TOSHKENT TIBBIYOT AKADEMIYASI URGANCH FILIALI
JANUBIY OROLBO‘YI TIBBIYOT JURNALI
2 - TOM, MAXSUS SON. 2026
14.00.00 - TIBBIYOT FANLARI ISSN: 3093-8740

UDK: 618.314-003-003.232+578.152.4

# CLINICAL AND LABORATORY CHANGES IN THE LIVER THAT DEVELOP AGAINST THE BACKGROUND OF INTESTINAL DYSBACTERIOSIS.

**Shodiyeva Musharraf Sadirovna-** Associate Professor of the Department of Normal Physiology, DSc, Bukhara State Medical Institute, Uzbekistan.
shodiyeva.musharraf@bsmi.uz
https://orcid.org/0000-0001-5672-8664
Tel: +998936880891

**Kaxxorova Feruza Maxmudovna-** Independent researcher at the Department of Normal Physiology, Bukhara State Medical Institute, Uzbekistan.
dilnoratursunova49@gmail.com
https://orcid.org/0009-0009-5738-1071
Tel: +998938472255

**ABSTRACT**

This article presents information about the clinical signs, laboratory test results, and pathological changes in the liver that occur when intestinal dysbacteriosis occurs, when the balance of intestinal bacteria in the body is disrupted and toxins and inflammatory factors enter the liver through the blood.

**Keywords:** dysbiosis, dysbacteriosis, mitochondrial dysfunction, liver.

**Kaxxorova Feruza Maxmudovna**
Normal fiziologiya kafedrasi mustaqil izlanuvchisi
Buxoro davlat tibbiyot instituti
Ilmiy rahbar: DSc, dotsent Shodiyeva M.S

**“Ichak disbakteriozi fonida jigarda rivojlanadigan klinik-laborator o‘zgarishlar”**

**ANNOTATSIYA**

Ushbu maqolada ichak disbakteriozi kasalligi yuzaga kelganda organizmda ichakdagi bakteriyalar muvozanati buzilganda toksinlar va yallig‘lanish omillari qon orqali jigarga tushishi natijasida yuzaga keladigan klinik belgilar, laborator tekshiruvlarning amalga oshirilishi natijasidagi ko‘rsatkichlar, jigarda yuzaga keladigan patologik o‘zgarishlar haqida ma’lumotlar keltirilgan.

**Kalit so‘zlar:** disbioz, disbakterioz, mitoxondrial disfunksiya, jigar.

TOSHKENT TIBBIYOT AKADEMIYASI URGANCH FILIALI
JANUBIY OROLBO‘YI TIBBIYOT JURNALI
2 - TOM, MAXSUS SON. 2026
14.00.00 - TIBBIYOT FANLARI ISSN: 3093-8740

**Каххорова Феруза Махмудовна**
Кафедра нормальной физиологии
Бухарский государственный медицинский институт
Научный руководитель: DSc, доцент Шодиева М.Ш

# «Клинические и лабораторные изменения в печени, развивающиеся на фоне кишечного дисбактериоза»

## АННОТАЦИЯ

В данной статье представлена информация о клинических симптомах, результатах лабораторных анализов и патологических изменениях в печени, возникающих при нарушении баланса кишечной микрофлоры в организме, в результате чего токсины и воспалительные факторы попадают в печень через кровь.

**Ключевые слова:** дисбиоз, дисбактериоз, митохондриальная дисфункция, печень.

Intestinal dysbiosis (disorder of intestinal microflora) can also affect the liver if it persists for a long time. This condition is explained by the gut–liver axis: when the balance of bacteria in the intestine is disturbed, toxins and inflammatory factors enter the liver through the blood. As a result, functional and sometimes organic changes can occur in the liver[1,3,7,10].

**The aim of the study**. It was long believed that bacteria colonizing the mucosal surface formed a biofilm adjacent to the apical portion of the epithelium. However, it has recently been demonstrated that microbial consortia form colonies on the apical surface of the epithelium.

These microorganisms constitute the so-called normal, or resident (autochthonous), microflora of a specific biotope, in contrast to microorganisms found in the intestinal lumen, trachea, etc. Normal microflora is immersed in the mucous, or enteric, environment of the body. It includes mucin, microbial waste products (metabolites), low-molecular-weight food fragments, and humoral and cellular components of the immune system. This special environment within the hierarchy of the body's internal environments possesses properties intermediate between those of the external and internal environments [2,7].

