

ОРИГІНАЛЬНІ ДОСЛІДЖЕННЯ

УДК 616.34-002-009

DOI: 10.26565/2617-409X-2020-6-01

IRRITABLE BOWEL SYNDROME WITH CONSTIPATION: ISSUES OF PATHOGENESIS, DIAGNOSTICS AND TREATMENT

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Summary: Issues related to the diagnosis and treatment of irritable bowel syndrome occupy one of the central places in gastroenterology, due to the fact that in recent years there has been a significant increase in the incidence of this syndrome, its long-term recurrent, often lifelong course, leading to a decrease in the performance of patients, despite good quality, and a significant cost to the health care system. Irritable bowel syndrome, despite its functional nature, occurs quite often - from 14-50% of the adult population according to population epidemiological studies, and the ratio of women to men is from 2: 1 to 4:1. In the structure of gastroenterological pathology, this disease accounts for 40-70% of all cases of seeking medical help. Irritable bowel syndrome is a complex of functional disorders of the distal intestines, lasting more than 3 months and accompanied by abdominal pain that disappears after a bowel movement, flatulence, a feeling of incomplete bowel movement, changes in the frequency and consistency of stools. Factors in the pathogenesis of irritable bowel syndrome are dysfunction of mental activity with changes in autonomic and humoral functions; visceral hypersensitivity and impaired intestinal motility, past intestinal infection; endocrine disorders; food allergies, sedentary lifestyle; genetic predisposition. Endothelial dysfunction has recently played an important role in the onset of irritable bowel syndrome. The most famous among the factors of vascular endothelium today are the powerful vasoconstrictor endothelin-1 and the vasodilator - nitric oxide. The study investigated the level of vasoconstrictor endothelin-1 and vasodilator of nitric oxide in patients with irritable bowel syndrome with constipation. It was found that such patients have severe endothelial dysfunction, which manifests itself in an increase in the level of endothelin-1 ($p < 0,01$), a decrease in the level of nitric oxide ($p < 0,01$). The data obtained indicate the role of dysfunction of the vascular endothelium in the pathogenesis of irritable bowel syndrome with constipation. An inverse correlation was found between the content of endothelin-1 and nitric oxide ($p < 0,01$), which indicates an increase in the activity of vasoconstrictor mechanisms with a simultaneous decrease in vasodilation factors. The effectiveness of complex therapy in the group of patients in whom folic acid and zinc were used as part of complex therapy in improving the clinical picture of the disease (complete relief of dyspeptic syndrome and a significant decrease in the severity of pain, constipation and asthenic syndromes), restoration of vascular endothelial function (significant decrease in the level of endothelin-1 and an increase in the level of nitric oxide) in comparison with the group of patients in the treatment of which only basic therapy was used.

Key words: irritable bowel syndrome, constipation, endothelin -1, nitric oxide, endothelial dysfunction

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Introduction. Irritable bowel syndrome (IBS) is defined as an independent nosological disease of the intestine, which is manifested by a number of functional motor-secretory disorders of the intestine of an inorganic nature: mental dysfunction, impaired intestinal motility, immune function of the intestine, visceral hyperalgesia and a change in intestinal microbiome [1].

The leading factors in the pathogenesis of IBS is a violation of the function of mental activity with a change in vegetative and humoral functions. Patients with IBS have a higher level of anxiety and depressive disorders, sleep disturbances than in healthy individuals. In such patients, increased excitability of neurons of the posterior horns of the spinal cord is noted. In this area, a high content of catecholamines and serotonin is noted, in the future afferent signals

entering the brain are amplified. Activation of 5HT₃ receptors of enterochromaffin cells with catecholamines and increased production of serotonin leads to an increase in intracellular calcium, which causes an increase in pain with stimulation of peristalsis and the development of visceral hypersensitivity [2, 3].

Visceral hyperalgesia (hypersensitivity to mechanical, thermal, chemical and other peripheral stimuli) is an important cause of abdominal pain in IBS, as well as motor and secretory disorders that occur in response to subthreshold stimuli (allodynia). Psycho-social stress, chronic physical overload, intestinal infections, heredity are forms of visceral hypersensitivity. [1, 2, 4].

