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The significance of serum hepcidin on iron status in overweight and obese patients with iron-deficiency anemia

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Abstract:

BACKGROUND: Deficiency of iron is one of the most prevalent nutritional disorders, and obesity is an increasing nutritional problem, but only a few studies mention a possible association between them in Iraq. Adipocytes secrete adipokines, some of them are related to the inflammatory response in addition to hepcidin, a hormone that mediates iron metabolism.

OBJECTIVES: This study aimed to assess the significance of serum hepcidin in obese patients with iron deficiency.

PATIENTS MATERIALS AND METHODS: Ninty patients were separated into Group 1 (normal weight), Group 2 (30 overweight), and the Group 3 (30 obese). All patients were investigated by complete blood count, serum hepcidin, iron, total iron-binding capacity, and ferritin using the standard laboratory techniques.

RESULTS: There were no significant differences among the groups regarding the severity of anemia, red cell indices, white blood cells, and platelets count. The obese group had significantly higher serum hepcidin and ferritin ($P = 0.003$, 0.040, respectively), while serum iron is lower. Serum hepcidin positively correlated with the serum ferritin but inversely correlated with serum iron. Increased hepcidin level in obesity could be related to inflammatory adipokines that effect on hepatic hepcidin transcription and hepcidin mRNA expression, in addition to the nonhepatic production of hepcidin in an autocrine manner; hepcidin, in turn, is responsible for low serum iron, but a high ferritin level in correlation to high hepcidin may explain by low-grade chronic inflammation associated with obesity.

CONCLUSIONS: The severity of iron-deficiency anemia is not affected by body weight; however, significantly higher serum hepcidin and ferritin in the obese patient with a lower serum iron should be considered during the assessment of iron status in those patients.

Keywords:

Ferritin, hepcidin, iron deficiency, obese

Introduction

Globally, the most common disorder of nutrition is anemia due to the lack of iron, about 1.6–2 billion people are anemic and 30%–50% of them are iron-deficiency anemia (IDA).[1,2] On the other hand, about 13% of the world's adults are obese and 39% are overweight, and between 1980 and 2014, there was an increase in the prevalence of obesity more than twice.[3] In spite of that, only a few studies mention a possible association between IDA and obesity.

Iron-deficiency anemia

Iron deficiency is the first cause of anemia worldwide, particularly in developing countries caused by inadequate iron intake and blood loss. The red cells in IDA are hypochromic microcytic with low mean corpuscular hemoglobin and mean corpuscular volume and low serum iron,

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serum ferritin, and serum hepcidin but high total iron-binding capacity (TIBC). Bone marrow iron stores and erythroblast iron are diminished.[4]

Overweight and obesity

Overweight and obesity can be defined as increased fat accumulation which may cause health impairment. Body mass index (BMI) is a simple index which is used for the classification of obesity and overweight in adults by dividing weight in kilograms by the square of the height in meters (kg/m^2). The WHO defines those whose BMI ≥25 as overweight, while obesity refers to persons who have BMI ≥30.[5]

Recently, an association is thought to be present between obesity and chronic inflammation because adipocytes secrete about 50 proteins (adipokines), some of them are related to the inflammatory response, such as "tumor necrosis factor-α, adiponectin, interleukin-1 β, interleukin–10, interleukin-6, interleukin-8, haptoglobin, vascular endothelial growth factor, nerve growth factor, macrophage migration inhibitory factor, monocyte chemoattractant protein-1, and plasminogen activator inhibitor-1."[6]

Hepcidin

Is a hormone synthesized principally by the cells of the liver and is secreted in the plasma then excreted in the urine, it is also synthesized by adipose tissue, with an increased expression of hepcidin messenger RNA in adipose tissue of the obese person.[7]

Hepcidin regulates the absorption of iron and the release of iron from macrophages; it also mediates innate immunity and regarded as Type II acute-phase protein.[8]

The production of hepcidin is regulated by many mechanisms which include an inflammation-related mechanism "via interleukin-6, interleukin-1, interferon-gamma, and tumor necrosis factor alpha" and by iron status and erythropoietic activity-related mechanism.[9,10] Therefore, the study aimed to evaluate the serum hepcidin level in normal weight, overweight, and obese Patients with IDA and to find if there is a significant correlation with iron status (serum iron and serum ferritin).