Obligate microflora accounts for over 90% of all bacteria available for cultivation in clinical practice. This part of the intestinal microbial spectrum is considered the permanent symbiotic microflora. Interaction between the microbiome and the microorganism occurs at several levels: the level of saccharolytic anaerobes and colonocytes, and the interaction of facultative and saccharolytic anaerobes with the vascular and nervous system of the colon[3,5].

Recent studies have demonstrated a significant association between dysbiotic disturbances in the intestinal microflora and the pathogenesis of NAFLD, which occurs due to mitochondrial damage. Mitochondrial dysfunction has been shown to play a significant role in the development of lipid peroxidation, which leads not only to membrane damage, necrosis, and apoptosis of hepatocytes, but also to the progression of steatosis.

**Material and Method**. Clinical manifestations of acute and chronic liver diseases indicate that, regardless of their etiology, mitochondrial dysfunction is the predominant clinical feature. The data presented in this article demonstrate the significance of dysbiotic changes in the development of mitochondrial dysfunction, the formation of steatosis in non-alcoholic fatty liver disease, followed by its transformation into steatohepatitis and progression to fibrosis and cirrhosis, and the equilibrium metabolism of dietary substrates and low-molecular-weight metabolites, which influence the human body through the modulation of physiological reactions [3,8].

Given the numerous metabolic functions of microflora, impaired colonization resistance can be considered one of the most likely triggers for the development of various diseases. When a pathological process occurs in any organ, it is quite difficult to isolate a violation of the colonization

resistance of the intestinal microflora as an independent pathogenetic link, since various metabolic disorders occurring in the body are combined into a single dysmetabolic process [2,7,10].

Some authors suggest considering short-term changes in the ratio of normal intestinal microflora as transient dysbacteriosis, while persistent changes are considered dysbacteriosis. In foreign literature, such phenomena are described as disturbances in human endoecology with changes in the microbiocenosis of the gastrointestinal tract (GIT) mucosa, accompanied by clinical symptoms[2].

Intestinal dysbiosis is known to manifest itself through microbiological changes in the ratio of aerobic and anaerobic microbiota, as well as a decrease in the content of bifidobacteria, lactobacilli, and bacteroides; an increase in the number of opportunistic bacteria; an increase in the number of E. coli with altered biological properties (with reduced enzymatic activity, lactose-negative, non-motile, indole-free, etc.); the appearance of hemolytic forms of E. coli and staphylococci that are normally absent; and the spread of microflora beyond their natural habitat [3]. In addition to microbiological changes, NAFLD is characterized by the development of so-called intestinal metabolic dysbiosis, which is based on changes in the metabolic pathways of the intestinal microbiota under the influence of various factors leading to qualitative and quantitative changes in the microbiome metabolome and disruption of the integration of microbial metabolism with human metabolism [6,3,9].

Disturbances in microbial metabolism are of particular interest because they can lead to significant changes in the concentrations of both proinflammatory and anti-inflammatory metabolites in the tissues and fluids of the host organism, including metabolites not characteristic of endogenous metabolism. To date, approximately 200 microbial metabolites have been identified that may be associated with the pathogenesis or sanogenesis of a number of human diseases and act as potential biomarkers [4,6].

Metabolomics provides a tool for assessing biochemical activity by directly monitoring substrates and products transformed during cellular or bacterial metabolism. While gene and protein function is subject to epigenetic regulation and post-translational changes, metabolites serve as direct signals of biochemical activity, which are much easier to correlate with the disease phenotype.

In this context, metabolomics is a powerful approach that can be used for the purposes of clinical diagnostics and prognosis (due to the possibility of identifying clinically significant biomarkers), identifying therapeutic targets, as well as solving fundamental problems related to the study of the etiology and pathogenesis of human diseases [2,5].

