MORPHOLOGY, PHYSIOLOGY AND PATHOPHYSIOLOGY

LIPOPOLYSACCHARIDE-BINDING SYSTEMS IN THE PATHOGENESIS OF VASCULAR COMPLICATIONS IN PATIENTS WITH TYPE 1 DIABETES MELLITUS

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RESUME

Rationale. *Disturbance of glycemia in type 1 diabetes mellitus (DM1) leads to the development of oxidative stress and damage to the barrier organs for lipopolysaccharide (LPS), which is accompanied by its increased translocation into the systemic bloodstream, inducing vascular damage.*
The aim. *Determination of the influence of the level of major lipopolysaccharide-binding systems on the risk of macro- and microvascular complications of DM1.*
Materials and methods. *The study included 92 patients with a verified diagnosis of type 1 diabetes mellitus. Patients underwent examination of biomaterial (blood plasma) by enzyme-linked immunosorbent assay (ELISA) to determine the level of lipopolysaccharide-binding protein (LBP), bactericidal permeability-increasing protein (BPI) and sCD14, as well as a marker of systemic inflammation – CRP. ROC-analysis with ROC-curve construction was used to assess the quality of the prognostic model efficiency, as well as to find the optimal point (cut-off point) of the threshold value of the level of the investigated markers.*
Results. *ROC-analysis revealed statistically significant patterns of relationship between peripheral blood LBP level and risk of arterial hypertension (AH) in patients with DM1 ($p = 0.014$), as well as relationship between peripheral blood LBP and sCD14 level and risk of diabetic nephropathy (DN) in patients with DM1 ($p = 0.042$ and $p = 0.048$).*
Conclusion. *We have revealed a statistically significant influence of LBP and sCD14 concentrations on the development of vascular lesions in DM1, with a decrease in the level of the main LPS-binding systems accompanied by an increased risk of AH and DN. Lipopolysaccharide of Gram-negative flora plays an important role in the development of complications of DM1, which is largely due to the peculiarities of the response to LPS under conditions of hyperglycemia and dysfunction of the normal response to LPS, accompanied by protective reactions and subsequent clearance of LPS.*

Key words: *type 1 diabetes mellitus, complications, nephropathy, arterial hypertension, endotoxin, lipopolysaccharide, imbalance*

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ЛИПОПОЛИСАХАРИД-СВЯЗЫВАЮЩИЕ СИСТЕМЫ В ПАТОГЕНЕЗЕ СОСУДИСТЫХ ОСЛОЖНЕНИЙ У ПАЦИЕНТОВ С САХАРНЫМ ДИАБЕТОМ 1-ГО ТИПА

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РЕЗЮМЕ

Обоснование. *Нарушение гликемии при сахарном диабете 1-го типа (СД1) приводит к развитию окислительного стресса и повреждению барьерных органов для липополисахарида (ЛПС), что сопровождается повышенной его транслокацией в системный кровоток, индуцируя сосудистое поражение.*

Цель исследования. *Определение влияния уровня основных липополисахарид-связывающих систем на риск развития макро- и микрососудистых осложнений СД1.*

Материалы и методы. *В исследование было включено 92 пациента с верифицированным диагнозом Сахарный диабет 1-го типа. Пациентам было проведено исследование биоматериала (плазмы крови) методом иммуноферментного анализа (ИФА) для определения уровня липополисахарид-связывающего белка (ЛСБ), бактерицидного белка, повышающего проницаемость (BPI) и sCD14, а также маркера системного воспаления – СРБ. Для оценки качества эффективности прогностической модели, а также для нахождения оптимальной точки (точка cut-off) порогового значения уровня исследуемых маркеров применялся ROC-анализ с построением ROC-кривой.*

Результаты. *В результате ROC-анализа выявлены статистически значимые модели взаимосвязи уровня ЛСБ периферической крови с риском развития артериальной гипертензии (АГ) у пациентов с СД1 (p = 0,014), а также взаимосвязи уровня ЛСБ и sCD14 периферической крови с риском развития диабетической нефропатии (ДН) у пациентов с СД1 (p = 0,042 и p = 0,048).*