Patients and Methods

Patients

This study was conducted on 90 patients selected according to the results of complete blood count (CBC), blood film, and iron profile study including serum iron, TIBC, and serum ferritin.

Patients with IDA were arranged into three groups: Group 1 included 30 normal weight patients, Group 2 included 30 overweight patients, and Group 3 included 30 obese patients.

The study included adult patients with newly diagnosed IDA of both the genders.

Exclusion criteria

Pregnant women; individuals with recent blood transfusion or donation in the previous 3 months; individuals with iron supplement intake within the previous 3 months; and patients with malignant diseases, chronic inflammatory diseases, acute and chronic infections, and liver and renal diseases were excluded from this study, after good history taking, physical examination, and review of laboratory investigations including CBC, blood film, erythrocyte sedimentation rate (ESR), C-reactive protein, and liver and renal function test.

Ethical issue

This study was approved by review ethical committee of Iraqi council for medical specializations. It was conducted on patients with IDA, in accordance with the ethical standards and after obtaining informed consent from the participants.

Laboratory methods

Eight milliliters (ml) of peripheral blood were withdrawn by aseptic technique, each sample was divided into two tubes, first 4 ml in K3 EDTA-coated tube for CBC, blood film, and ESR tests and the second 4 ml in gel and activator tubes to obtain sera.

The following laboratory investigations were applied to all patients:

1. CBC using (Sysmex KX-21N, Japan) hematology autoanalyzer and blood film and ESR were done manually
2. The direct colorimetric assay was used to measure serum iron and TIBC using a spectrophotometer (UK, Cecil CE1011) and using the commercial kit from Human Diagnostics worldwide[11,12]
3. Serum ferritin was measured using automated immunoanalyzer (mini Vidas, France, bioMérieux) enzyme immunoassay and the commercial kit (France, bioMerieux, Ferritin, VIDAS, 30 411)[13]
4. Serum Hepcidin was estimated by enzyme-linked immunosorbent assay (ELISA) which use standard enzyme reader from Diagnostic Automation Inc., USA (ELISA Reader), using a commercial kit (Human Hepcidin kit ELISA, CUSABIO, CSB-E14239h, China).[14]

Statistical analysis

Statistical Package for the social sciences, IBM SPSS Statistics 25.0.0.0 was applied for the data analysis. Using

the test of one-way analysis of variance, the significant differences among studied groups were assessed. The correlation between the variables was considered statistically significant if $P < 0.05$.

Results

In normal weight group of patients, the mean age was 28 ± 8 years, while in overweight and obese groups, it was 22 ± 6 and 40 ± 8 years, respectively, with a significant difference among these groups ($P = 0.041$) indicating that obesity is more among older age patients. There was a slightly higher female-to-male ratio in all the three groups of patients, with no significant differences among them.

The differences were insignificant among the groups regarding the severity of anemia, red cell indices, white blood cells, and platelets count.

Serum hepcidin levels were significantly higher in the obese patients (Group 3), while serum ferritin was low in Group 1 and 2, whereas in Group 3, the value of serum ferritin varied between low and normal level and was significantly higher in the obese Group 3, while serum iron is lower, as seen in Table 1.

The main cause of IDA was chronic blood loss in 65% of the patients, while other causes such as increased demands and poor iron intake or malabsorption form 35% of causes.

Serum hepcidin correlated positively with serum ferritin ($r = 0.82$, $P < 0.003$) but negatively correlated with serum iron ($r = -0.37$, $P = 0.043$) in Group 3 patients.

