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# Nutritional Factors of Inflammation Induction or Lipid Mechanism of Endotoxin Transport

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**Abstract**—Integral parameters of bacterial lipopolysaccharide concentration and antiendotoxin immunity activity were determined in the blood serum of subjects with two extreme variants of eating disorders: obesity and anorexia nervosa (in its clinical model, long-term starvation). The results of the study showed that obese patients had initially higher endotoxin concentrations (2.41 ± 0.11 vs 1.13 ± 0.05 *EU*/mL in the control), which significantly decreased as a result taking a course of orlistat or after starvation (for no longer than 20 days) (to 1.34 ± 0.04 and 1.01 ± 0.09 *EU*/mL, respectively). The decrease in the endotoxin serum level was associated with an increase in the concentration of high-density lipoproteins (HDLs) and a decrease in the concentration of low-density lipoproteins (LDLs). This allowed us to assume that the complex of the latter with the endotoxin is the LDL fraction that may function as a depot of the hydrophobic form of the lipopolysaccharide molecule in the bloodstream. Long-term starvation (starting from day 20) led to the appearance of symptoms characteristic of septic states, which was preceded by a twofold increase in the concentration of the endotoxin and antibodies against the enterobacterial common antigen and subsequent increase in the level of anti-glycolipid antibodies (from 133.2 ± 2.6 to 355.6 ± 15.0 optical density arbitrary units) starting from day 25–27 of starvation, which is characteristic for the initial phase of the systemic inflammatory response syndrome.

*Keywords:* endotoxin, inflammation, obesity, lipid metabolism, anorexia, medical starvation, antiendotoxin immunity

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## INTRODUCTION

"Inflammation is a fallback mechanism of immune defense, aimed at the identification, destruction, and elimination of foreign and own antigens, which has an adaptive and/or pathogenic nature... always a malicious process, even when it is indispensable to life ..." [1]. It is well known that errors in diet often precede various inflammatory diseases and can be the sole cause of their initiation and that national food culture features are directly related to lifespan. It is believed that the long average lifespan of Japanese people is due to the predominance of seafood in their diet and that of the indigenous inhabitants of mountain regions is associated with the calm and harmonious way of life or with the intestinal microflora composition, which was regarded by I.I. Mechnikov as the key element of aging. There is no doubt that nearly all diseases have an inflammatory nature (including atherosclerosis and diabetes); that excess intestinal endotoxin (ET), known as the "endotoxin aggression" (EA), may be the only factor in the initiation and progression of a disease [2–5]; and that the most common cause of EA is stress [6]. However, the mechanisms for delivering the ET, which is a lipopolysaccharide (LPS), into the portal blood remain unknown (although it is known that food intake leads to an increase in the LPS concentration in blood [7, 8]). It was assumed that ET may be either delivered as a component of chylomicrons or be actively transported by mucosal *M* cells. Any denial or confirmation of these assumptions in the available scientific literature is missing. The lack of interest in this problem seems strange, because the ability of excess intestinal LPS in the general circulation to initiate inflammation was postulated a quarter of a century ago [2], and the innate immunity receptor *TLR*4, by which ET realizes its activatory effect (including the pathogenic one), was discovered 15 years ago [9, 10]. With this in mind, we decided to make the first attempt to study the role of nutritional factors in the mechanisms of LPS's entry from the intestine into the bloodstream. This seems extremely important to us, because EA may be the sole cause of diseases and syndromes (including those of autoimmune and allergic nature) [1–6, 10], and the identification of the nutritional factors that can reduce the amount of intestinal ET entering the portal circulation may be useful for medical purposes. In view of this, the fundamental question arises as to how to solve this problem and which clinical model can be used for this

purpose. The most appropriate clinical model to study this problem at the phenomenological level are volunteers from two extreme original states in terms of the alimentary aspect—patients with an excess nutritional component and patients with anorexia nervosa (the long-term starvation model). These two conditions are accompanied with an increased proinflammatory background (a high concentration of the tumor necrosis factor alpha and interleukin-6 [11–13]), which can be provided by only one factor—an excessive content of intestinal LPS in the general circulation [1].

In view of the above, we decided to take the first attempt to elucidate the ability of the nutritional factor to affect the concentration of ET in the systemic circulation and assess the involvement of the lipid component in the mechanism of transport of the intestinal LPS.

