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Metabolic and Inflammatory Aspects of Iron Deficiency in Obese

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Abstract:
Obesity is a chronic disease with a complex etiology, characterized by a persistent inflammatory state induced by various pro-inflammatory cytokines, including interleukin-6. This condition leads to increased production of hepcidin, a protein hormone responsible for regulating iron homeostasis. Hepcidin's primary function is to inhibit iron absorption by enterocytes, the cells lining the small intestine. Symptoms of iron deficiency, which is crucial for oxygen transport, energy production, and immune system support, can be varied and often nonspecific, such as general weakness, pallor, or concentration difficulties, potentially prolonging the diagnostic process. This article aims to analyze the relationship between obesity and iron deficiency in the metabolic context. Obesity, being one of the most prevalent health issues of the modern world, is associated with numerous complications, including disturbances in iron metabolism. Iron deficiency in obese individuals can lead to anemia, reduced physical performance, and cognitive impairments. Traditional treatment methods for this micronutrient deficiency involve supplementation. However, supplementation shows reduced efficacy in overweight and obese individuals, likely due to elevated hepcidin levels. A more effective approach should include interventions targeting not only the supplementation of the missing micronutrient but also weight reduction.

Keywords: obesity, iron, iron deficiency, hepcidin, inflammation, adipose tissue

Introduction

In contemporary society, obesity and iron deficiency have become significant global health issues, affecting millions of individuals daily.[1] These two conditions are not random combinations. They directly influence each other at the biochemical and molecular levels. Undoubtedly, obesity is the most commonly occurring metabolic disease in the world. The WHO defines obesity as an abnormal or excessive fat accumulation that presents a risk to health. It is primarily the result of a prolonged positive energy balance, where energy intake exceeds energy expenditure.[2] The increase in the number of overweight and obese people is primarily the result of a sedentary lifestyle and stress, which is most often accompanied by a diet rich in simple carbohydrates and saturated fats, which stimulates lipogenesis, leading to metabolic disorders in adipose tissue.[3] Interestingly, the prevalence of obesity among adults is only marginally higher in women than in men. [4] Obesity leads to numerous complications, including cardiovascular diseases, type 2 diabetes, osteoarthritis, and malignant tumors. All these complications result in a decreased quality of life and a shortened life expectancy. European research clearly shows that excess body fat, regardless of its type, is significantly associated with an increased risk of premature death. Obesity can shorten life expectancy by as much as 8–10 years compared to people with a normal body weight.[5] Disorders of iron metabolism, including its deficiency, can lead to anemia, reduced physical performance, as well as cognitive disorders.[6]

Aim of the study

The aim of this study is to analyze the complex relationship between obesity and iron deficiency, with a particular focus on the metabolic and inflammatory mechanisms that contribute to disturbances in iron homeostasis in obese individuals. This article seeks to investigate how chronic inflammation associated with excess adipose tissue leads to elevated levels of hepcidin, a key regulator of iron metabolism, and how this impacts iron absorption and metabolism. Additionally, the study aims to evaluate the efficacy of traditional iron supplementation in obese patients and to propose more comprehensive treatment strategies that include weight reduction and dietary interventions to improve iron metabolism and overall health outcomes. This article based on a literature review that has facilitated the collection and analysis of current data on this topic, forming the basis for the conclusions drawn.

Obesity diagnostics:

Body Mass Index (BMI) is undoubtedly the most important and widely used screening tool for diagnosing obesity and overweight. A BMI over 30 is classified as obese. However, it is essential to recognize that this metric has its advantages and limitations. BMI varies with age, sex, and even ethnic background. Furthermore, it does not account for the proportion or distribution of body fat relative to muscle tissue, nor does it reflect hydration status. Therefore, BMI should not be routinely used to assess excess body fat in individuals with sarcopenia or athletes. It is also not appropriate for evaluating body fat in pregnant women.[7] The previously mentioned athletes and bodybuilders, due to their significantly developed muscle body, are characterized by an increased BMI value, which, of course, does not directly correlate with their health. For children, a BMI less than the fifth percentile is underweight and above 95.