**Results and discussion**. Biofilm microbiota are the first to interact with all substances entering the body, transforming chemicals into non-toxic end products or intermediate compounds that are easily destroyed in the liver and eliminated from the body. Disruption of the interaction between the liver and intestine leads to mutual functional and structural changes within them and throughout the body as a whole [3], making hepatoenteric regulation of various organic and inorganic compounds a key homeostatic mechanism. Reduced detoxification by the microflora during intestinal dysbiosis increases the load on the liver's enzymatic systems, which contributes to the development of metabolic and structural changes [10]. Colonization of the intestine with opportunistic and pathogenic microflora in CLD accelerates the disruption of parietal digestion, inhibits the synthesis of B vitamins, disrupts hepatoenteric circulation with the formation of toxic substances, and increases the permeability of the intestinal wall epithelium to bacteria, toxic products, and micro- and macromolecules. Thus, a vicious circle arises that maintains mutually aggravating damage to the intestine and liver [4,6]. Studies conducted in recent years demonstrate a significant association between dysbiotic disturbances of the intestinal microbiota and the pathogenesis of chronic liver diseases, primarily NAFLD (Quigley E.M. et al., 2013).

After the significant role of the microbiota in the pathogenesis of obesity was established, studying changes in the composition and functional activity of the intestinal microbiota became inevitable in patients with NAFLD [8,10]. Thus, an experimental in vivo study demonstrated a close

relationship between the intestinal microbiota and metabolic processes occurring in the liver, which affected glycogenogenesis even before the onset of triglyceride synthesis. Intestinal microflora also modified the expression of Cyp8b1 in the liver, subsequently altering bile acid (BA) metabolism, which are important regulators of lipid absorption. Researchers have demonstrated a significant link between the intestinal microbiota, specifically members of the Coriobacteriaceae family, and the level of lipid metabolism in the liver (Claus S.P. et al., 2011).

At the same time, impaired synthesis and excretion of bile components in NAFLD contributes to changes in the qualitative and quantitative composition of the intestinal microflora. It has now been proven that the microbiota can modulate fatty acid metabolism and their de novo synthesis in the liver through a feedback mechanism. In turn, the microbiota, by modulating fatty acids, which are powerful signaling molecules, can influence insulin sensitivity and lipid metabolism processes in the liver, which play a significant role in the pathogenesis of NAFLD (Quigley E.M., Monsour H.P., 2015) [7].

Intestinal dysbiosis, along with other pathogenetic factors, also contributes to increased intestinal wall permeability and the development of metabolic endotoxemia, followed by the formation of steatosis, steatohepatitis, and liver fibrosis, accompanied by TLR-4 activation and increased production of TNF-α, IL-1β, IL-6, and other proinflammatory cytokines and chemokines (Miele L. et al., 2013; de Faria Ghetti F. et al., 2017). Once in the liver, endotoxins first cause mitochondrial dysfunction, as mitochondria are the most labile intracellular structures and are the first to undergo changes, followed by damage to hepatocytes. Since each hepatocyte contains 800 mitochondria, which occupy approximately 18% of the liver cell, mitochondrial function is one of the main aspects of liver fat regulation. On the one hand, this process is realized by increased permeability of the inner mitochondrial membrane to calcium ions and disruption of the synthesis of apolipoproteins A and C, which are the transport form of triglycerides during the formation of VLDL, which contributes to the development of liver steatosis [1,4,9].

On the other hand, a deficiency of choline, an important component of cellular and mitochondrial membranes, also contributes to the development of mitochondrial dysfunction and steatosis. Thus, research by Romano K.A. demonstrated that choline deficiency can be caused not only by its deficiency in the diet but also by high levels of choline-utilizing bacteria. Choline-utilizing bacteria are primarily represented by the Enterobacteriaceae family, and in particular the genus Escherichia. They compete for it with the host, significantly influencing the level of methyl group donor metabolites in blood plasma and liver (Romano K.A. et al., 2017)[2,7,9].

**Materials and Methods**. The mitochondria of hepatocytes host key biochemical processes related to energy metabolism: the Krebs cycle (tricarboxylic acid cycle), fatty acid oxidation, the carnitine cycle, electron transport in the respiratory chain, and oxidative phosphorylation. Upon entering hepatocytes, fatty acids initiate their activation through the formation of acetyl-CoA. Activated fatty acids enter the mitochondrial matrix as acylcarnitine, a transmembrane carrier [2, 7].

