Research Article

Serotonin Level and Lipid Metabolism Indices in Patients with Irritable Bowel Syndrome with Constipation Against the Background of Various Degrees of Obesity

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Abstract
Recent research shows that the number of diseases associated with obesity has been increasing. In obese persons, association with functional constipation is noted in 24.0% of cases, and obesity is recorded in 60.0% of patients with functional constipation. Among the possible mechanisms for the development of such a combination are changes in serotonin level in the blood, although the existing data are ambiguous and sometimes controversial. The objective of the study is to investigate the changes in serotonin level in the blood of obese patients in combination with constipation and its relationship with the lipid profile of the blood.

Materials and methods. 63 patients with obesity in combination with irritable bowel syndrome with constipation (IBSc), 24 patients with normal body mass index and 10 practically healthy people were examined. 25 patients with obesity and constipation had a body mass index of 32.8 ± 0.24 kg/m², 28 patients - 37.8 ± 0.5 kg/m², and 10 patients - 42.6 ± 0.5 kg/m². In patients with irritable bowel syndrome without obesity, the body mass index was 21.7 ± 0.4 kg/m². The blood serotonin level and lipid profile of the blood was determined in all patients.

Results. It was determined that in case of irritable bowel syndrome with constipation, serotonin level in the blood was reduced. In obesity with IBSc, the concentration of serotonin, on the contrary, was elevated. All patients with IBSc and obesity were marked an elevated level of total cholesterol and triglycerides. A direct correlation between high levels of triglycerides and serotonin concentration in serum of such comorbid patients was detected. The increase in the degree of obesity in the presence of IBSc was accompanied by a decrease in the concentration of cholesterol of high density lipoprotein. Patients with IBSc without excessive body weight had no such deviations.

Conclusions. With an increase in the degree of obesity, serotonin level in the blood increases and the lipid blood spectrum worsens.

Keywords
irritable bowel syndrome with constipation; obesity; serotonin; lipidogram

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Problem statement and analysis of the recent research

Obesity is characterized by varying degrees of excess body weight and is associated with an increase in morbidity from other organs and systems. According to Global Burden of Disease Study, the global prevalence of overweight and obesity in the world in the three prior decades has grown by 27.5% for adults and 47.1% for children [14]. Most often, obesity is diagnosed in US residents, 34% of whom are overweight, and 27% are obese [12]. In Europe, according to the project of multinational monitoring of trends and factors in the development of cardiovascular diseases, obesity and associated metabolic syndrome affects 15% of men and 24% of women, and every 10 years prevalence Obesity is increasing by 10-40% in most European countries [32]. According to Cerhan J.R. et al., Ogden CL et al. [10, 25] in the United States, the annual direct and indirect costs associated with the treatment of obesity and its consequences were about $ 215 million [28].

In Ukraine, according to the study of 20 risk factors in the urban population of the city of Dnipro, based on 5 outpatient clinics, it was found that only 29.3% of the population had normal body mass, and 70.7% had excess body weight and obesity of I-III degrees [21]. Among people with excessive body weight, obesity of the I degree was diagnosed in 22.75%, the II - in 7.68%, and III - in 1.03% of the subjects [22]. The high prevalence of obesity is due to urbanization, decreased physical activity, high caloric intake of food, depression due to poor evaluation of its appearance, negative emotional responses to diet.

Recent research shows that the number of diseases associ-
ated with obesity is increasing. Along with violations of lipid and carbohydrate metabolism, the development of insulin resistance and type 2 diabetes, arterial hypertension, ischemic heart disease, the organs of the gastrointestinal tract are often involved in the process. Among these diseases, dyskinesia of the large intestine with constipation syndrome, diverticular disease, and polyposis of the colon are common. According to vd Baan-Slootweg O.H. et al [37] in obese persons, functional constipation, diagnosed according to Rome criteria III, is noted in 24% of cases, and obesity is recorded in 60.0% of patients with functional constipation. Animal experiments have shown that exogenous obesity associated with constipation is accompanied by slow passage of intestinal contents, although the mechanisms of this phenomenon remain unclear, and one of them is likely to be a decrease in the bioavailability of serotonin in the large intestine [23, 33]. Data from epidemiological studies indicates a relationship of obesity with functional disorders of the gastrointestinal tract, including irritable bowel syndrome, functional dyspepsia, abdominal pain [27]. With regard to the mechanisms of such a connection, obesity can be associated with changes in the motility of the gastrointestinal tract, in particular, dysmotoria of the stomach, due to the formation of a sense of hunger and the regulation of the rate of digestion of food [7]. The feeling of hunger and the intake of high calorie foods cause hormonal imbalance through cholecystokinin, glucagon, leptin, peptide PY, which slows down the empty stomach and grelin, which stimulates appetite and accelerates this function. Along with obesity, also non-alcoholic steatohepatitis that occurs with it can play a role in the development of motor disorders of the colon, which are the basis of constipation [30].