Percentile child is considered obese. [8] it is also important to note that in individuals with overweight (BMI >25) or class I obesity (BMI 30-34.9), measuring waist circumference is crucial. This measurement serves as an indirect indicator of visceral fat distribution and allows for the assessment of metabolic risk. According to the diagnostic criteria of the International Diabetes Federation (IDF) for European adults, abdominal obesity is identified with a waist circumference ≥94 cm in men and ≥80 cm in women. Abdominal obesity is associated with an increased cardiovascular risk.[9] Another simple parameter that can be used to assess the distribution of adipose tissue in the body is the waist-to-hip index (WHR), which is calculated as the quotient of waist and hip circumference (in centimeters), according to which abdominal obesity is diagnosed with WHR >0.85 in women and WHR >0.9 in men.[7]

BMI = weight (in kg)/ height^2 (in m^2)

Severe underweight: BMI below 16.5 kg/m²
Underweight: BMI below 18.5 kg/m²
Normal weight: BMI from 18.5 to 24.9 kg/m²
Overweight: BMI from 25 to 29.9 kg/m²
Obesity: BMI of 30 kg/m² or higher

- **Class I obesity**: BMI from 30 to 34.9 kg/m²
- **Class II obesity**: BMI from 35 to 39.9 kg/m²
- **Class III obesity**: BMI of 40 kg/m² or higher, also referred to as extreme obesity

Addipose tissue/Adipocyte

Obesity is characterized by an excessive accumulation of adipose tissue, which is a type of connective tissue. The primary structural component of this tissue is adipocytes, which are the largest energy reservoir in the body. They store energy in the form of triglycerides. To accommodate lipids, adipocytes can increase their diameter by up to 20 times and their volume by several thousand times. Lipids make up 90% of the adipocyte's volume. The release of triglycerides from adipose tissue is facilitated by the action of hormone-sensitive lipase and lipoprotein lipase. [11]. Furthermore, adipose tissue is also a complex and highly active metabolic and endocrine organ. Among its functions, it produces leptin, which informs the brain, specifically the hypothalamus, about the level of stored fat in the body. It also produces TNF-α, a key mediator of inflammation, which induces the production of other pro-inflammatory cytokines such as IL-1 and IL-6, as well as chemokines. Resistin, produced by adipocytes, is a protein and pro-inflammatory cytokine that also promotes insulin resistance.[12] Certainly, adipose tissue produces a range of other substances that act both autocrinely and paracrinely, contributing to the broader regulation of body homeostasis. [13]

Iron Bioavailability

By definition, bioavailability refers to the ability to absorb, utilize, and process a substance for the body's needs. There are numerous factors that can directly influence iron bioavailability and make it more challenging to achieve. These primarily involve the efficient delivery of iron through the diet.

It is important to note that not only iron deficiency is associated with serious health consequences, but also excess iron in the body can be dangerous and even toxic. Excessive iron stimulates the formation of reactive oxygen species, which cause lipid peroxidation, DNA damage, and tissue fibrosis. [14] Dietary iron exists in two forms: heme and non-heme iron. Heme iron, which is derived from hemoglobin and myoglobin, is found in animal meat, poultry, and fish, and is readily absorbed. Non-heme iron is predominantly found in plant foods such as beans, nuts, dark chocolate, legumes, spinach, and fortified grains. Although non-heme iron has approximately two-thirds the bioavailability of heme iron, it is not as readily absorbed.[15] it is estimated that the bioavailability of iron ranges from 14% to 18% in individuals consuming animal-based products, while it is only 5% to 12% in those consuming plant-based products.[16] Iron deficiency occurs when the total iron stores in the body are low or when inflammation causes the sequestration of iron in the plasma, particularly through the action of hepcidin, the principal regulator of systemic iron homeostasis.[17]

Iron Absorption and Metabolism

Iron metabolism must be tightly regulated at both cellular and systemic levels to prevent both deficiency and excess. Excess iron in the body is dangerous and can be toxic, as it promotes the formation of reactive oxygen species. These species lead to lipid peroxidation, DNA damage, and tissue fibrosis.[18] Iron is the fourth most abundant element in the Earth's crust, yet its absorption and metabolism are highly complex processes. Heme iron (Fe^{2+}) is absorbed via endocytosis by enterocytes in the proximal duodenum through the Divalent Metal Transporter 1 (DMT1). Non-heme iron (Fe^{3+}), however, must be reduced to Fe^{2+}, a process facilitated by a reductase enzyme located on the surface of enterocytes. Once absorbed, Fe^{2+} can be stored within enterocytes as ferritin, a protein that binds iron and protects the cell from its toxic effects. Alternatively, it can be transported into the bloodstream.[19] Only 1-2 mg of iron are absorbed daily in the gastrointestinal tract, compensating for a similar amount of loss; the majority of iron is recycled by macrophages following the phagocytosis of erythrocytes. [20] It is primarily found in hemoglobin, ferritin as well as in other heme and non-heme proteins. [21] Humans don’t have an active iron excretion system therefore, intestinal iron absorption is essential for maintaining iron homeostasis in the body. Iron is involved in several critical functions within the human organism, including oxygen transport and storage, energy production, hormone synthesis and the proper functioning of the immune system. [22]