Fat degradation also occurs in the hepatocyte mitochondrial matrix through oxidative cycle reactions, which sequentially cleave C2 units to form acetyl-CoA (activated acetic acid). The sequential cleavage of acetyl groups begins at the carboxyl end of the activated fatty acid at the position between the C2 (α-atom) and C3 (β-atom) atoms; therefore, the degradation reaction cycle is called β-oxidation of fatty acids [2,5]. It should be noted that among the causes of non-alcoholic steatosis, a deficiency of enzymes involved in peroxisomal β-oxidation of fatty acids (FA) and, as a consequence, the accumulation of dicarboxylic acids are distinguished. Their deficiency leads to hyperactivation of genes regulating the expression of PPAR-γ receptors, MDA, and hydroxynonenal [2,6,10].

To date, direct and indirect toxicity of fatty acids has been established, which contributes to the inhibition of K+/Na+-ATPase, suppression of glycolysis, uncoupling of oxidative phosphorylation, activation of the pathway for utilization of excess fatty acids by involving PPAR-α receptors in the process. Thus, the mechanisms that contribute to the accumulation of fat in

hepatocytes are: an increase in the supply of fatty acids to the liver, a decrease in the rate of β-oxidation of fatty acids and an increase in their synthesis in the liver mitochondria, as well as a decrease in the synthesis or secretion of VLDL [58]. Also, a deficiency of multifunctional enzymes involved in mitochondrial β-oxidation of fatty acids can lead to the development of fatty liver disease. Broken medium and long chains of acetyl-CoA dehydrogenase genes, defects in β-oxidation of fatty acids can become one of the causes of the development of micro- and macrovesicular steatosis of the liver [6]. It is known that the catalyst for β-oxidation of long-chain fatty acids is the mitochondrial trifunctional protein (MTP), a heterothree-dimensional protein consisting of four α-subunits and four β-subunits [6]. Primary or secondary mitochondrial dysfunction is an important mechanism in the development of microvesicular steatosis, in which disturbances in mitochondrial β-oxidation of non-esterified fatty acids lead to their accumulation in the liver and esterification into triglycerides, which accumulate in hepatocytes as inclusions [3].

TNF-α, with high levels observed in this group of patients, plays a key role in the pathogenesis of steatosis and the development and/or progression of steatohepatitis. The primary source of TNF-α are hepatocytes and Kupffer cells. TNF-α induces mitochondrial swelling with a decrease in matrix density and loss of septa. It is important to note that elevated serum TNF-α levels, both spontaneous and induced, are also observed in the presence of intestinal dysbiosis, with TNF-α levels directly related to the severity of dysbiotic disorders. Anti-TNF-α treatment promotes the restoration of the activity of complexes I, II, III, and V, the activity of FA β-oxidation, and liver architecture [3,6,8,10]. Clinical manifestations of acute and chronic liver diseases indicate that, regardless of their etiology, symptoms characteristic of mitochondrial dysfunction predominate in clinical manifestations, such as increased fatigue, asthenic syndrome, sleep disturbances, psychoemotional instability, muscle weakness, exercise intolerance, a tendency to tachycardia, etc. [1,3]. Since the severity of the pathological process in the liver is associated with the efficiency of aerobic oxidation in liver cells, correction of mitochondrial dysfunction is an important task.

Recently, a new group of drugs affecting the intestinal microbiocenosis has emerged – metabiotics [4]. Metabiotics are biologically active exometabolites of probiotic (symbiotic) microorganisms that have a positive effect on the host and/or its microbiota and are capable of optimizing the body's physiological functions, including its regulatory, metabolic, and behavioral responses. One of the representatives of this group is Actoflor-S, a next-generation metabiotic developed by leading Russian scientists. It contains 12 active compounds—amino acids and organic acids (analogs of probiotic strain metabolites)—selected in such a way and in such a concentration that the components significantly enhance (potentiate) each other's effects.

The synergistic action of metabolites increases the activity and stimulates the growth of the body's own microflora, while suppressing the growth of pathogenic microorganisms and pathobionts. Metabiotics have demonstrated potential efficacy in experimental and clinical studies. For example, Actoflor-S has a positive effect not only on the microbiota but also on the human body, stimulating the regeneration of intestinal epithelium and the functioning of the immune system [5].

Considering the probable pathogenetic role of microbial endotoxins (LPS) and bacterial ethanol in NAFLD, the potential of metabiotics to reduce the negative effects of ethanol, restore the impaired function of tight junction proteins, improve the intestinal barrier, reduce alcohol-induced liver damage, and potentially exert an anticarcinogenic effect (prevention of hepatocellular carcinoma) appears clinically promising [4]. Thus, studies conducted in recent years provide insight into the nature of the changes occurring in the liver in nonalcoholic steatosis and demonstrate possible mechanisms for its development and progression. Among several mechanisms for the development of steatosis, disruption of microbiota function plays a key role [6].