## MATERIALS AND METHODS

To achieve the objectives of the study, we formed two groups of volunteers. The first group (obesity grade 1 and 2) included seven subjects of either sex 46 to 65 years of age (mean age, 54.7 ± 2.54 years) who normally ate fat spicy foods combined with daily drinking 50–100 g (of ethanol equivalent) alcohol. Before each meal for three weeks, these subjects received a capsule with a selective inhibitor of intestinal lipases (orlistat, 120 mg), which was necessary to establish the involvement of the lipid component in the mechanism of LPS transport from the intestine into the portal circulation. The second group consisted of seven patients who received a course of fasting therapy by the method of Professor Y.S. Nikolaev [14]. The control group included 135 apparently healthy volunteer subjects (first-year university students) without excess weight 17 to 26 years of age (mean age, 18.9 ± 2.3 years). All participants gave their informed consent to participate in the study; the study was approved by the local ethics committee.

In all the patients, we measured the integrated characteristics of the intestinal ET using the micro-*LAL* test, our modification of the *LAL* test (*Limulus amoebocyte lysate test*), which is based on the ability of LPS to induce the formation of protein fractals. This method was adapted by the personnel of the Institute of General and Clinical Pathology to clinical conditions and allows the integrated concentrations of all LPSs in the blood serum to be determined due to interaction solely with the Re glycolipid, a common fragment of the ET molecule. The integrated activity of the antiendotoxin immunity (AEI) was determined using the immunity status screening assessment (ISSA) by ELISA. This procedure is based on the determination of the titers of antibodies to the most common antigenic determinants of the ET molecule—glycolipid (GL) of the *Re* chemotype and the enterobacterial common antigen (ECA) in arbitrary units of optical density (OD arb. units). In the group of patients treated with orlistat, as well as in the control group, we additionally evaluated the lipid profile, which included the determination of the levels of total cholesterol, low-density lipoproteins (LDLs), high-density lipoproteins (HDLs), cholesterol, and triglycerides (TGs) by conventional methods. The significance of the differences between the parameters studied was estimated using Student's *t* test. The relationships between the quantitative indices were analyzed by the parametric Pearson correlation analysis using MS Excel software (version 5.0).

## RESULS AND DISCUSSION

In the first group of subjects with obesity grade 1 and 2, a significant ($p < 0.05$) increase in the level of the intestinal endotoxin (2.69 ± 0.13 *EU*/mL) before the beginning of orlistat therapy was detected compared to the control group (1.13 ± 0.05 *EU*/mL). Weight loss in the treatment group varied from 3 to 7.5 kg (on average, 4.9 ± 0.5 kg). Interestingly, a three-week treatment with orlistat led to a significant decrease in the ET level in the blood serum (Table 1, Fig. 1).

The titers of antibodies to GLP and ECA before and throughout the course of orlistat treatment remained within the reference range and did not differ significantly from the control group. However, even a short-term course of treatment with intestinal lipase inhibitors significantly improved the lipid profile. The LDL level before treatment was 3.5 ± 0.12 mmol/L, which was significantly higher than in the control group (2.65 ± 0.08 mmol/L). The orlistat therapy significantly reduced the level of LDL (from 3.5 ± 0.12 to 3.5 ± 0.1 2.84 ± 0.26 mmol/L). The time course of changes in the level of TG in the experimental group was similar (1.29 ± 0.21 mmol/L before the treatment and 0.7 ± 0.08 mmol/L after a 21-day course). The total cholesterol content tended to decrease; however, this decrease was statistically nonsignificant and was possibly due to the small size of the sample. Importantly, the concentration of HDL in patients after orlistat treatment significantly increased (from 1.17 ± 0.12 to 1.5 ± 0.08 mmol/L at the end of the course of administration with the intestinal lipase inhibitor).

