ENGLISH VERSION: INCLUSION OF QUERCETIN IN TREATMENT REDUCES THE LEVEL OF INTERLEUKIN 6 IN WOMEN WITH IRON DEFICIENCY ANEMIA AND OBESITY*

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According to the modern concepts of obesity (O), there is a condition of chronic low intensity inflammation with high content of proinflammatory cytokines, involving transcription factors, in particular nucleic Kb (NF-kB), which may be accompanied by a change in the concentration of iron in the serum. Quercetin is positioned as an anti-inflammatory agent with suppressive effects on NF-kB. The aim of the research was to determine the effect of quercetin inclusion on the systemic inflammatory markers in the comprehensive treatment of women with iron deficiency anemia (IDA) and O. Methods: 30 women with IDA and O participated in the study. Hemogram indicators, parameters of iron exchange (serum iron, ferritin, hepcidin, total iron binding capacity of serum, saturation of transferrin by iron) and inflammation markers were evaluated: C-reactive protein (CRP) and interleukin-6 (IL-6) in serum before and after treatment with iron sulfate. All patients were females of an average age of 40.3±7.59 years. In the distribution of patients based on the origin of the disease, the severity of IDA and basic indicators, there was no reliable difference between the groups (p>0.05). In the process of treatment, CRP and hepcidin had a significant difference in the comparison and study group (p<0.05), but in contrast, there was no difference between them on the 60th ± 3 days of treatment (p<0.05). IL-6 on the 60th ± 3 days of treatment revealed a significant decrease in the study group as opposed to the comparison group (p<0.05). In the course of treatment, ferritin had a significant difference between the comparison and study groups (p<0.05). Conclusion. Comprehensive treatment with inclusion of quercetin in female patients with IDA and O reduces the level of IL-6 and promotes the recovery of the iron depot.

Key words: iron deficiency anemia, obesity, quercetin.

Introduction

From the modern point of view, obesity (O) is considered as an inflammatory process, which develops as a result of lipolysis with subsequent active secretion in adipose tissues of a series of proteins, which are grouped into an adipocyne group [1]. This is accompanied by a characteristic increase of cellular inflammation biomarkers in blood plasma without any visible clinical signs, which in turn leads to the development of chronic low-intensity inflammation and often occurs due to transcription factors, in particular nucleic kB (NF-kB). NF-kB is the most important pro-inflammatory nuclear transcriptional factor that responds to most of external and internal stimuli and provokes inflammation, activating or suppressing the transcription of many genes involved in the inflammatory response [8].

The high content of proinflammatory cytokines such as interleukin-6 (IL-6) and C-reactive protein (CRP) in serum, increases the expression of hepcidin [3], which is a peptide hormone and the main regulatory protein of the systemic iron metabolism, mediator of immune protection and inflammation [6]. As a result of this interaction, the absorption of iron from food is decreased by hepcidin-mediated reduction of expression of enterocytes ferroportin (the only exporter of iron known as of today), that leads to a decrease in the content of circulating levels of iron, which is aggravated by inhibition of its export from macrophages by the same mechanism.

Obesity increases the level of hepcidin and reduces the response to oral treatment with iron preparations of iron deficiency anemia in children [11].

Quercetin (3,3',4',5,7- pentahydroxyflavone), a member of the bioflavonoids family, is one of the most common food components found in vegetables, fruits, tea, and wine. Quercetin is positioned as an anti-inflammatory agent with suppressive effects on NF-kB.

The aim of the research is to determine the effect of quercetin inclusion on the systemic inflammatory markers in the comprehensive treatment of women with iron deficiency anemia (IDA) and O.

Materials and methods

The study was conducted with the permission of Bioethics Commission of Ukrainian Medical Stomatological Academy, all subjects signed the voluntary informed consent.

