КЛІНІЧНА МЕДИЦИНА

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THE PATHOGENESIS OF IRON DEFICIENCY ANEMIA IN OBESITY*

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Залізодефіцитна анемія та ожиріння стали глобальними проблемами, які стосуються не тільки країн з високим рівнем якості життя, але й країн, що розвиваються. Експериментальні та клінічні дослідження вказують на те, що існує взаємозв'язок між метаболізмом мікроелемента заліза та надмірним накопиченням білої жирової тканини. Ожиріння пов'язане з низько інтенсивним хронічним запаленням та збільшеним рівнем концентрації гепсидину в крові. Гепсидин є ключовим регулятором системного гомеостазу мікроелемента заліза. У цьому огляді узагальнено сучасні уявлення про зміни гомеостазу заліза при ожирінні та наведено припущення щодо лікування.

Ключові слова: ожиріння, низько інтенсивне хронічне запалення, гепсидин, залізодефіцитна анемія.

Introduction

Iron deficiency anemia and obesity are global health problems that occur in everyday activities of various medical practices. They affect not only medical aspects but also social - economic aspects and disrupt the quality of life of these patients.

Iron deficiency anemia is the leading cause of anemia and is found in more than 2 billion people around the world. This statistic was confirmed by analyzing a large number of reports from 187 countries from 1990 to 2010[1] and showed a decrease in quality of life, low productivity, difficulty concentrating, decreased cognitive functions, weakness and fatigue.

Obesity is a common metabolic disease and is characterized by excessive accumulation of white adipose tissue due to increased food intake and lifestyle changes. [2] As of 2014 more than 1.9 billion people aged 18 and older are overweight and 600 million are clinically obese; [3] this puts them at risk of many diseases including metabolic syndrome, diabetes, cardiovascular disease and cancer.

There is a standing close relationship between the metabolism of iron and obesity due to immunological abnormalities in molecular - biological level.

Unfortunately, there are still unanswered questions about the prognosis and treatment of obesity in combination with iron deficiency anemia and the effects on the common pathogenetic links of these diseases.

Hypotheses of hypoferremia in obesity

Wenzel et al (1962) first reported on the link between the iron metabolism and obesity. They found lower concentrations of iron in the blood serum in adolescents with obesity compared to individuals who had normal weight. These findings were confirmed by subsequent studies.

In recent decades, formed three main hypotheses of hypoferremia obesity have been suggested:

– Nutritional hypothesis, which establishes iron deficiency as comorbidity obesity in different age groups, irrespective of its consumption.[4]

– The blood volume hypothesis to increase blood volume in patients with obesity due to weight gain, which was confirmed only in experiments. [5]

– The inflammatory hypothesis [6] is based on the participation of systemic inflammation in violation disruption of the iron metabolism in obesity. This hypothesis is the most reasonable and is logically combined with previous research on low-grade systemic inflammation as a new model of the pathological process.

Revealing the essence of this hypothesis is in the should pay attention to two key components: low-grade systemic inflammation and dysregulation of iron metabolism involving hepcidin - a peptide hormone that is the primary regulator of systemic iron metabolism protein, mediated immune defense and inflammation. [7]

One of the definitions of "inflammation" is a series of cellular and humoral responses aimed at protecting the body from various injuries, including infection and eventually leads to the restoration of functional and morphological integrity of the affected tissue; [8] it is generally characterized by increased local and systemic cytokine levels, with increasing numbers of immune cells (primarily neutrophils) that enter the site of inflammation, dominating mainly in the acute phases and macrophages in more chronic conditions. [9] Chronic systemic inflammation is characterized by increased cytokines by 3-5 times, but remains consistently high. [10]

Low-grade systemic inflammation transforms abnormal external and internal stimuli to disrupt intracellular metabolism; this leads to chronic internal diseases. The effect of it in the hyperactivation of the immune system is caused by the disruption of the normal human biology. [11]

Although, in many ways, obesity resembles the immune inflammation in its classical form, the difference is

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that this low intensity inflammation produces lower levels of circulating cytokines, such as C-reactive protein (CRP) and interleukin -6 (IL-6), and absent of clinical signs of inflammation. [12] In addition, it is believed that this chronic inflammation requires a relatively longer period of treatment (> 8 weeks in animal models) before there are noticeable changes in adipose tissue. [13]

A potential basis for the initiation of inflammation in obesity is endoplasmic reticulum (ER) stress, mainly in the liver and adipose tissue due to excess lipid accumulation and a disturbed energy metabolism. ER stress activates a stress response signaling network - "unfolded protein response" (UPR) that drives protective but also apoptotic and, particularly, inflammatory reactions. During ER stress, activated transmembrane protein, including protein kinase/endoribonuclease IRE1, which induces inflammatory signaling cascade by activating IKK, MAPKs p38 and JNK, and finally the main inflammatory transcription factor NF-KB, [14] which is a central integrator of pro-inflammatory signals and the main regulator of genes involved in inflammation, innate and adaptive immunity and apoptosis. [15]

Adipose tissue is infiltrated many immune cells, especially macrophages, which make up 40% of the fat cells, [13] which is a major source of inflammatory mediators in adipose tissue of mice and humans. Inflammatory cytokines affect intracellular pathways that regulate inflammation by activating nuclear transcription factors.

