



Iron Fortification and Supplementation: Fighting Anemia of Chronic Diseases or Fueling Obesity?

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ABSTRACT

The significant worldwide increase in obesity has become a major health problem. Excess adiposity has been extensively linked to inflammation. Recently, studies have shown that dietary intake and microbiota dysbiosis can affect the health of the gut and lead to low-grade systemic inflammation, worsening the state of obesity and further exacerbating inflammation. The latter is shown to decrease iron status and potentially increase the risk of anemia by inhibiting iron absorption. Hence, anemia of obesity is independent of iron intake and does not properly respond to increased iron ingestion. Therefore, countries with a high rate of obesity should assess the health impact of fortification and supplementation with iron due to their potential drawbacks. This review tries to elucidate the relation between inflammation and iron status to better understand the etiology of anemia of obesity and chronic diseases and wisely design any dietary or medical interventions for the management of anemia and/or obesity. *Curr Dev Nutr* 2021;5:nzab032.

Keywords: inflammation, adiposity, obesity, iron metabolism, chronic diseases, gut microbiota

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Abbreviations used: ACD, anemia of chronic disease; CRP, C-reactive protein; FPN, ferroportin; HFD, high-fat diet; NCD, noncommunicable disease; NTBI, non-transferrin-bound serum iron; TLR, Toll-like receptor.

Introduction

Over the past decades, obesity has become a major public health problem. The prevalence of obesity has increased dramatically, and it has been described as an epidemic. The increase in weight and adiposity has been shown to decrease the quality of life and is associated with many noncommunicable diseases (NCDs) such as cardiovascular diseases, type 2 diabetes, cerebrovascular diseases, asthma, and cancer (1). Surprisingly, despite the low status of micronutrients among patients with obesity (2), little attention has been given to iron deficiency and anemia in obesity.

In 2019, the prevalence of anemia was estimated to be 22.8% globally (3). Anemia is most commonly caused by nutritional deficiencies of iron and vitamins and results in microcytic erythrocytes (4), making iron supplementation a predictable and first-line intervention in case of anemia. However, not all anemias are nutritional ones, and iron supplementation might not always be the answer. This review addresses anemia in the case of obesity and presents evidence that iron supplementation should be carefully administered.

Iron Metabolism, in Brief

Iron is an essential mineral that is vitally needed by the body for a number of fundamental functions, including transport of oxygen in the blood, mitochondrial energy production, and DNA synthesis (5). Iron metabolism starts when the molecules enter the stomach and the small intestine, where they are directly broken down by acid and proteolytic enzymes (6). Maximal absorption of iron occurs in the small intestine, where homeostasis is tightly regulated. In fact, the control occurs at the level of absorption (7), and no regulation takes place at the level of excretion (8). For instance, iron absorption is shown to increase in cases of deficiency through the upregulation of the duodenal iron ferroportin (FPN), divalent metal transporter 1 (DMT1), and duodenal cytochrome b (DCYTB) (9), which are involved in the transport, uptake, and reduction of ferric iron (Fe^{3+}) to the ferrous form (Fe^{2+}), respectively.

Obesity, a State of Low-Grade Inflammation

It has been widely accepted that obesity is a state of low-grade inflammation in both white and brown adipose tissues that are actively involved in

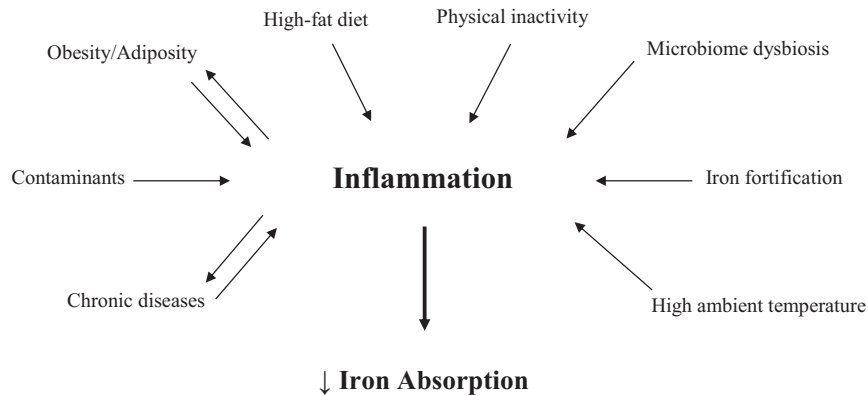


FIGURE 1 The interaction between inflammation-triggering factors.

immunity (10–12). In fact, the accumulation of activated macrophages in the adipose tissues eventually results in an increase in inflammatory responses (13–17); this was observed with a high-fat diet (HFD) that is associated with an upsurge in the expression of adhesion molecules in adipose tissues, leading to leukocyte accumulation (18).