We examined 30 patients with IDA and concomitant O that were treated at the polyclinic department of the 1st City Clinical Hospital of Poltava in the period from March 2016 to January 2017. Patients were distributed in the study group - 15 patients (n=15), receiving the basic treatment with iron sulfate ("Euromedox", France), 1 tablet (equivalent to 80 mg of iron (II)) 2 times a day, 30 minutes before meals) with oral inclusion of quercetin at a daily dose of 4.0 (Closed JSC "Borschagivsky ChPhP", Kyiv, Ukraine) and the comparison group - 15 patients (n=15), receiving only the basic treatment.

The inclusion criteria included the presence of IDA that was diagnosed on the basis of: hemoglobin level (Hb)≤120 g / L for women, signs of microcitosis and hypochromic anemia, mean corpuscular volume (MCV)≤80 fl, mean corpuscular hemoglobin (MCH)≤27.5 pg, mean corpuscular hemoglobin concentration (MCHC)≤335 g/l, in the presence of serum iron (SC) <11.5 μmol/L and ferritin level≤12 ng/ml in serum. The degree of severity of anemia was determined in accordance with the order of Ministry of Public Health of Ukraine No. 709 as of 02/11/2015.

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Determination of blood hematological parameters was performed on the analyzer BC3000 Plus Mindray, Shenzhen Mindray Bio-Medical Electronics Co., Ltd., China.

The level of iron in the blood serum was determined by photometric method using a set of reagents of "SpaynLab", Ukraine.

The level of ferritin (LLC «Alkor-Bi», Russia), hepcidin (Peptide Enzyme Immunoassay (EIA) Protocols, Peninsula Laboratories, LLC, USA), CRP (LLC «Gema», Russia) and IL-6 (JSC «Vector-Best, Russia) in the blood serum was carried out by the enzyme-immunoassay method.

Furthermore, all patients were examined as to the level of total protein, total bilirubin, ALT, AST, creatinine. To exclude ulcerative and inflammatory diseases at the time of the study, patients underwent endoscopic and X-ray examination of the gastrointestinal tract.

For all patients, examination included measurements of anthropometric indicators: height, body weight, waist and hip circumferences, body mass index (BMI). The index is calculated as the ratio of the body weight in kilograms (kg) to the square of the body height in meters (m^2).

O in adults is diagnosed according to the WHO definition based on the body mass index ≥ 30 kg / m^2.

The distribution of adipose tissue is determined by the coefficient of waist and hip circumferences. The waist and hip circumferences ratio in women > 0.85 indicates the abdominal type of O.

The study excluded patients who at the time of the study: consumed iron preparations for the last 3 months, used NSAIDs more than 3 times a week during the last 6 months, had conditions associated with significant bleeding over the past 6 months, oncopathology, autoimmune diseases, acute and chronic diseases that can lead to tissue hypoxia, chronic renal insufficiency, chronic liver disease with hepatocellular insufficiency, vegetarianism, pregnancy and lactation.

The statistical processing of the obtained data was performed using the SPSS 17.0 software package. The reliability of discrepancies (p) was estimated according to Student's t-test for independent samples and statistics of paired samples. For analysis, differences at p <0.05 were considered statistically significant.

Results and discussion

All patients were females of an average age of 40.3±7.59 years. In the distribution of patients based on the origin of the disease and the severity of IDA, there was no reliable difference between the groups

As compared to anthropometric data and hemogram parameters, there was no statistical difference between the examined women.

The analysis of the ratio of waist and hip circumferences revealed that all women had an abdominal type of adipopexia.

The baseline parameters of Hb, MCV, MCHC, MCH, serum iron, total iron binding capacity and transferrin saturation in the groups of women with IDA and O had statistically significant differences in these indicators (p>0.05).

There was no significant difference between the groups in the hemogram rates at the beginning of treatment and on the 60th± 3days of treatment (p>0.05) (Table 1).