Thus, it can be postulated that lipids are involved in the mechanisms of intestinal LPS transport into the bloodstream. Apparently, this applies only to the hydrophobic (fat-soluble) moiety of the ET molecule (responsible for the full range of general biological properties of various LPSs [1]). In this regard, the question arises as to where the ET molecule loses its polysaccharide (hydrophilic) part, in the intestine and/or in the liver? If solely in the liver, then the lipid mechanism of LPS transport applies only to the recirculating (not consumed by the system of fixed macrophages) portions of the intestinal ET, which is returned with the bile into the intestine. Although the possibility of fermentolysis of the LPS molecule in the

**Table 1.** Time course of concentrations of intestinal endotoxin, antiendotoxin immunity activity, and blood lipid profile of the subjects who received orlistat therapy

| Index | Beginning of therapy | 6–7 days | 13–14 days | 21–22 days | Control |
|---|---|---|---|---|---|
| Number of patients (*n*) | 7 | 7 | 7 | 7 | 135 |
| Intestinal endotoxin level, *EU*/mL | 2.69 ± 0.13* ** | 2.25 ± 0.13* | 1.66 ± 0.1* | 1.34 ± 0.04* | 1.13 ± 0.05 |
| GL (norm, 200 OD arb. units) | 126.5 ± 3.4 | 123.5 ± 2.1 | 103.8 ± 6.3* | 102.0 ± 1.7* | 149.9 ± 8.4 |
| ECA (norm, 400 OD arb. units) | 246.0 ± 14.7 | 257.0 ± 12.1 | 272.5 ± 0.7 | 296.1 ± 10.8* | 313.6 ± 14.8 |
| Total cholesterol (3.0–5.2 mmol/L) | 5.87 ± 0.5 | 5.46 ± 0.44 | 4.6 ± 0.38 | 4.29 ± 0.41* | 4.16 ± 0.24 |
| HDL (0.–2.1 mmol/L) | 1.17 ± 0.12 | 1.24 ± 0.14 | 1.43 ± 0.05 | 1.5 ± 0.08* | 1.17 ± 0.1 |
| HDL (1.1–3.0 mmol/L) | 3.5 ± 0.12** | 3.33 ± 0.14 | 3.24 ± 0.22 | 2.84 ± 0.26* | 2.65 ± 0.08 |
| TG (0.45–1.7 mmol/L) | 1.29 ± 0.21** | 1.1 ± 0.14 | 1.0 ± 0.11 | 0.7 ± 0.08* | 0.67 ± 0.12 |

Note: For explanation of the abbreviations in Tables 1 and 2, see the Materials and Methods section. * Differences between the initial and resultant values were significant at $p < 0.05$; ** differences between the initial and control values were significant at $p < 0.05$)

intestine cannot be ruled out, the hepatic origin of the hydrophobic ET form is most likely (or more important). In any case, the lipid mechanism of transport of the intestinal LPS into the bloodstream is intended, at least, to ensure the process of ET recirculation from the intestine to the liver and back. Apparently, this provides for the economic consumption of the intestinal LPS, which is regarded as an exohormone by the endotoxin theory of physiology and pathology and is important for adaptation processes [1, 3].

The involvement of the lipid factor in the mechanisms of intestinal ET transport, apparently, is not limited to its entry from the intestine into the bloodstream and, probably, extends to ensuring the possibility of its deposition and circulation in the bloodstream. Our results indirectly confirm this assumption.

The decrease in the concentration of LPS in the blood serum is accompanied by a decrease in the concentration of LDL ($r = -0.44$, $p = 0.041$) and an increase in the concentration of HDL ($r = 0.49$, $p = 0.032$). This finding suggests that the HDL + LPS complex (in the hydrophobic form) represents an LDL fraction (or a substantial part of it). Although this assumption requires more evidence, the results of this study allowed us to propose a working scheme for a detailed study of the lipid mechanism of the intestinal ET transport in the blood, substantiating the possibility of it being deposited in the blood circulation (Fig. 2).

Thus, according to the scheme shown in Fig. 2, of all the possible mechanisms of the intestinal LPS transportation into the blood, only the lipid mechanism can be considered to actually exist today. This mechanism ensures the delivery of the hydrophobic ET form (without the polysaccharide moiety) back to the liver, where its fate can be different: the consumption by the system of fixed macrophages (activation of innate immunity), complexing with HDLs (LDL formation?), and excretion with bile back into the intestine. Fat deficiency in the diet (in the clinical model of inhibition of intestinal lipases), along with a decrease in the concentration of LPS, causes weight loss through the loss of fat tissue. It is also likely that the hydrophobic form of ET can be deposited in the adipose tissue and that the stress response can induce its release from this store into the general blood circulation (these important aspects of the problem require independent studies).