Hepcidin as the second part of the hypothesis was found by Krause et al (2000-2001) by ultrafiltration of blood. This peptide is composed of 25 amino acids with antimicrobial activity was called LEAP-1 (antimicrobial peptide - 1 expressed by the liver). In the same period, Pigeon et al. (2001) identified the gene (HAMP), which regulates the metabolism of iron and encodes for the LEAP-1 high expression from the liver, and significantly lower expression in the kidney, adipose tissue, heart, brain, calling it hepcidin (hep - liver and cidin - bactericidal protein). [16]

The action of hepcidin on cellular iron homeostasis is detected by binding to the only known exporter of iron, protein ferroportin that leads to its internalization and degradation. [17] As a result of this interaction, the absorption of iron from food is reduced due to reduction hepcidin - mediated expression ferroportin enterocytes, which leads to lower circulating levels of iron, with it increases the inhibition of macrophage iron export by the same mechanism. [18]

This regulatory peptide can be synthesized in response to inflammatory stimuli in quantitative terms the liver to a lesser extent, other tissues and cells, heart, kidney, adipose tissue, spinal cord, myeloid cells, alveolar macrophages and monocytes. [19]

Bekri et al (2006) provided the assumptions that hepcidin is synthesised not only in the liver but also in adipose tissue. This research demonstrated the increased content of mRNA hepcidin in the adipose tissue of patients suffering from obesity. The level of mRNA positively correlated with markers of inflammation (IL-6, CRP) and body mass index. In contrast, HAMP expression in the liver was not related to CRP; however, liver HAMP was positively correlated with serum transferrin saturation. Also, results showed that in obese patients, 68% had a low ratio of transferrin saturation and 24% had anemia. [20]

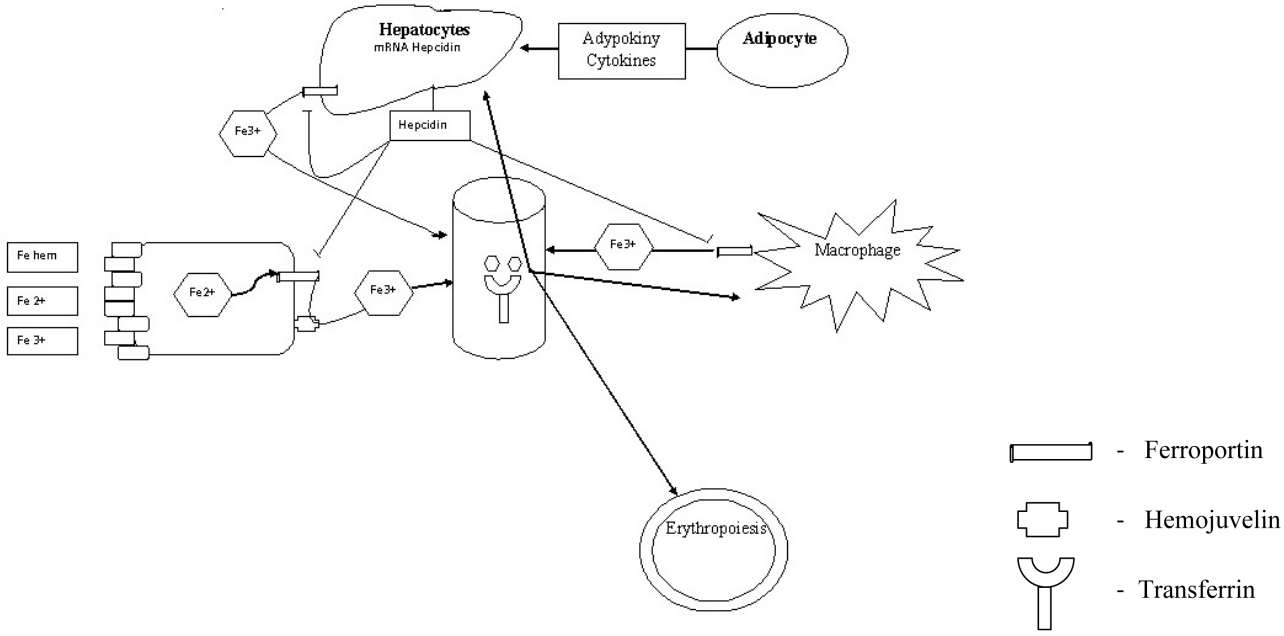

Figure 1. The pathogenesis of hypoferremia in obesity

In this regard, it is believed that adipose tissue can make a significant contribution to circulating levels of hepcidin. This assumption is confirmed by the presence of a significant direct relationship between the level of hepcidin and the degree of obesity. [21]

In recent years, studies have shown a link between hepcidin, chronic inflammation and a low concentration of iron in patients with obesity, with the possible emergence of hypoferremia determination mechanism. But despite the large number of studies clearly defined impact adipose tissue on levels hepcidin not fully understood.

There are assumptions that in obesity chronic inflammation leads to real iron deficiency as a result of long-term decreased iron absorption and unregulated iron loss. [22] The qualifiers for iron deficiency in obese individuals may therefore be similar to those seen in anemia of chronic disease coexisting with real iron deficiency. However, this definition of iron deficiency has not

always been the case in studies measuring iron status in obese populations, and further research is needed.

Conclusions

Thus, the traditional treatment of iron deficiency anemia, which consists of adding foods with increased iron content, and giving iron supplementation, cannot be fully effective for obesity because it changes the absorption of iron and its metabolism associated with low-grade systemic inflammation.

The complex treatment of iron deficiency anemia is significantly associated with inflammation and requires pharmacological modulation of inflammatory activity aimed at the central molecular basis of systemic inflammation, such as cascade reactions associated with NF-kb.

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Summary

Iron deficiency anemia and obesity have become a global problem affecting not only high income countries but also developing countries. Experimental and clinical studies indicate that there is a relationship between iron metabolism and weight status. Obesity is associated with low-grade systemic inflammation and elevated hepcidin concentrations. Hepcidin is the key regulator of systemic iron homeostasis. This review summarizes the current understanding of the dysregulation of iron homeostasis in obesity and leads assumptions about treatment.

Key Words: obesity, low-grade systemic inflammation, hepcidin, iron deficiency anemia

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