Заключение. *Нами выявлено наличие статистически значимого влияния концентрации ЛСБ и sCD14 на развитие сосудистых поражений у пациентов с СД1, при этом снижение уровня основных ЛПС-связывающих систем сопровождается повышением риска развития АГ и ДН. Липополисахарид грамотрицательной флоры играет важную роль в развитии осложнений СД1, что во многом связано с особенностями ответа на ЛПС в условиях гипергликемии и нарушения функции нормального ответа на ЛПС, сопровождающегося защитными реакциями и последующим клиренсом ЛПС.*

Ключевые слова: *сахарный диабет 1-го типа, осложнения, нефропатия, артериальная гипертензия, эндотоксин, липополисахарид, дисбаланс*

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Recent studies have shown that the number of individuals suffering from type 1 diabetes mellitus (DM1) in Russia has reached 277,100 and is continuing to increase [1]. Specifically, the mortality rate among women with DM1 is worsening, with the average age at death over the last 12 years decreasing from 62.1 to 56 years [1]. Individuals with DM1 face a significantly increased risk of developing high blood pressure at a younger age compared to healthy individuals. In the group of young individuals with DM1, there is an increased prevalence of arterial hypertension (AH) (4–7 %), compared to those without diabetes (1–5 %) [2]. This is due to factors such as long-term hyperglycemia, development of diabetic nephropathy, oxidative stress, lipid metabolism disorders, and damage to the vascular structure. Hypertension contributes to the development of both micro- and macrovascular complications in patients with DM1 [3].

In most cases, hypertension in people with DM1 begins to manifest concurrently with the onset of albuminuria, suggesting a renal origin for the hypertension. However, it is important to note that the development of hypertension in individuals with DM1 cannot be solely attributed to nephropathy development [4]. Thus, diabetic nephropathy does not appear to be a universal factor contributing to hypertension in those with DM1. Additionally, hypertension development in these patients is influenced by other factors such as oxidative stress, advanced glycation end product exposure, endotoxin exposure, and intracellular lipoprotein accumulation, leading to endothelial dysfunction [5]. These processes can contribute to the development of vascular lesions and increase the risk of hypertension.

In real-world clinical practice, achieving optimal glycemic control is not feasible for all patients due to various factors. A combination of abnormal blood glucose levels, low-grade inflammation, and lipid metabolism disorders can lead to oxidative stress and vascular damage, increasing the risk of cardiovascular complications in individuals with DM1 [6]. Damage to vital organs, especially the small intestine, and changes in the intestinal microbiome can result in increased translocation of bacterial components, such as lipopolysaccharides (endotoxins) from gram-negative bacteria, into the lymphatic and circulatory systems. This can lead to the development of "metabolic endotoxemia" [7].

Even at relatively low levels of LPS, a sustained activation of the signaling pathways associated with soluble CD14 receptors (sCD14) and toll-like receptors 4 (TLR4) has been observed [8]. This is linked to prolonged low-grade inflammation, alterations in the extracellular matrix architecture of the pancreas, endothelial dysfunction, and vascular inflammation.

In 2011, a study conducted by Russian researchers found that LPS levels in the blood of individuals with newly diagnosed DM1 were ten-fold higher than in healthy individuals [9]. This indicates that people with DM1 are exposed to an increased level of endotoxin. To date, there have been only a limited number of studies investigating the issue of endotoxinemia and LPS-binding mechanisms in individuals with DM1 [10-13]. These studies have primarily focused on analyzing LPS levels, LPS antibodies (EndoCAb), and the level of systemic inflammation. However, they have not addressed the relationship between LPS and vascular damage in these patients.

In this regard, **the aim of our study** was to investigate the impact of the levels of key lipopolysaccharide-binding proteins on the risk of macro- and microvascular complications in patients with type 1 diabetes mellitus.

MATERIALS AND METHODS

The study involved 92 patients diagnosed with type 1 diabetes mellitus who were admitted to the Endocrinology Department of the N.A. Semashko Republican Clinical Hospital in Simferopol for treatment. All patients underwent a blood plasma sample upon admission to the study.