Another, no less important object of the study, were seven middle-aged subjects (41.3 ± 3.6 years) with less significant excess body weight (90.2 ± 0.96 kg), with obesity grade 1, which received little or no food (except water) for a long time. The results of the laboratory tests are shown in Table 2 and Fig. 3.

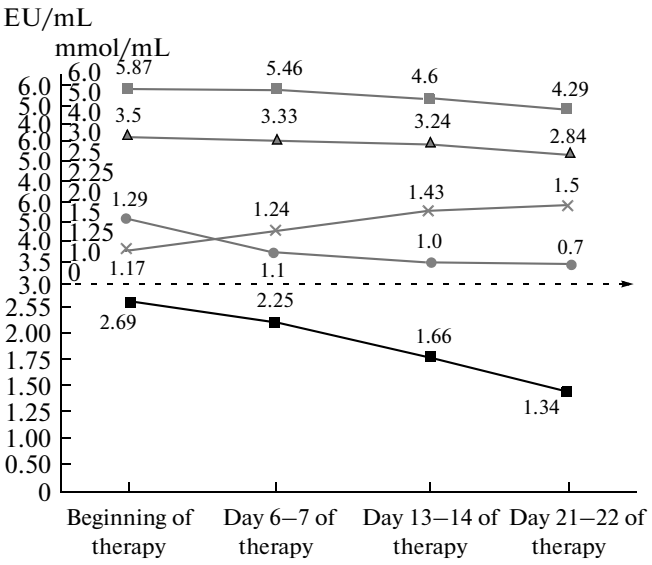


**Fig. 1.** Time course of the intestinal endotoxin concentration, antiendotoxin immunity activity, and lipid profile of the blood of subjects before orlistat therapy. For abbreviation here and in Figs. 2–4, see the Materials and Methods section.