Thus, the association of obesity and obstipation syndrome is not coincidental, and this is confirmed by the fact that in Asian countries, the association of chronic constipation with obesity, age, and feminine gender is also observed despite the traditionally high amount of plant food in the diet [31].

Excessive bacterial growth, chronic immune inflammation of low activity, acceleration of transit through the proximal small intestine can be considered among possible other mechanisms of association of obesity and constipation [6, 18, 20].

As a result of experimental studies, it has been shown that in obese mice on a high-fat diet there was a decrease in serotonin levels, one of whose functions is an increase in peristalsis of the large intestine through 5-HT4 receptors, due to the reduction of the number of enterochromat cells in it [5]. Serotonin also plays an important role in synchronization of the motility of various parts of the gastrointestinal tract [11], which explains the high efficiency of 5-HT receptor agonists in the treatment of irritable bowel syndrome [35]. Data on the level of serotonin in the blood of patients with constipation and obesity are heterogeneous and sometimes controversial and studied only separately in each of them. Thus, according to O.A.Rossyhina’s [29] studies in patients with irritable bowel syndrome and constipation (IBSc), the serotonin concentration in serum was elevated, although somewhat lower than in patients with irritable bowel syndrome with diarrhea, and it increased after food intake, that in the author’s opinion may be the cause of pain in the intestine. At the same time, M.G. Gershon [13] determined a decrease in the concentration of serotonin and enzymes of its metabolism in IBSc and an increase in diarrhea syndrome. The literature reports on the relationship between the degree of obesity and the level of serotonin, leptin, grelin, endothelin-1, the index of leptin/adiponectin and the low content of the last one [36]. Effect of serotonin on the energy homeostasis can be either through the central regulation of food intake and through a direct effect on adipose tissue [24]. It has also been established that the serotonergic brain system plays an important role in controlling appetite and eating behavior. Data on serotonin level in obesity is also heterogeneous. Thus, N.V. Anikina et al. [3] marked an increase of its level in obese women compared with those in normal body weight. According to the results of the same research of N.S. Alekseeva and co-authors [1], the basal serotonin level in the blood of patients with excess body weight was reduced, while after taking of easily digestible carbohydrates and the state of emotional discomfort, the activity of serotonergic systems increases due to increased tryptophan insensitivity through the hematoencephalic barrier and enhanced synthesis of serotonin, which in turn accelerates the feeling of satiety. The consumption of food rich in carbohydrates stimulates the activity of serotonergic systems of the brain, and in case of violation of the food behavior, their exhaustion is recorded. Reduction of serotonin level in patients with excessive body weight has led to an increase in the incidence of eating behavior disorders [2]. Increasing serotonin content in obese adolescents correlates with clinical, hormonal and psycho-emotional factors [16].

Thus, as it is seen from the published literature data, the question of serotonin levels in patients with obesity and constipation, and especially in their combination, is insufficiently studied, and the findings are often contradictory.

The objective of research was to study changes in serotonin levels in the blood of obese patients in combination with constipation and its relationship with lipid profile of blood.