Adipocytes are known for their endocrine function, which is tightly involved in the regulation of inflammation through the release of proinflammatory cytokines (19). This is the reason why studies have focused on adipocytes as inflammatory mediators in obesity (11, 17). In fact, adipocyte hypertrophy, usually seen in obesity, further secretes proinflammatory cytokines, adipokines, lipokines, and other molecules such as TNF- α , IL-6, leptin, and resistin (19, 20) that exacerbate the existing inflammation. This increased release is caused by the state of hypoxia induced by the reduced blood supply to the multiplied adipocytes (17). Interestingly, IL-6 concentrations were reported to correlate with BMI significantly, and the concentrations were reduced in patients post-bariatric surgery (21).

Other than the proinflammatory markers secreted, adipose tissue releases fatty acids. Free SFAs accumulate in the liver and other organs, which, in turn, activate the Toll-like receptor (TLR) family, leading to an increased inflammatory state and susceptibility to further develop non-communicable chronic diseases (nonalcoholic fatty liver disease and insulin resistance) (22). The activation of TLR4 was reported to induce inflammation and increase adiposity (23). These mechanisms are regulated by the inflammatory pathways c-Jun N-terminal kinase/inhibitor of κ B kinase (JNK/IKK) and nutrient sensor mammalian target of rapamycin (mTOR), along with the serine/threonine kinase Akt pathway (22, 23). In addition, IL-6, along with free fatty acid drainage, is one of the most prominent modulators of C-reactive protein (CRP) production in the liver, which is in itself linked to obesity (24, 25).

Other Factors Affecting Inflammation

Other than adiposity, the inflammatory status is known to be associated with several factors (10), such as physical activity and lifestyle (26), HFD (27, 28), environmental factors (e.g., temperature) (discussed below), microbiome dysbiosis (discussed below), chronic diseases (insulin resistance, cardiovascular diseases, pulmonary arterial hypertension,

Alzheimer disease, and others) (29–32), and some micronutrient supplementation including iron (discussed below). An interplay between these factors exists (Figure 1), which increases the severity of the inflammation, hence complicating the situation and the potential treatment. The following sections describe how some of these factors contribute to inflammation.

Environmental factors

The incidence of infections is known to be affected by seasonal variations, in which the majority of infections increase with elevated ambient temperatures (33). It has been stated that, during the summer season—hence, under conditions of high temperature and humidity—there is an increase in gram-negative bacteria (such as *Escherichia coli*) in the bloodstream (34), in addition to other types of bacteria that cause several enterically transmitted diseases (33). The occurrence of these infections is highly correlated with the induction of inflammation.

On the other hand, other than the outdoor atmospheric conditions, environmental and industrial toxicants also contribute significantly. The rapid change and rise in urbanization over the last centuries brought a sudden and severe increase in exposure to xenobiotics, including air pollutants, hazardous waste products, and industrial chemicals (per- and polyfluoroalkyl, bisphenols, polycyclic aromatic hydrocarbons, etc.) (10). The inflammatory activity is promoted through induced oxidative stress by cytotoxins (35).

Gut microbiota

Both genetics and diet have been shown to affect microbiota composition, impair gut barrier function, and eventually lead to gut inflammation. However, scientific data have suggested that the quality of the diet influences the quality of the gut bacteria more than weight and genetic status do (36). Indeed, the gut microbiota plays a pivotal role in energy harvest, storage, and expenditure (37, 38). Furthermore, the gut microbiota alters lipid metabolism by enhancing the storage of liver-derived triglycerides and increasing the activity of lipoprotein lipase (LPL) (39–41). This illustrates how an HFD alters gut microbiota and leads to diet-induced intestinal inflammation (42). It has been suggested that the consumption of an HFD, even prior to the development of weight gain,

adiposity, and insulin resistance, can induce changes in the intestine, further exacerbating inflammation (11, 43).