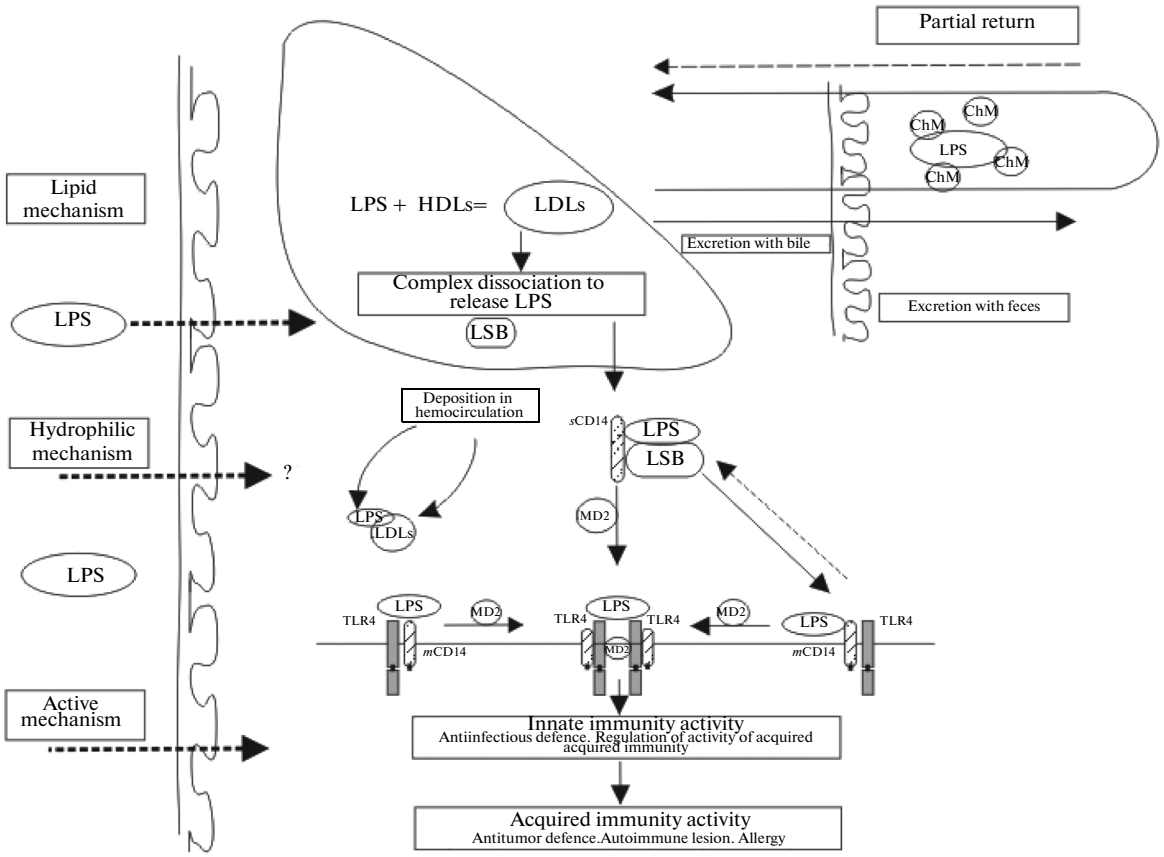


**Fig. 2.** Scheme of lipid transportation mechanism of the intestinal endotoxin into the blood and its depositing it in bloodstream. Designations: LBP, LPS-binding protein; ChM, chylomicrons.

The initial values of the ET concentration and anti-endotoxin immunity (AEI) activity in these subjects significantly differed from those in the control and reference groups (high LPS concentrations and reduced AEI activity). Five to seven days after the beginning of the experiment, all the subjects showed an improvement in health (improving efficiency, "a sense of ease," and good mood), which was accompanied by a significant decrease in the average concentration of ET (from 2.1 ± 0.1 to 1.21 ± 0.06 *EU*/mL) and an increase in the AEI activity to the reference values. This indicates the involvement of the nutritional factor in the regulation of the intestinal LPS concentration in the general circulation.

The positive dynamics in the average ET concentration in the blood serum of subjects was observed until the third week of the experiment (to 1.01 ± 0.08 *EU*/mL); they also maintained their well-being and working capacity, as well as gradually losing weight lss, which decreased on average by 7.7 kg (from 90.2 ± 0.96 to 82.5 ± 2.5) kg on day 17–20 of starvation.

Starting from the fourth week of starvation, almost all the subjects mentioned a deterioration of their health, reduced working capacity, and increased weakness. In two subjects, the weakness was accompanied by vertigo and pain in the heart, and they were withdrawn from the experiment. A characteristic feature of the fourth week of starvation was more intense weight loss (from 82.5 ± 2.5 to 76.6 ± 2.66 kg) and a rapid doubling in the average concentration of LPS (from 1.01 ± 0.08 to 2.15 ± 0.1 *EU*/mL), which was accompanied by an equally rapid and significant increase in the titer of antibodies to ECA (from 185.8 ± 10.1 to 431.2 ± 9.1 OD arb. units) in the blood serum, whereas the titer of anti-GL antibodies remained the same. The dynamics of the studied parameters indicate the entry of the hydrophilic form of the ET intestinal, i.e., the whole LPS molecule containing the polysaccharide moiety. In view of this, the question arises as to what can ensure its delivery, which mechanism—active transportation or something else? Or, perhaps, the increased permeability of the intestinal barrier is due to the degenerative changes in the mucosal epithelial cells? To answer these questions, purpose-oriented independent studies are required. To date, the only clear issue is that the mechanism of the excess entry of intestinal ET in the bloodstream of subjects in the fourth week of fasting was not due to lipid (hydrophobic) transport, which was discussed in the first part of this paper. Such an intense weight loss

**Table 2.** Time course of changes in the endotoxin concentration and antiendotoxin immunity activity as a result of medical starvation

| Parameter | Starvation duration | | | | | | Control |
|---|---|---|---|---|---|---|---|
| | 0 days | 5–7 days | 10–13 days | 17–20 days | 25–27 days | 35–39 days | |
| Number of patients (*n*) | 7 | 7 | 7 | 7 | 5 | 3 | 135 |
| Endotoxin concentration (*EU*/mL) | 2.1 ± 0.1** | 1.21 ± 0.06* | 1.08 ± 0.09* | 1.01 ± 0.08* | 2.15 ± 0.1 | 1.41 ± 0.06 | 1.13 ± 0.05 |
| GL (norm, 190–200 OD arb. units) | 117.0 ± 3.25 | 191.0 ± 2.6 | 176.1 ± 2.8 | 161.1 ± 4.0 | 133.2 ± 2.6 | 355.6 ± 15.0** | 149.9 ± 8.4 |
| ECA (norm, 380–400 OD arb. units) | 219.0 ± 6.0 | 397.5 ± 5.4 | 488.7 ± 9.4 | 185.8 ± 10.1 | 431.2 ± 9.1 | 333.6 ± 12.7 | 313.6 ± 14.8 |