Motility disorders in IBS are manifested by spastic and hypermotor dyskinesia. With spastic dyskinesia, there is a slowdown in the transit of chyme along the colon, which leads to constipation. With this type of dysmotility, there is an increase in water absorption by the intestine with a decrease in the volume of feces and an increase in their density. With hypermotor dyskinesia, there is an acceleration of the transit of intestinal chyme with the development of diarrhea [1-3].

The constituents of the intestinal microflora have different effects on intestinal motility. Thus, short-chain fatty acids produced by the intestinal microbiota stimulate enterochromaffin cell receptors, thus contributing to an increase in the production of serotonin, activation of sensitive neurons in the submucosal layer of the intestine and increase its contraction. In contrast, nitric oxide, which is synthesized by propionobacteria, and a vasointestinal peptide affect neuromuscular synapses, followed by relaxation of the intestinal wall [1, 2, 5].

The occurrence of IBS as a multifactorial disease is also promoted by: past intestinal infection; endocrine disorders (dysmenorrhea, menopause, diabetes, hypothyroidism, obesity); disaccharidase deficiency, especially hypolactasia; food allergies and intolerances to certain foods; sedentary lifestyle; widespread use of drugs (antibiotics, antacids, beta-blockers); genetic predisposition [1-3].

A certain role in the occurrence of IBS is given to endothelial dysfunction. The vascular endothelium is involved in many physiological

and pathophysiological processes in the human organism, produces and releases into the bloodstream and subendothelial space biologically active substances that regulate vascular tone, growth processes, affect the state of smooth muscle cells, circulating blood elements, and fibroblast proliferation. One of the most famous among these substances today is the powerful vasoconstrictor endothelin - 1 (ET - 1) and the vasodilator - nitric oxide (NO) [6-9].

It was established that with IBS there is an increased level of ET-1 and vascular endothelial growth factor in blood plasma. The maximum increase in ET-1 and vascular endothelial growth factor was found in patients with IBS with constipation, with a painful form - the indicators were slightly lower, in patients with diarrhea the increase in ET-1 was minimal [9, 10].

The role of another vasoactive peptide with the property of vasodilation, nitric oxide, is also being investigated in the pathogenesis of IBS. NO helps to relax the smooth muscles of the small and large intestines, the anal sphincter with the help of the neurogenic NOS (NO-synthase) contained in nitrergic neurons. NOS content was detected in Auerbach plexus neurons, in the adventitia of the gastrointestinal vessels [11].

Mucosal processes in the intestinal epithelium are associated with NO. NO improves microcirculation in mesenteric vessels and helps maintain intestinal mucosa integrity. With IBS, there is a reduced level of NO both in the blood and in the mucous membrane of the colon, with a more pronounced decrease in NO in the blood than in the tissues. A decrease in NOS activity was revealed when it was examined in the blood and colon mucosa in IBS, and a direct correlation was found between the level of NO in the blood and in the colon mucosa [11, 12].

NO plays an important role in the processes of regulation of motility (increased tone of the intestines and sphincters with its deficiency), secretion (stimulation of such), in the protection of the gastrointestinal mucosa (damage with NO deficiency), microcirculation (vasoconstriction and thrombosis with NO deficiency) [12].

Further study of the function of the vascular endothelium is undoubtedly relevant and has

great scientific and practical importance, since endothelin - 1 and nitric oxide occupy a leading place in the pathogenesis of many conditions, including diseases of the gastrointestinal tract, namely irritable bowel syndrome. Many issues related to the participation of these substances in various physiological and pathophysiological mechanisms currently remain open and require further study, which will change the understanding of the development of many diseases, develop new methods for influencing the course of physiological and pathophysiological processes.