In fact, emerging evidence from animal models has highlighted the contribution of the gut microbiota to obesity-associated inflammation (11, 44). Among moderately obese Danish people (45) and severely obese French women (46), gut microbiome composition showed significant changes with higher fat mass, proinflammatory markers, and insulin resistance (10). The alteration of the bacteria composition and the increase in LPS are associated with intestinal permeability, mucosal damage, and endotoxemia and are proposed to be activated through TLRs (10, 47, 48). The latter would cause an increased release of endotoxins and cytokines (TNF- α , NF- κ B, IL-1, IL-6, IL-17, etc.) (49, 50) in the circulation, worsening the inflammatory state and ultimately increasing the risk of adiposity, metabolic disorders, and poor iron status.

Mediators between Iron and Inflammation

Ferritin and hepcidin are key mediators for the regulation of iron homeostasis (51, 52), and they both happen to be acute-phase reactants (53), playing important roles in inflammatory processes. Ferritin, the primary iron storage protein, helps in the transport (54) and the release of iron in a very controlled fashion (55). Hepcidin, on the other hand, acts by altering the FPN function and therefore decreases iron release in the blood (51). The concentration of hepcidin is synergistically related to ferritin, and their increased concentrations are associated with reduced iron absorption (56). Together, they decrease under conditions of low iron availability and increase following iron supplementation (57, 58). Furthermore, the secretion of both hepcidin and ferritin from hepatocytes is induced by infection and inflammation, and suppressed by hypoxia (56, 59). Other than the classical hepatic secretory pathways, these compounds can derive from several different organs. For instance, proximal tubule kidney cells and the splenic macrophages form potential sources of ferritin (60). Hepcidin can also be secreted by adipose tissues, macrophages, and pancreatic islet cells. Therefore, these proteins can act as a double-edged sword where their constantly elevated concentrations in the blood, due to reasons other than high iron availability, can lead to defective duodenal iron absorption (31, 61) and increased macrophage recycling (31, 62).

Iron Metabolism under Inflammation

Iron metabolism is affected by both dietary factors and inflammation. Under conditions of inflammation, anemia of chronic diseases (ACD), also known as anemia of inflammation, may develop. This makes it the second most common type of anemia following iron deficiency anemia, leading to abnormal intracellular sequestration of iron and a decrease in circulating iron (63, 64). ACD is thought to be a consequence of the host defense response mediated by inflammatory cytokines and TNF (29).

Anemia of chronic diseases

ACD is characterized by iron restriction, reduced iron absorption, diminished erythropoiesis (decreased erythrocyte production), and shortened erythrocyte lifespan (65). Iron restriction, when the amount of iron available for the synthesis of hemoglobin is restrained, is influ-

enced by a systemic immune activation where iron trafficking changes, leading to retention of iron in the cells and reduction in intestinal iron absorption (63, 64). Iron sequestration in macrophages and other cells, a hepcidin-independent regulatory mechanistic response to inflammation through the activation of TLR2 and TLR6 (66), is a hallmark of ACD (63, 67). The TLR pathways inhibit macrophage iron release via direct interaction with FPN, the protein iron transporter (68), hence leading to a reduction in iron export from cells into the plasma (69). This phenomenon is considered protective and defensive against bacterial growth and the development of oxidative damage that would otherwise aggravate inflammation (67). This status leads to iron overload and thus increases the rate of tissue injury and organ failure (70) that would contribute to the development of chronic diseases and complications. The mechanisms are stimulated by LPS, through the release of lipocalin-2 from macrophages (71) and multiple inflammatory cytokines, such as IL-6, which enhances the activity of hepcidin via the signal transducer and activator of transcription 3 (STAT3) (63, 64). Another pathway involved in ACD is the suppression of the hormone erythropoietin and, thus, erythropoietic activity (64), resulting in a decrease in RBC count. In addition to their reduced production, erythrocyte numbers are further diminished due to their destruction. The lifespan of erythrocytes decreases through erythrophagocytosis by hepatic and splenic macrophages (64).

ACD can be inferred by several indicators, including elevated neutrophils, monocytes, and platelets (64). Serum iron and transferrin saturation can also be used as signs of ACD because their concentrations tend to decrease in this type of anemia as well, indicating limited iron supply to erythrons (72, 73). Due to the boost in inflammatory markers, the increase in the positive acute-phase reactants, hepcidin and ferritin, constitutes one of the strongest trademarks in ACD.