1. Materials and methods

63 patients with obesity in combination with irritable bowel syndrome with constipation (IBSc), 24 patients with IBSc and normal body weight and 10 practically healthy people with normal body weight were examined. Among patients with obesity and constipation 25 patients’ body mass index (BMI) was 32.8±0.24 kg/m², 28 - 37.8±1.9 kg/m², and 10 - 42.6±0, 5 kg/m². In patients with IBS without obesity BMI was 21, 7±0, 4 kg/m². In 93, 7% of examined patients with this combined pathology, arterial hypertension of stage II also occurred, whereas in the case of IBSc, it was diagnosed in 75.0% of patients. The IBSc diagnosis was performed according to Rome criteria IV [17] with the degree of severity. The frequency of defecation in patients with obesity of the first degree was 2.0±0.1 acts, II degree - 1.5±0.1 and III degree
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- 1.4±0.2 acts per week. In patients with IBS and normal body weight, defecation was 1.9±0.04 times a week. The dull or colicky abdominal pains in the lateral abdomen was occasionally found in 68.0% of patients with constipation and obesity of the I degree, 96.4% with constipation and obesity of the II and 60.0% with obesity of the III degree. In patients with constipation without obesity dull pain in the abdominal flanks disturbed only 45.8% of patients. Flatulence was noted by 64.0% of patients with obesity of the I degree and constipation, 92.9% - of the II and 70.0% - of the III degree. Feeling of incomplete bowel movement occurred in case of constipation against the background of obesity of the I degree in 56.0% of such patients, of the II degree - 71.4% and 100% of obese subjects of the III degree. 64.0% of patients with obesity of the I degree, 89.3% - of the II and all patients with obesity of the III degree noted the necessity to apply their efforts during bowel movements. In patients with IBS with constipation without obesity the flatulence, feeling of incomplete defecation, the need for effort during defecation noted, respectively, 54.2; 83.3% and 90.0% of the examined persons.

In addition to a detailed analysis of complaints and anamnesis, evaluation of the results of endoscopic examination of the colon and the elimination of the symptoms of the “red flag” in all patients with comorbid pathology and isolated IBSc, blood serum serotonin level was determined by immune enzyme method using "Serotonin ELISA IBL International GMBH" (Germany). At the same time, the study of lipid profile, in particular total cholesterol, lipoproteins of low, very low and high density, triglycerides was performed by enzyme-colorimetric method on the analytical modular test-system Cobs 6000 Roche Diagnostics (Switzerland). The obtained results were statistically analyzed using the standard program package "Statistica 8.0 for Windows" and the Microsoft Exell software statistical function package. The probability of differences between dependent and independent variants was estimated using the Student’s t-criterion, and the difference was considered to be reliable in p<0.05. A pair factor correlation analysis was also performed with the Pearson-r correlation coefficient.

2. Results and their discussion

Table 1 shows the results of serotonin level and lipidogram indices in patients with IBSc without obesity and in their comorbidty in comparison both between themselves and with analogue indexes in healthy people with normal body weight. As one can see from the given data, in IBSc the serotonin level in blood serum is reduced 1.6-fold (p<0.05) compared with healthy ones. In patients with constipation on the background of obesity of the I degree serotonin concentration in blood serum, on the contrary, increased 2.8-fold (p<0.05). Such changes can probably be explained by the fact that regulation of the contractile activity of the intestinal walls through 5-HT signaling can occur both directly and indirectly in constipation against the background of obesity [9]. With an increase of body weight and an increase of blood pressure and a severe degree of IBS with constipation, serotonin level in blood serum was higher, respectively, 1.7-; 3.9- and 6.3-fold more than in healthy persons (p1,2,3<0.05). Compared with those in patients with IBSc without obesity, such an increase was even more significant (2.8-, 6.3- and 10.2-fold, respectively) with increasing body weight. Statistically significant increase in serotonin concentration in blood serum in obesity was found by other researchers, moreover, both in childhood and adulthood [3, 40]. An elevated serotonin level in obese patients is likely due to its association with the biological marker of pleasure - dopamine, responsible for motivational processes and appetite [15]. On the other hand, the intestine is an active participant in neurohumoral regulation of eating behavior [4, 38], and emotional discomfort that occurs with prolonged congestion and excessive body weight contributes to elevated levels of serotonin [39]. In addition, as a result of overeating and intake of food with high blood protein and carbohydrates by the obese people, the level of tryptophan, as the main substrate for the synthesis of serotonin in the central nervous system, increases; and as a result of insulin stimulation of the tryptophan synthesis in peripheral tissues serotonin concentration also increases the [8]. Consumption of fatty foods, requiring less energy, does not cause a feeling of satiety, stimulates repeated meals, inhibits intestinal peristalsis and violates lipid metabolism in such patients. Thus, the level of total cholesterol significantly exceeded the indicators in healthy both in IBS without constipation and in its development against the background of different stages of obesity, respectively 1, 2, 3; 1.3-; 1.4- and 1.75-fold. The concentration of triglycerides in the combination of IBSc against the background of obesity of the II and III degrees exceeded the similar index in healthy persons 1.4- and 1.7-fold (p1,2<0.05). A direct correlation between high triglyceride levels and serum serotonin concentration in obesity of the II and III degrees and IBSc (correlation coefficients +0.68 and 0.85, p1,2<0.05) was determined. At the same time, there was no difference between the level of triglycerides in patients without obesity and the first stage of obesity (Table 1). The increase of the degree of obesity in combination with IBSc was accompanied by a decrease of the concentration of high-density lipoprotein cholesterol (LDL cholesterol) at 27.7% in obesity of the II and at 48.18% of the III degree. The level of LDL cholesterol did not differ in patients with isolated IBSc and in its combination with obesity of the I degree. The concentration of low density lipoprotein (LDL) in the blood serum of patients with isolated IBSc and in combination with obesity was significantly higher than that of the healthy persons. As the body mass of the patients with constipation increased, the concentration of LDL cholesterol exceeded their level 1.3-fold in the healthy persons in the obesity of the II and 1.5-fold of the III degrees. Other researchers [1] pointed out more significant impairment of lipidogram rates, an increase in the severity of abdominal obesity, and the progression of other components of the metabolic syndrome in patients with a higher serum serotonin concentration at the same time as the emotional type of eating...
behavior. Deep violations of lipid metabolism lead to narrowing of the lumen of arteries of the small and large intestines by atheromas, fibroatheromas, reduction of contractile ability of smooth muscle cells of arterioles, allocation of leukotrienes in their localization zones, thromboxane A2, vasoconstriction prostaglandins [19] and possible decrease of intestinal wall motility. In addition, the development of constipation at a high concentration of serotonin in patients with obesity may be a violation of its interaction with serotonin receptors of smooth muscles of the intestine. This is evidenced by the absence of a physiological response from the smooth muscles of the intestine for the administration of serotonin adipinate in high concentrations [34].