Particular attention is paid to therapeutic approaches aimed at restoring or maintaining the function of the vascular endothelium. Folic acid, as well as zinc, which includes zinc, have a positive effect on endothelial function, along with other drugs. Zinc helps to eliminate damage to the mucous membranes of the digestive tract, the phenomena of intestinal dysbiosis, normalizes the microflora of the epithelial integument. Zinc and folic acid are essential elements for restoring the structure of damaged intestinal cells. [13-16].

Purpose of the study - study the level of Et - 1 and nitric oxide in patients with IBS with constipation and to correct the revealed violations with zinc and folic acid as part of complex therapy.

Materials and methods: 88 patients with IBS with constipation were examined: women - 61 (68.6%), men - 27 (31.4%) aged 20 to 50 years. The control group included 18 healthy individuals. The diagnosis is verified. All patients, depending on the therapy taken, were divided into 2 groups: patients of the first group (59 patients) received standard folic acid (prokinetics, probiotics, laxatives) additionally folic acid at 0.001 g 3 times a day and zinc 0.124 g 3 times per day for 3 weeks, patients of the second group (29 patients) received standard therapy.

Results and discussion: The clinical picture of the disease in patients of both groups was dominated by pain, constipation, asthenic and dyspeptic syndromes.

In the first group, pain syndrome was detected in 51 patients with IBS ($81.7 \pm 4.99\%$). An objective examination showed pain during palpation along the colon in 48 patients ($81.4 \pm 4.5\%$), constipation syndrome in all examined patients, asthenic syndrome in 44 ($76.3 \pm 5.4\%$), and dyspeptic in 36 patients ($54.1 \pm 6.1\%$).

After the treatment (21 days from the start of treatment) with a subjective examination, the pain syndrome disappeared in 40 ($64.1 \pm 6.7\%$) patients, decreased in intensity - in 13 ($18.1 \pm 5.5\%$); an objective examination: was absent in 29 ($47 \pm 6.36\%$), decreased in intensity - in 25 ($33.2 \pm 6.13\%$). Constipation syndrome disappeared in 53 ($83 \pm 4.35\%$) patients, and constipation persisted in 7 ($6.8 \pm 3.14\%$) patients. Asthenic syndrome was arrested in 46 ($71.6 \pm 5.35\%$) patients; weakness and irritability persisted in 4 patients ($3.18 \pm 2.48\%$). Dyspeptic syndrome was stopped in all patients in this group.

In the second group: pain was observed in 22 ($74.7 \pm 8.12\%$) patients. An objective examination showed pain in all patients. Constipation syndrome was observed in all patients, asthenic - in 13 ($46.4 \pm 9.17\%$), dyspeptic - in 8 ($33.6 \pm 9.46\%$).

After the treatment, the pain syndrome was stopped in 12 ($51 \pm 11.8\%$) patients, in 10 ($48 \pm 11.3\%$) it decreased in intensity. The abdomen on palpation in 6 ($19.43 \pm 8.64\%$) patients became painless, in 16 ($82.4 \pm 8.42\%$) - during palpation along the colon, the pain decreased in intensity. Constipation syndrome was arrested in 8 ($35.6 \pm 10.13\%$) patients, and persisted in 14 ($64.7 \pm 10.13\%$) patients. Asthenic syndrome disappeared in 10 ($67.3 \pm 11.8\%$) patients, and in 3 ($30.1 \pm 16.3\%$) patients, the general disturbance of health remained.

When analyzing the clinical picture of the disease of patients with IBS with constipation in the dynamics of treatment, one can note a significant improvement in subjective and objective clinical symptoms in the first group of patients who received folic acid and zinc in addition to standard therapy in comparison with patients of the second group who received standard therapy (Fig. 1).