Notes: * Differences between the experimental group and the medical-starvation group before the beginning of fasting were significant at $p < 0.05$;

** differences between the experimental and control groups were significant at $p < 0.05$.

by test subjects in the fourth week of the experiment was, apparently, due to the activation of catabolic processes, which may involve the intestinal barrier.

Only three subjects reached the last control point (day 35–39 of starvation). Two subjects had to stop participating in the experiment due to serious health problems, such as retrosternal pain, nausea, severe weakness, and feeling faint and dizzy, which continued to increase in the course of starvation. For this reason, on days 35–39 of the study, we expected to detect an increase in the LPS concentration in the blood serum of subjects; however, that actually was not the case. The average ET concentration significantly decreased

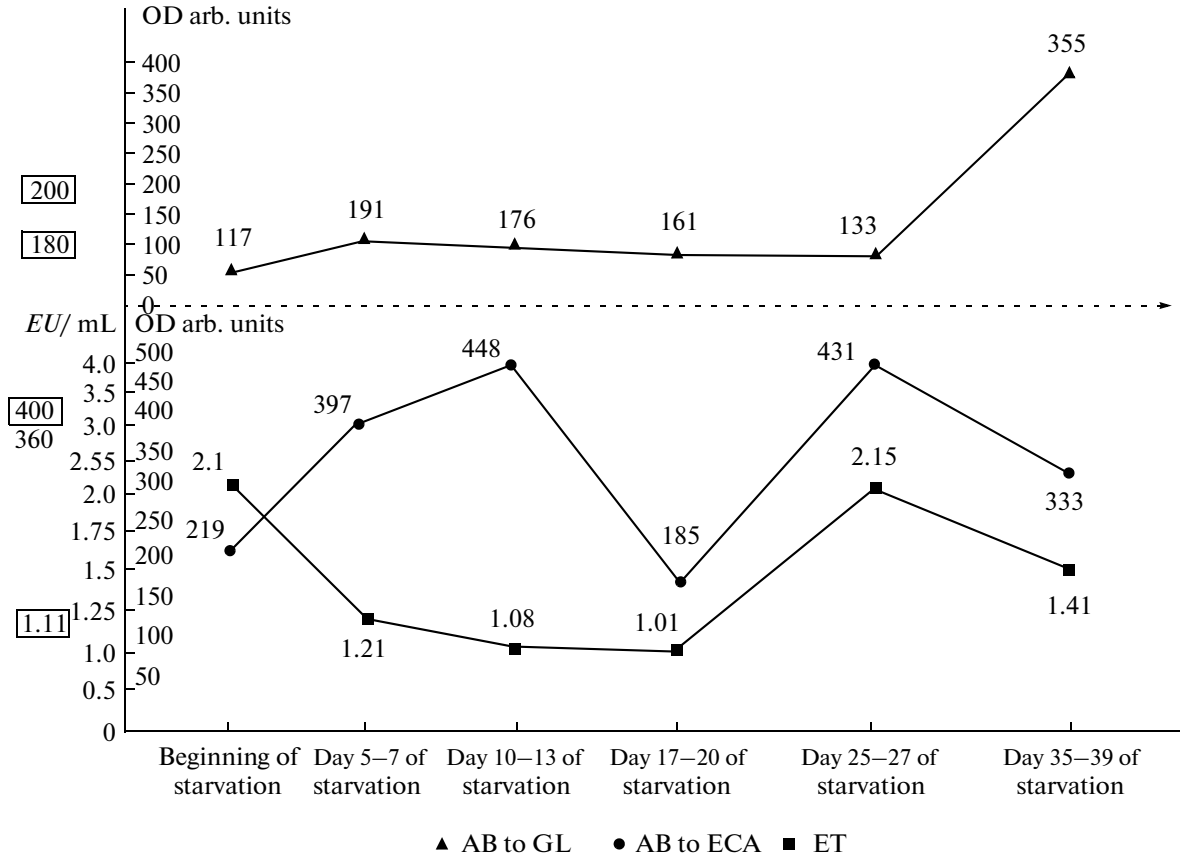


**Fig. 3.** Time course of changes in the intestinal endotoxin concentration and antiendotoxin immunity activity after medical starvation. Normal values are shown on the left.