### Table 1. Indices of serotonin and lipid profile in blood of patients with irritable bowel syndrome with constipation and obesity.

<table>
<thead>
<tr>
<th>Indicators</th>
<th>Healthy people</th>
<th>IBSc without obesity</th>
<th>IBSc with obesity of the I degree</th>
<th>IBSc with obesity of the II degree</th>
<th>IBSc with obesity of the III degree</th>
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<tbody>
<tr>
<td>Serotonin, ng/ml</td>
<td>39.13 ± 2.99</td>
<td>24.20 ± 1.35</td>
<td>67.53 ± 5.37</td>
<td>153.29 ± 10.98</td>
<td>247.09 ± 19.78</td>
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<td>Total cholesterol, mmol/l</td>
<td>4.93 ± 0.09</td>
<td>5.8 ± 0.2</td>
<td>6.2 ± 0.14</td>
<td>6.9 ± 0.16</td>
<td>8.63 ± 0.23</td>
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<td>HDLC</td>
<td>3.49 ± 0.23</td>
<td>4.17 ± 0.08</td>
<td>4.10 ± 0.11</td>
<td>4.62 ± 0.08</td>
<td>5.37 ± 0.16</td>
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<td>LDLC</td>
<td>1.37 ± 0.08</td>
<td>1.05 ± 0.04</td>
<td>1.17 ± 0.05</td>
<td>0.99 ± 0.08</td>
<td>0.71 ± 0.07</td>
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<td>Triglycerides</td>
<td>1.55 ± 0.09</td>
<td>1.87 ± 0.05</td>
<td>1.82 ± 0.06</td>
<td>2.17 ± 0.04</td>
<td>2.66 ± 0.07</td>
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### 3. Conclusions

Thus, with the increase in the degree of obesity, serotonin level increases in blood serum, and the violation of the lipid blood spectrum increases, which is likely to confirm the interaction between neurohormonal and metabolic parameters and requires further study of such an interconnection.

### References


[8] Crane JD. Inhibiting peripheral serotonin synthesis reduced obesity and metabolic dysfunction by promotion brown adipose tissue thermogenesis. Nat. Met. 2015; 21(2):166-172. DOI: https://doi.org/10.1038/nm.3766 [PMid:25485911 PMCid:PMC5647161]


Received: 2 Jan 2018

Revised: 25 Mar 2018

Accepted: 26 Mar 2018