In case of obesity

Figure 2 illustrates the vicious cycle that takes place between obesity, inflammation, and low iron status. The association between the above-mentioned indicators and low iron status or anemia has been explored in the context of obesity (30, 74–76). The increase in the size and number of adipocytes in obesity stimulates the secretion of leptin, CRP, IL-6, and other proinflammatory cytokines, which amplify hepcidin release from hepatocytes and lipocalin-2 synthesis from adipocytes and mononuclear cells, restricting the production of erythrocytes (69, 71, 77, 78). In support, hepcidin concentrations were reported to be related to children's and adolescents' BMI (79). In addition to those of CRP, the concentrations of hepcidin were found to increase with BMI in adults (80, 81). Similarly, it has been shown that the low iron status of overweight children was associated with an increase in hepcidin concentrations despite high dietary iron intake (78).

Moreover, marked central adiposity is associated with increased serum hepcidin concentrations, hence causing a greater impairment in iron homeostasis and reduced iron absorption from supplements (76). In support, low iron status among obese Mexican children and women was found to be the result of inflammation rather than low dietary iron intake (69). Indeed, adiposity has also been associated with reduced iron absorption in response to iron fortification (82, 83). Data from Thai women and Indian and Moroccan children confirmed the inverse association between BMI and iron absorption (82). Higher adiposity was accompanied by less improvement in iron status upon fortification or

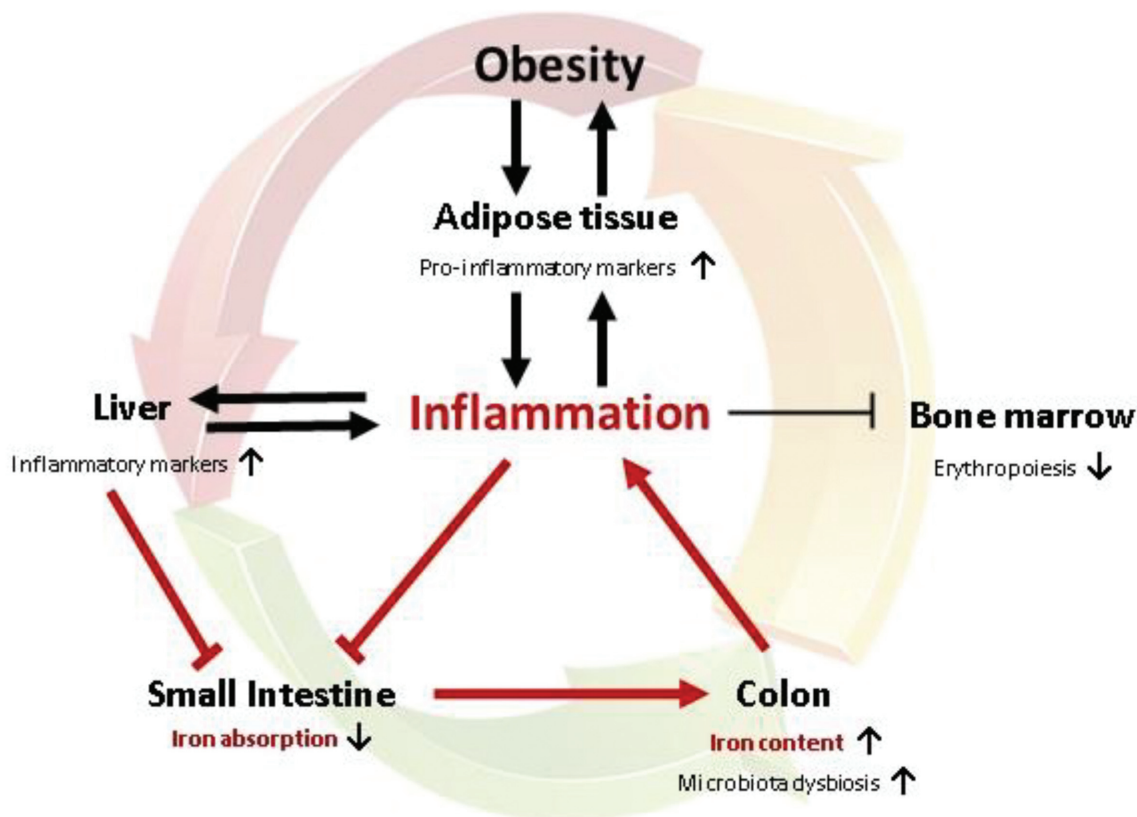


FIGURE 2 The vicious cycle between obesity, inflammation, and low iron status.