**Conclusion.** Thus, NAFLD-associated dysbiosis of the colon in adult patients is characterized by an increase in the number of endotoxin- and ethanol-producing gram-negative bacteria, primarily of the Enterobacteriaceae family and the Escherichia genus (phylum Proteobacteria), as well as the

Bacteroides genus (phylum Bacteroidetes). Dysbiosis aggravates the disturbances of the intestinal barrier function, contributing to an even greater increase in the permeability of the intestinal barrier and the translocation of bacteria and endotoxins of gram-negative microorganisms with subsequent activation of TLR-4, production of proinflammatory molecules and cytokines, and the development of low-grade inflammation in the liver tissue. These dysbiotic changes contribute to the development of mitochondrial dysfunction, the formation of steatosis in NAFLD with subsequent transformation into steatohepatitis and progression of the disease to the stages of fibrosis and cirrhosis. Conflict of interest: The authors declare that they have no conflict of interest in the writing of this article.

**References**

1. Radchenko VG et al. The treatment algorithm for non-alcoholic fatty liver disease and the role of mitochondrial dysfunction in the development of NAFLD. Pharmatek, 2017, 6: 14-21.

2. Bondarenko VM The role of opportunistic pathogenic bacteria in chronic inflammatory processes of various localizations. Tver: Triada, 2011, 88 p.

3. Bondarenko VM, Matsulevich TV Intestine dysbacteriosis as a clinical and laboratory syndrome: status update on the problem: a guide for practitioners. Moscow: GEOTAR-Media, 2007. 304 p. / Bondarenko VM, Matsulevich TV. Intestine dysbacteriosis as a clinical and laboratory syndrome: status update on the problem: a guide for practitioners. Moscow: GEOTAR-Media, 2007. 304 p.

4. Bondarenko VM Dysbacteriosis. Moscow: Meditsina, 1994, p. 334. / Bondarenko VM Dysbacteriosis. Moscow: Meditsina, 1994, p. 334.

5. Vorobyov AA, Lykova EA Bacteria of normal microflora: biological properties and protective functions. Zhurnal Mikrobiologii, Epidemiologii i Immunobiologii, 1999, 6: 102–105. / Vorobiev AA, Lykova EA. Normal microflora bacteria: biological properties and protective.

6. Vorobiev AA, Nesvizhsky YuV, Zudenkov AE, et al. A comparative study of parietal and luminal colon microflora in an experiment in mice. Zhurn. Mikrobiol., Epidemiol. i Immunobiol., 2001, 1: 62–7.

7. Gabrielyan NI, Gorskaya EM, Snegova ND. Functions of the gastrointestinal tract microflora and consequences of its disorders after surgical interventions. Antibiotics and Chemotherapy, 2000, 9: 24–29. / Gabrielyan NI, Gorskaya EM, Snegova ND. Functions of the gastrointestinal tract microflora and the consequences of its disorders after surgical interventions. Antibiotics and Chemotherapy, 2000, 9: 24–29.

8. Grinevich VB, Uspensky YuP, Dobrynin VM, et al. Clinical aspects of diagnosis and treatment of intestinal dysbiosis in general therapeutic practice. SPb., 2003, p. 36.

9. Sitkin SI et al. Dysbiosis in ulcerative colitis and celiac disease and its therapeutic correction by butyric acid plus inulin. Experimental and Clinical Gastroenterology, 2017, 142(6): 77-98. /Sitkin SI, et al. Dysbiosis in ulcerative colitis and celiac disease and its therapeutic correction by butyric acid plus inulin. Eksp Klin Gastroenterol, 2017,(6):77–98.

10. Erofeev NP, Seliverstov PV, Radchenko VG. Clinical physiology of the colon. Mechanisms of action of short-chain fatty acids in health and pathology. Moscow: OOO 4TE ART, 2012. 56 p. / Erofeev NP, Seliverstov PV, Radchenko VG. Clinical physiology of the colon. Mechanisms of action of short-chain fatty acids in normal and pathological conditions. M.: “4TE ART” LLC, 2012. 56 p.