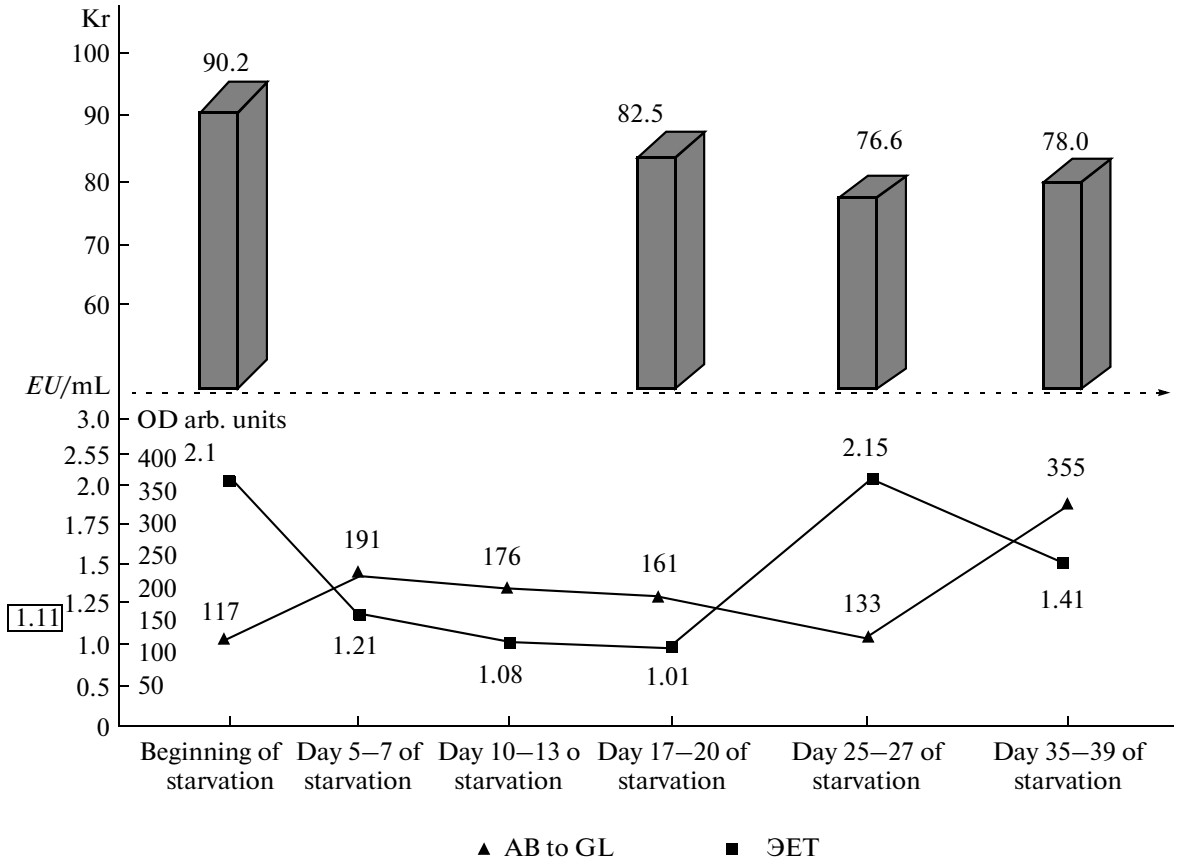


**Fig. 4.** Time course of changes in the body weight, endotoxin concentration, and the titer of antibodies to *Re*-glycolipid (the hydrophobic moiety of LPS) in subjects during medical starvation. Normal values are shown on the left.