supplementation (82, 83). Furthermore, ferritin is also increased in anemia of obesity due to high adiposity (72). The constantly elevated ferritin concentrations (due to high adiposity) are considered a trademark of dysregulated iron homeostasis in the presence of inflammation, obesity, and metabolic syndrome (84, 85). Therefore, the inflammation caused by adiposity can play a role in the hypoferrremia of obesity (69). This type of metabolic syndrome is referred to as the dysmetabolic iron overload syndrome (31). A recent work elicited the differences in iron concentrations between metabolically healthy and metabolically unhealthy prepubertal children with obesity (75). In their study, the authors showed that metabolically unhealthy obese children have higher ferritin concentrations than metabolically healthy obese children, which could possibly be linked to liver function and injuries (75). This has also been confirmed in previous studies that showed a positive association of BMI with plasma ferritin but negative with serum iron (85–87).

On the other hand, weight loss was shown to reduce hepcidin concentration and improve the iron status of obese children (88) and adults (89). Both iron status and inflammation were improved by weight reduction, and the improvement in inflammatory markers during weight reduction was independently associated with enhanced iron status (13). In brief, low iron status and anemia of obesity seem to be highly attributed to inflammation rather than iron intake. In fact, iron intake was reported to be equal, if not higher, among people with obesity compared with people with normal weight (69, 78). Thus, it is crucial to understand the potential sources of inflammation in order to address the problem.

A reciprocal relationship

The association between chronic diseases and iron metabolism is reciprocal; the markers of iron status, when elevated, affect normal physiology, and vice versa some conditions may directly disrupt iron metabolism. Elevated concentrations of hepcidin in obese subjects can potentially increase the risk of NCDs, such as cardiovascular diseases, through the increased level of inflammation, which is a primary causal factor in NCDs (29, 30). In fact, iron has the ability to accelerate the oxidation of LDLs, which are taken up by the receptors on macrophages, leading to the development of foam cells, and eventually atherosclerosis (72, 90).

In addition, elevated concentrations of ferritin, as well as other iron markers such as transferrin, serum iron, and non-transferrin-bound serum iron (NTBI), have been associated with peripheral insulin resistance at the level of the adipose tissues (91) and the skeletal muscles (32)—thus, with type 2 diabetes, blood pressure, and high cholesterol concentrations (31). An interesting review illustrated the importance of NTBI in iron homeostasis (92). In fact, the inflammation caused by adiposity can affect macrophage-mediated iron recycling (29). The metabolism of iron by macrophages (93) increases the risk of cardiovascular mortality (90) and carotid atheroma (94). Furthermore, high iron stores among women with polycystic ovarian syndrome were attributed to hyperinsulinemia and insulin resistance rather than reduced menstrual losses (95). Therefore, iron metabolism and chronic diseases are deeply intertwined, and they grossly influence one another due to several pathways, including the involvement of oxidative stress, where iron plays a key role as a pro-oxidant when it is found in excess.

Iron Supplementation under Inflammation

Iron supplementation was reported to be coupled with several unfavorable consequences, especially in areas with a high rate of infectious diseases, like malaria, as well as in subclinical inflammation (96, 97). Iron supplementation was associated with increased rates and severity of infections, hospital admissions, and mortality in young children (98, 99). In a study examining the role of iron on production of proinflammatory markers, it has been reported that iron supplementation increases neutrophil counts and proinflammatory cytokine production in the colon of IL-10 knock-out mice (100). These results are thought to be linked to the increased reactive oxygen species release through the Fenton reaction, which is mediated by NF- κ B, a transcription factor that regulates the gene expression of many inflammatory markers (100). A follow-up study in Sri-Lankan women looking at the change of baseline iron concentrations post-iron supplementation showed that women with low-grade inflammation and a BMI (kg/m²) >25 did not benefit from iron supplementation (101). The interplay between iron fortification and obesity is elucidated among the low-socioeconomic-status populations with high obesity rates (102), whose diets are high in carbohydrates (103). They are more likely to consume more iron from the subsidized iron fortification of wheat flour. In addition, iron fortification of anemic African children was reported to produce a potentially more pathogenic gut microbiota profile, which, in turn, was associated with increased gut inflammation (104), a suggested contributor to the increased risk of developing diarrhea upon oral iron administration (105). Similar results were found in a study conducted in African infants (106); iron fortification increased the abundance of specific enteropathogens (such as *E. coli*) and fecal calprotectin concentrations in infants. These consequences may have been partially attributed to the increased iron availability for bacterial growth. In line with these findings, researchers concluded that iron administration might impair intestinal integrity due to the pro-oxidative characteristics of iron (107). The oxidative damage in the gut increases its permeability, hence increasing the susceptibility to infectious diseases (107). The same concept was supported by the *E. coli* sepsis outbreak in the 1970s that affected New Zealander children who received intravascular iron supplementation over a short-term period (99). However, most cases recovered only after the cessation of the supplementation (99).