Obesity and Inflammation

Inflammation is a physiological and rapid response of the body to harmful external and internal environmental factors that derange homeostasis and could result in tissue damage. It involves the mobilization of immune cells that aid in combating pathogens. A proper inflammatory response includes the delivery of plasma components and leukocytes to the site of injury, initiated by macrophages and mast cells in the tissues. This process leads to the production of various inflammatory mediators. In contrast, obesity induces a chronic, low-grade inflammatory state throughout the body. [23] This occurs because adipose tissue produces a significant amount of pro-inflammatory cytokines, including TNF-α, IL-6, leptin, adiponectin, and resistin, which are examples of adipokines.[24]

Hepcidin:

Hepcidin is a crucial 25-amino acid peptide hormone produced by hepatocytes in response to iron overload, inflammation, hypoxia, or anemia. [25] Hepcidin reduces circulating iron levels by binding to and inducing the degradation of ferroportin. Ferroportin is a protein responsible for the release of iron from cells into the bloodstream. [26] Additionally, hepcidin slows the release of iron from macrophages.[27] Elevated levels of hepcidin are directly associated with chronic diseases that involve inflammatory states. Disruptions in iron metabolism are often among the initial manifestations of these conditions, potentially leading to microcytic anemia with a range of diverse, often nonspecific symptoms. Conversely, decreased levels of hepcidin can result in iron overload, as seen in hemochromatosis. The synthesis of hepcidin by hepatocytes is transcriptionally regulated by IL-6 via the STAT-3 signaling pathway. Increased pro-inflammatory IL-6 stimulates hepcidin production, thereby reducing iron absorption. [28]

Iron deficiency anemia

Iron deficiency anemia is the most common type of anemia.[29] Its development is predisposed by impaired heme synthesis due to iron deficiency in the body. It is characterized by the presence of small erythrocytes with reduced hemoglobin content. [30] It may result from a systemic inflammatory state triggered by expanded adipose tissue, which produces elevated levels of pro-inflammatory cytokines. Disruption of heme synthesis represents one of the most severe consequences of obesity. Furthermore, it can be hypothesized that pro-inflammatory cytokines disrupt the production of erythropoietin.[31] The primary treatment for iron deficiency anemia involves the regular administration of iron supplements, either orally or intravenously. It is also important to periodically monitor hemoglobin and ferritin levels to confirm the effectiveness of the therapy. The mode of iron supplementation depends on the patient's condition and the severity of the anemia.[32] The efficacy of iron supplementation is notably diminished in individuals with overweight and obesity compared to those with normal body weight. This reduced effectiveness is attributable to impaired iron absorption resulting from elevated hepcidin levels associated with excessive body weight. Elevated hepcidin levels inhibit both iron absorption and the mobilization of iron stores, leading to decreased iron bioavailability in obese individuals. Consequently, microcytic anemia related to obesity presents significant treatment challenges. The primary therapeutic recommendation for obese patients is weight reduction, achieved through a well-balanced diet and increased physical activity. Reducing adipose tissue can decrease pro-inflammatory cytokine levels, which may subsequently lower hepcidin levels and enhance iron homeostasis. [33]

Conclusion

Obesity is a multifaceted health condition with profound effects on iron metabolism and systemic homeostasis. The chronic inflammatory state associated with obesity, mediated by pro-inflammatory cytokines such as interleukin-6, leads to elevated hepcidin levels. Hepcidin, a pivotal regulator of iron metabolism, inhibits both gastrointestinal iron absorption and the mobilization of iron from storage sites. This dysregulation results in iron deficiency, which can present as anemia, diminished physical capacity, and potentially impaired cognitive function.

Traditional iron deficiency treatments, primarily involving supplementation, are markedly less effective in individuals with obesity. This reduced efficacy is likely attributable to the increased hepcidin levels induced by the persistent inflammatory state. Consequently, a comprehensive approach to managing iron deficiency in the context of obesity should incorporate strategies for weight reduction. Such strategies can mitigate inflammatory responses and restore optimal iron homeostasis. Interventions including dietary modification and enhanced physical activity may significantly improve iron absorption and overall health in obese individuals.

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