Discussion

Increased hepcidin level in obesity was mentioned in other studies conducted on children and women with obesity who had significantly higher serum hepcidin levels in comparison to persons whose weight was normal, and this may be a cause that inhibits absorption of dietary iron in patients with obesity.[15-17]

The higher serum hepcidin level could be related to inflammatory adipokines (particularly interleukin-6 and adipokine leptin that have common biological features with interleukin-6) that affect on hepatic hepcidin transcription and hepcidin mRNA expression via the JAK-STAT three pathway, in addition to the inflammatory-induced nonhepatic production of hepcidin in an autocrine manner.[18-21]

Hepcidin, in turn, is responsible for low serum iron by decreasing the absorption of iron from the intestinal mucosa and by raising the rate of sequestration of iron in macrophages,[22] but a high ferritin level in correlation to high hepcidin has not yet been explained; however, low-grade chronic inflammation associated with obesity could be responsible for higher serum ferritin; similarly, other studies mention high serum ferritin in those with severe adiposity and consider it an acute-phase reactant that is elevated even if true iron deficiency is present, and its production is induced by many inflammatory cytokines.[23-25]

On the other hand, Fleming and Sly mention a similar elevation in hepcidin levels that correlate with serum ferritin and they thought that the increased ferritin levels cause increase in the secretion of hepcidin by mechanisms which are unknown, leading to lowering in the absorption of iron from the intestine, and propose that there may be an additional unknown factor which can affect both ferritin and hepcidin levels as a response to iron state and inflammatory process.[22] Similar changes in serum iron markers that are typical

Table 1: Descriptive parameters in three groups of patients with iron-deficiency anemia

	Group 1 (normal weight)	Group 2 (overweight)	Group 3 (obese)	Significant, $P<0.05$
Age (years)	28±8	22±6	40±8	0.041
Gender (female:male)	1.1:1	1.5:1	1.3:1	NS
WBC ($10^3/\mu l$)	6.98±1.9	7.1±1.45	8.21±2.0	NS
RBC ($10^3/\mu l$)	4.380±0.5	4.1±0.61	4.00±0.57	NS
Hb (g/L)	8.30±1.50	8.06±1.28	7.66±2.14	NS
PCV (%)	27.5±5	27±5.5	26±6	N.S
MCV (fL)	67.8±3.0	67.5±2.75	68.2±3.8	NS
MCH (pg)	20.8±3.0	20.2±3.1	20.0±3.2	NS
MCHC (g/L)	29.1±1.4	28.0±1.3	28.1±1.5	NS
Platelets ($10^3/\mu l$)	335.2±86.8	334.8±86.6	336.0±79.9	NS
Serum ferritin (ng/mL)	11.2±2	12.6±4.3	26.5±9.2	0.040
Hepcidin (ng/ml)	33.10±11.46	38.65±10.40	53.20±15.0	0.003
Serum Iron (mmol/L)	7.11±1.4	6.71±1.5	5.0±1.2	0.043
TIBC (mmol/L)	126.9±25.2	127.2±26.0	128.5±26.9	NS

NS=Not significant, TIBC=Total iron-binding capacity, Hb=Hemoglobin, WBC=White blood cells, RBC=Red blood cell, MCH=Mean corpuscular hemoglobin, MCV=Mean corpuscular volume, MCHC=Mean corpuscular hemoglobin concentration, PCV=Packed cell volume

of chronic inflammation but are not actually associated with "anemia of inflammation" are also mentioned by a population-based study by Ausk and Ioannou.[26]

Conclusions

Significantly higher serum hepcidin and ferritin in overweight and obese patients with a lower serum iron should be considered while assessing the status of iron in those patients. Further studies are recommended to evaluate hepcidin and the inflammatory adipokines associated with obesity in anemia of chronic diseases and IDA.

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Conflicts of interest

There are no conflicts of interest.

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