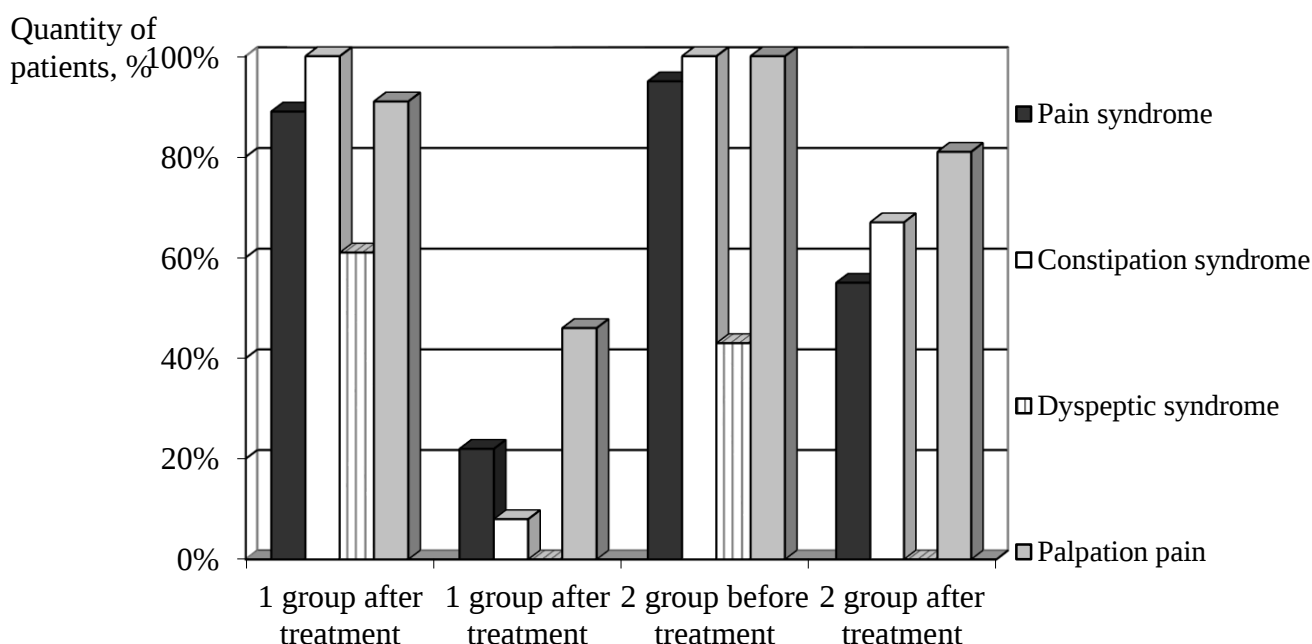


Fig.1. The dynamics of clinical manifestations in the examined patients before and after treatment

When studying endothelial function in patients with IBS with constipation, a level of Et - 1 was significantly increased, compared with the control group, and NO was significantly reduced, compared with the control group. Data on the content of Et - 1 and NO in the blood of patients with IBS with constipation and persons of the control group are presented in table.

Table 1. The content of Et -1 and NO in the blood of patients with IBS with constipation and in the control group

Groups	Et -1 /pmol/l, M±m	NO/mg/l, M±m
Patients with IBS with constipation	4,64±0,26	1,67±0,04
Control group	1,85±0,15	2,38±0,06
p	p<0,01	p<0,01

Note: p - when comparing indicators Et - 1 and NO in patients with IBS with constipation with indicators Et - 1 and NO in individuals of the control group

An inverse correlation was found between the content of Et - 1 and NO ($r = -0.63$) ($p < 0.01$), that is, with an increase in the activity of vasoconstrictor mechanisms, a decrease in vasodilation factors is noted.

Et - 1 causes a reduction in the smooth muscles of the colon in experimental animals, and insufficient formation of NO, in turn, contributes to impaired gastrointestinal motility. In this regard, it can be assumed that a reduced level of NO, along with an increased level of Et -1 in patients with IBS with constipation, are the mechanisms that lead to the development of intestinal dysmotoria with spastic phenomena and the development of constipation syndrome [12, 17].

All patients, depending on the therapy taken, were divided into 2 groups: patients of the first group (59 patients) received standard therapy (prokinetics, probiotics, laxatives) and additionally folic acid at 0.001 g 3 times a day and zinceral 0.124 g 3 times per day for 3 weeks, patients of the second group (29 patients) received standard therapy.