In this same context, it has been shown that anemic patients with chronic kidney disease have low responsiveness to erythropoiesis-stimulating agents, including intravenous iron administration (56), which supports the recommendation of the assessment of ferritin and hepcidin concentrations before any pharmacological supplementation. High iron administration elevates concentrations of ferritin and hepcidin, which inhibit iron absorption and macrophage recycling, and consequently reduce iron availability for use (56). This leads to a further increase in the inflammatory markers and exacerbation of the deficiency.

Fate of Unabsorbed Iron

Whether due to obesity or any other reason, inflammation reduces the percentage of iron absorption and increases the concentration of unabsorbed iron in the gut under conditions of supplementation or for-

tification, rendering it as a substrate for bacterial growth (108). This is one of the reasons why arbitrary iron supplementation should be carefully adopted, as it can be inefficient or even have undesirable effects (109). Several studies have highlighted the fate of unabsorbed iron on bacteria. It has been stated that iron serves as an essential substrate for microbial pathogen growth, acts as a gastric irritant, and increases inflammatory markers (110). Iron uptake in the upper intestine is limited; thus, any additional unabsorbed amount will eventually enter the colon and be available for gut microbiota (111). In addition, some bacteria have the capacity to store iron within their entities. For instance, an oligomeric protein in bacterioferritin contains heme in the form of protoporphyrin IX and helps the bacteria store iron for later energy production and biosynthesis (112).

Once the gut microbiota changes by excess iron, the responsiveness of the immune system may be altered. Several studies have proved the latter concept. It has been shown that the expression of antimicrobial agents such as lipocalin-2 was reduced during infection episodes only when the person was receiving iron supplementation (111). Note that lipocalin-2 plays a crucial role in iron homeostasis and innate immunity by withholding iron from bacterial pathogens (111). In addition, the alteration of the bacterial composition and the increase in LPS are associated with intestinal permeability, mucosal damage, and endotoxemia, and are proposed to be activated through TLRs (10, 47, 48). The latter would cause an increased release of endotoxins and cytokines (TNF- α , NF- κ B, IL-1, IL-6, IL-17, etc.) (49, 50) in the circulation, worsening the inflammatory state and ultimately increasing the risk of adiposity, metabolic disorders, and poor iron status.

Studies conducted in Pakistani (113) and African (106) children have all concluded that iron supplementation increases the colonic iron concentration and reduces the concentrations of beneficial barrier commensal gut bacteria such as bifidobacteria and lactobacilli, while it increases the count of the pathogenic bacteria, including the enteropathogenic *E. coli* (68, 108). Evidence shows that iron fortification establishes a pathogenic ground for gut inflammation (104). In this regard, an in vitro study confirmed that pathogenic overgrowth is induced upon increasing iron availability; this includes the growth of *Salmonella* Typhimurium (114). However, in this study, iron did not affect the count of the nonpathogenic *Lactobacillus* Plantarum (114). Hence, it has become clear that unabsorbed iron promotes the virulence and replication of enteric pathogens, favors dysbiosis, exacerbates existing inflammation, and contributes to the development of obesity (69).

Conclusions

Low iron status is known to be treated through iron supplementation. However, this approach has to be carefully recommended in case of obesity as it holds potential side effects. People with obesity, a state of chronic low-grade inflammation, suffer from a type of anemia similar to ACD characterized by poor iron absorption, diminished erythropoiesis, and short erythrocyte lifespan. When iron is not properly absorbed, a significant fraction goes into the gut and serves as nutrients for the bacteria. Consequently, the supplementation in this particular case alters the gut microbiota, stimulates the release of proinflammatory markers, and further exacerbates the former inflammation that can also trigger and aggravate the status of obesity. In conclusion, iron

supplementation should be carefully recommended and closely monitored in case of obesity. Ideally, we suggest that people with obesity treat their prevailing inflammation before curing their anemia.

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