo QQ et al. [52] reported that IRP-1 mRNA level was elevated in a long-term hypoxic environment. Although there is a mutual inhibitory relationship between the activities of HIF and IRP, the regulatory mechanism in hypoxia has not been fully detailed.

4.4. Iron Deficiency in Gut Microbiota

Long-term energy intake that exceeds energy consumption, especially for a high-fat diet, can lead to obesity or being overweight. Obesity and being overweight are associated with the intestinal flora, but the mechanism of this association in unclear [53−55]. A high-fat diet can increase oxygen consumption by adipocytes and the oxidation function of mitochondria [56]. In addition, intestinal microorganisms need iron for growth; when the host iron is limited, microorganisms compete for iron, thereby changing the composition and function of the intestinal flora. The quantities of Firmicutes and Proteus increase, and the quantities of Bifidobacteria and Bacteroides diminish [34, 57, 58]. The mechanism of iron competition is yet to be defined. Lactobacillus metabolites, such as 1, 3-diaminopropane and reuterin, inhibit HIF-2α by inhibiting its heterodimerization, and the metabolites increase ferritin of intestinal tract, which reduces host intestinal absorption of iron [34] because destruction of ferritin increases iron absorption capacity.

Bifidobacteria produce beneficial short-chain fatty acids [59], for example, acetate, propionate, and butyrate. Butyrate activates the erythrocyte phagocytosis ability of $CD169^+$ macrophages in bone marrow to recover and release iron, maintain the available iron level in bone marrow, and promote hematopoietic stem cells to differentiate into mature erythrocytes [60]. When the production of butyrate decreases, the amount of iron released by bone marrow macrophages decreases. This effect reduces the local iron concentration and hinders regeneration and hematopoiesis of bone marrow hematopoietic stem cells. Propionate or butyrate can reduce the ability of pathogens such as salmonella to invade intestinal epithelial cells, thereby inhibiting development of mild inflammation [61, 62]. Intestinal invasion and infection by harmful bacteria can release bacterial lipopolysaccharide that activates Toll-like receptor 4 (TLR4). This activation induces a gut stress and inflammatory response, which increases macrophage production of inflammatory factors such as IL-6 and TNF-α [63, 64]. Inflammatory factors stimulate hepatocytes to produce hepcidin. Lipopolysaccharide also induces secretion of hepcidin from intestinal myeloid type 2 conventional dendritic cells, which limits iron release from intestinal phagocytes [65]. TLR4 also activates NF-κB and promotes the expression of downstream inflammatory factors, for example, IL-6 and TNF- α, which increase hepcidin expression [66, 67].

5. Conclusion

Obesity and iron deficiency are common nutritional disorders in children, and their co-existence can produce synergistic effects leading to serious harm, which is an urgent nutritional health problem to be solved in clinic. The mechanism of obesity-associated iron deficiency is complex and may be related to inflammatory response, intestinal cells, anoxic microenvironment and intestinal flora. In the future, more research is needed to clarify the biological mechanism, find monitoring indicators and molecular biological therapeutic targets, and then conduct more accurate clinical intervention.

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