During treatment, patients of the first group showed a significant decrease, compared with the group before treatment, of the level of Et - 1, which contributed to an improvement in the functional state of the vascular endothelium, a decrease in spasm of the smooth muscles of the colon and an improvement in intestinal motility.

Data on the content of Et - 1 in blood plasma in patients of the first and second groups in the dynamics of treatment are presented in table 2.

Table 2. The content of ET-1 in blood plasma in patients of the first and second groups before and after treatment

Groups	ET-1 - 1 before treatment, M $\pm$ m	ET-1 - 1 before treatment, M $\pm$ m
First group	4,64 $\pm$ 0,26 pmol/l	2,1 $\pm$ 0,2 pmol/l *
Second group	4,64 $\pm$ 0,26 pmol/l	4,2 $\pm$ 0,3 pmol/l **
Control group	1,85 $\pm$ 0,15 pmol/l	

Note: * $p < 0.001$ - when comparing the indicators Et - 1 of the first group with the group before treatment.

** $p < 0.05$ - when comparing the indicators Et - 1 of the second group with the group before treatment.

In patients of the second group, during the treatment process, a decrease in the level of Et - 1 was not statistically possible ($p < 0.05$), compared with the group before treatment. A significant difference ($p < 0.01$) was noted when comparing the Et - 1 indices of the first and second groups after treatment.

In the study of the level of NO in patients of the first group in the dynamics of treatment, a possible increase was noted in comparison with the group before treatment, which helped to reduce spastic phenomena of smooth intestinal muscles.

Data on the content of NO in blood serum in patients of the first and second groups before and after treatment are presented in table 3.

Table 3. The content of NO in the blood serum of patients of the first and second groups in the dynamics of treatment

Groups	NO before treatment, M $\pm$ m	NO after treatment, M $\pm$ m
First group	1,67 $\pm$ 0,04 mg/l	2,24 $\pm$ 0,08 mg/l *
Second group	1,67 $\pm$ 0,04 mg/l	1,83 $\pm$ 0,03 mg/l **
Control group	2,38 $\pm$ 0,06 мг/л	

Note: * $p < 0.001$ - when comparing the NO indicators of the first group with the group before treatment

** $p < 0.05$ - when comparing the NO indicators of the second group with the group before treatment

In patients of the second group who received standard therapy, an increase in the level of NO was noted, however, its value was not statistically significant ($p < 0.05$), compared with the group before treatment.

Conclusions: 1. In patients with irritable bowel syndrome with constipation, there is a violation of the function of the vascular endothelium in the form of an increased level of endothelin - 1 and a reduced level of nitric oxide in the blood.

2. An inverse correlation was found between the content of Et - 1 and NO ($r = -0.63$) ($p < 0.01$), that is, with an increase in the activity of vasoconstrictor mechanisms, a decrease in vasodilation factors is noted.

3. The inclusion in the complex therapy of patients with IBS with constipation of folic acid and zinc contributes to the positive dynamics of the clinical picture of the disease, the optimal restoration of endothelial function in comparison with standard therapy.

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СИНДРОМ ПОДРАЗНЕНОГО КИШЕЧНИКА З ЗАКРЕПАМИ: ПИТАННЯ ПАТОГЕНЕЗУ, ДІАГНОСТИКИ ТА ЛІКУВАННЯ

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Резюме: Питання, пов'язані з діагностикою та лікуванням синдрому подразненого кишечника є одним із центральних місць в гастроентерології, в зв'язку з тим, що в останні роки відзначається значне зростання захворюваності даними синдромом, його тривалий рецидивний, часто довічний перебіг, що призводить до зниження працездатності пацієнтів, незважаючи на доброякісний характер, і значних витрат системи охорони здоров'я. Синдром подразненого кишечника, незважаючи на його функціональну природу, зустрічається досить часто - від 14 до 50% дорослого населення за даними