Table 1.
Dynamics in the hemogram parameters in female patients with IDA and O (M±SD)

Parameter, unit of measurement	Study group (n =15)		Comparison group (n =15)	
	0 day	60th ±3 days	0 day	60th ±3 days
Erythrocytes, 10^9/L	3.9± 0.2	4.36±0.17†	3.98 ±0.26	4.27±0.15†
Hb, g / l	89.8 ±10.4	122.4±2.4†	90.4±10.3	121.2±3.2†
MCV, fl	72.3± 4.5	83.3±1.7†	71.6 ±5.1	82.9±2.1†
MCHC, g / l	314.0 ±19.8	337.2±10.2†	316.6 ±19.42	336.6±12.0†
MCH, g / l	22.6± 1.8	28.0 ±0.9†	22.6 ±1.95	27.9±1.0††

** - p <0.05 significant variation from the comparison group*

† - p <0.05 significant difference between paired samples

In the course of treatment, CRP, had a significant difference in the comparison and study groups (p<0.05), but, contrary to this, there was no discrepancy between these indicators on the 60th±3 days of treatment (p<0.05).

IL-6 on the 60th±3 days of treatment had a significant decrease in the study group as opposed to the comparison group (p<0.05).

Hepcidin, both before and after treatment, did not have a significant difference in the groups (p<0.05). By contrast, ferrin in the treatment process had a significant difference between the comparison and study groups (p<0.05) (Table 2).

Table 2.
Dynamics of inflammation markers and indicators of iron metabolism in the comprehensive treatment of patients with IDA and O (M±SD).

Parameter, unit of measurement	Study group (n =15)		Comparison group (n =15)	
	0 day	60th ±3 days	0 day	60th ±3 days
CRP, mg / ml	5.9±2.0	14.6±9.1†	5.8±1.9	13.9±10.0†
IL-6, pg / ml	1.5±0.9	0.9±0.8*†	1.6±0.8	1.8±1.3
Hepcidin, ng / ml	18.2±11.6	6.8±4.8†	15.1±12.5	5.7±3.7†
Ferritin, ng / ml	4.8±2.9	33.3±12.2*†	4.7±2.5	25.6±11.9†

** - p <0.05 significant variation from the comparison group*

† - p <0.05 significant difference between paired samples

According to modern concepts of obesity, there is a condition of chronic low intensity inflammation that occurs due to the increase in the mass of adipose tissue and excessive production of inflammation mediators, in particu-

lar IL-6 and CRP [7]. It is possible that proinflammatory cytokines cause greater expression of hepcidin and increase the synthesis of ferritin in reticuloendothelial cells [10], which results in reduced absorption of iron under conditions of high iron storage, whether within the limits of the reticuloendothelial system or within adipocytes. Clinically, it might be expected that this would lead to a combination of consumed iron deficiency and functional iron deficiency [12].

In our research, there was no significant difference in the effect of quercetin on CRP, as compared to the previous study of patients with O and overweight with metabolic syndrome [5].

Our data as to another marker of IL-6 inflammatory response, which had a significant decrease on the 60th ± 3 days of comprehensive treatment in the study group as opposed to the comparison group (0.9 ± 0.8 and 1.8 ± 1.5 pg / ml, respectively) are consistent with a study conducted in patients with bronchial asthma in combination with visceral obesity [2].

Hepcidin, which is an acute phase reagent, in our study had no significant differences in the groups before and after treatment, despite a positive correlation with IL-6 [3], which may be explained by the absence of a significant degree of obesity in female patients (Cheng et al. [4] and Karl et al. [9]).

The data of our research showed the statistical significance of the effect of comprehensive treatment with quercetin inclusion on ferritin, as a protein of acute phase of inflammation, in the study group as opposed to the comparison group (33.3±12.2 and 25.6±11.9 ng / ml respectively), which probably determines its anti-inflammatory activity.

Conclusion

Comprehensive treatment with inclusion of quercetin in female patients with IDA and O reduces the level of IL-6 and promotes the recovery of the iron depot.

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