(from 2.15 ± 0.1 to 1.41 ± 0.6 *EU*/mL). Almost identical dynamics were recorded for the average titer of antibodies to ECA (from 431.2 ± 9.1 to 333.6 ± 12.7 OD arb. units). However, the most interesting was the nearly tripling in the average titer of anti-GLP antibodies (from 133.2 ± 2.6 to 355.6 ± 8.15 *OD* arb. units), which may indicate the initial phase of development of the systemic inflammatory response syndrome (SIRS) induced by EA. An almost similar pattern was observed by Hasanova et al. [15] in one-third of HIV-infected patients, the development of immunodeficiency which is largely determined by the SIRS. High concentrations of anti-GLP antibodies are characteristic of patients with autoimmune disorders and cancer [16]. Another seemingly paradoxical fact (Fig. 4)—the trend for an increase in the average body weight in the fifth week of starvation (from 76.6 ± 2.66 to 78.0 ± 2.8 kg)—can be regarded from the standpoint of SIRS as the initial phase of the edema syndrome, which is a pathognomonic symptom of sepsis [1]. However, due to the small number of subjects, our interpretation of the results should be regarded as a hypothesis (which has some factual confirmation) rather than a postulation (Fig. 4).

Further development of this direction in the pathology of eating behavior, which is essentially a clinical model to study anorexia, could be very promising, because the existing schemes of anorexia treatment do not include the immune and, furthermore, endotoxin component of treatment and rehabilitation of these patients.

To conclude the presentation of the results of this study, we decided to compare the initial average ET of and anti-GL antibody titers in 14 subjects, all of whom had symptoms of obesity of varying degrees of severity, with those in the control group. These values were 2.41 ± 0.11 and 1.13 ± 0.05 *EU*/mL ($p < 0.05$) vs 121.7 ± 2.6 and 149.9 ± 8.4 OD arb. units ($t = 1.2$), respectively. These data suggest that obese patients suffer from chronic EA, which is characterized by endotoxin tolerance (i.e., the inability to respond to the excess LPS by fever) and an increased proinflammatory background [1]. Similar results were demonstrated by our foreign colleagues [7, 8, 17].

Thus, our results are indicative of the involvement of nutritional factors in the initiation of inflammation, because they could be the sole cause of EA, which is regarded by the endotoxin theory as a pre-

disease, or a versatile factor of the pathogenesis of human diseases [1–5].

## CONCLUSIONS

1. The nutritional factor can be the sole cause of the excess entry of the intestinal ET into the systemic circulation and, therefore, a probable inflammation inducer, which determines the appropriateness of further development of this research direction.

2. The lipid component of the diet plays a key role in the mechanism of transport of LPS (its hydrophobic form devoid of the polysaccharide moiety) into the blood. Intestinal lipase inhibitors cause a significant decrease in the ET concentration in the general circulation, which allows recommending fat-depleted foods for prevention and treatment of diseases.

3. The lipid mechanism of LPS transport, apparently, is not limited to ensuring the delivery of its hydrophobic form from the intestine into the blood and its recirculation in the intestine–liver–intestine route. It is likely that this mechanism is also involved in depositing ET in the bloodstream in combination with HDLs, which apparently represents a considerable part of low-density lipoproteins.

4. The concentration of LPS in the general circulation of obese patients is much higher than that in the control group. The hydrophobic form of LPS can be possibly deposited in adipose tissue. Obesity and increased levels of ET in the general circulation are the result of fat food abuse, which, in combination with ethanol, provides greater absorption of lipids in the blood.

5. The complete absence of food (except water) in the diet ensures a considerable decrease in the LPS concentration in the first 20 days of starvation, which can be used for preventive medical purposes.

6. Starvation for more than three weeks is dangerous for ones health, because it entails the development of acute EA, a drastic deterioration of the medical condition, and the induction of SIRS, which is not taken into account in the existing schemes of treatment and rehabilitation of patients with anorexia.

7. In the fourth week of starvation, intestinal LPS is delivered into the blood in the form of the whole ET molecule, which may be the result of alternative changes in the intestinal mucosa (due to the predominance of the catabolic processes) and/or evidence of a hydrophilic transportation mechanism of LPS from the intestine into the blood.

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SPELL: 1. lifespan, 2. microflora