популяційних епідеміологічних досліджень, а співвідношення жінок і чоловіків – від 2:1 до 4:1. У структурі гастроентерологічної патології на це захворювання припадає 40-70% всіх випадків звернень по лікарську допомогу. В роботі досліджено рівень вазоконстриктору ендотеліну-1 і вазодилататору оксиду азоту у хворих на синдром подразненого кишечника з запорами. Встановлено, що у таких пацієнтів має місце виражена ендотеліальна дисфункція, яка проявляється в підвищенні рівня ендотеліну-1 ($p < 0,01$), зниженні рівня оксиду азоту ($p < 0,01$). Отримані дані свідчать про роль порушення функції судинного ендотелію в патогенезі синдрому подразненого кишечника з запорами. Виявлена зворотня кореляційна залежність між вмістом ендотеліну – 1 та оксиду азоту ($p < 0,01$), що свідчить про підвищення активності вазоконстрикторних механізмів з одночасним зниженням факторів вазодилатації. Відзначено ефективність комплексної терапії в групі пацієнтів, у яких в складі комплексної терапії застосовувалася фолієва кислота і цинктерал в поліпшенні клінічної картини захворювання (повне купірування диспептичного синдрому і значне зменшення по виразності больового, констипаційного і астеничного синдромів), відновленні функції ендотелію судин (достовірне зниження рівня ендотеліну-1 і підвищення рівня оксиду азоту) в порівнянні з групою хворих, в лікуванні яких застосовувалася тільки базисна терапія.

Ключові слова: синдром подразненого кишечника, закреп, ендотелін -1, оксид азоту, ендотеліальна дисфункція

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СИНДРОМ РАЗДРАЖЕННОГО КИШЕЧНИКА С ЗАПОРАМИ: ВОПРОСЫ ПАТОГЕНЕЗА, ДИАГНОСТИКИ И ЛЕЧЕНИЯ

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Резюме. Вопросы, связанные с диагностикой и лечением синдрома раздраженного кишечника, занимают одно из центральных мест в гастроэнтерологии, в связи с тем, что в последние годы отмечается значительный рост заболеваемости данным синдромом, его длительное рецидивное, часто пожизненное течение, приводящее к снижению работоспособности пациентов, несмотря на доброкачественный характер, и значительным затратам системы охраны здоровья. Синдром раздраженного кишечника, несмотря на его функциональную природу, встречается достаточно часто - от 14-50% взрослого населения по данным популяционных эпидемиологических исследований, а соотношение женщин и мужчин – от 2:1 до 4:1. В структуре гастроэнтерологической патологии на это заболевание приходится 40-70% всех случаев обращений за врачебной помощью. В работе исследован уровень вазоконстриктора эндотелина-1 и вазодилататора оксида азота у больных синдромом раздраженного кишечника с запорами. Установлено, что у таких пациентов имеет место выраженная эндотелиальная дисфункция, которая проявляется в повышении уровня эндотелина-1 ($p < 0,01$), снижении уровня оксида азота ($p < 0,01$). Полученные данные свидетельствуют о роли нарушения функции сосудистого эндотелия в патогенезе синдрома раздраженного кишечника с запорами. Выведена обратная корреляционная зависимость между содержанием эндотелина – 1 и оксида азота ($p < 0,01$), что свидетельствует о повышении активности вазоконстрикторных механизмов с одновременным снижением факторов вазодилатации. Отмечена эффективность комплексной терапии в группе пациентов, у которых в составе комплексной терапии применялась фолиевая кислота и цинктерал в улучшении клинической картины заболевания (полное купирование диспептического синдрома и значительное уменьшение по выраженности болевого, констипационного и астенического синдромов), восстановлении функции эндотелия сосудов (достоверное снижение уровня эндотелина -1 и повышение уровня оксида азота) в сравнении с группой больных, в лечении которых применялась только базисная терапия.

Ключевые слова: синдром раздраженного кишечника, запор, эндотелин -1, оксид азота, эндотелиальная дисфункция

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Conflicts of interest: author has no conflict of interest to declare.

Конфлікт інтересів: відсутній.

Конфликт интересов: отсутствует.