Inclusion criteria for the study group with type 1 diabetes was a confirmed diagnosis of this condition.

Exclusion criteria included patients over the age of 50, pregnant women, individuals with a history of cancer, inflammatory bowel disease, clinical signs of acute inflammation or fever (Table 1).

Data on the presence of comorbid conditions were collected from medical records of previous hospitalizations (outpatient charts).

Patients underwent an enzyme-linked immunosorbent assay (ELISA) test of their blood plasma to measure levels of the main lipopolysaccharide-binding proteins (lipopolysaccharide-binding protein (LBP), bactericidal permeability-increasing protein (BPI), and sCD14) as well as the systemic inflammation marker CRP.

The concentrations of LBP (ng/ml), BPI (pg/ml), sCD14 (pg/ml), and CRP (mg/l) in blood plasma were measured using a quantitative, highly sensitive ELISA test manufactured by Cloud Clone Corporation (Wuhan, Hubei, China).

The studies were conducted in compliance with the Helsinki Declaration as revised in 2013, and all respondents provided written informed consent prior to participating in the study. The study (Protocol No. 10) was approved by the local ethics committee of the V.I. Vernadsky Crimean Federal University (Simferopol) on October 10, 2024.

RESULTS AND DISCUSSION

As a result of the ROC analysis of the relationship between peripheral blood LBP level and the risk of hypertension in patients with DM1, the area under the ROC curve was 0.771 ± 0.084, with a 95% CI: 0.605–0.936. The model was statistically significant (p = 0.014) (Fig. 1). The cut-off value for serum LBP concentration at the optimal point was 5.65 mg/l. If the LBP level was less than or equal to this value, there was a high risk of developing hypertension. The sensitivity and specificity of the method were 80.0 % and 70.8 %, respectively.

The ROC models for the effects of sCD14, BPI, and CRP were not statistically significant ($p > 0.05$).

In a ROC analysis of the relationship between peripheral blood LBP and sCD14 levels and the risk of developing DN in patients with DM1, the area under the ROC curve for LBP and sCD14 were 0.740 ± 0.099 with 95% CI: 0.547–0.934 and 0.702 ± 0.097 with 95% CI: 0.511–0.893, respectively. These models were statistically significant ($p = 0.042$ and $p = 0.048$) (Fig. 2). The cut-off values for serum LBP concentration at the cut-off point was 6.81 mg/l. The cut-off value for sCD14 was 10.6 pg/ml. At LBP and sCD14 levels less than or equal to these values, a high risk of DN was predicted. The sensitivity and specificity of the method for LBP were 69.2 % and 75.0 %, respectively. For sCD14, the sensitivity and specificity of the method were 73.1 % and 75.0 %, respectively.

ROC curve models for the effects of BPI and CRP were not statistically significant ($p > 0.05$).

The results of our study confirm the impact of the main lipopolysaccharide-binding systems, specifically LPS and sCD14, on the risk of developing DN and hypertension in patients with DM1. Intriguingly, there is a negative correlation: the lower the levels of LPS-binding systems are, the greater the risk of hypertension.

According to the literature, the levels of LPS in the blood of patients with DM1 significantly exceed those of healthy individuals and are correlated with inflammation levels [10-13]. Despite this increased LPS, however, Aravindhan V. et al. did not find statistical differences in sCD14 levels between patients with DM1 and the control group ($p = 0.61$). Moreover, the LBP level was even significantly lower in the group of patients with DM1 ($p < 0.001$). Additionally, the authors observed an increase in the levels of proinflammatory cytokines such as interleukin-6 (IL-6), IL-1β, tumor necrosis factor-α (TNF-α) and granulocyte-macrophage colony-stimulating factor (GM-CSF) in patients with DM1, and a direct correlation between LPS levels and TNF-α levels ($r = 0.312$; $p = 0.009$), IL-6 levels ($r = 0.245$; $p = 0.041$) and IL-1β levels ($r = 0.428$; $p < 0.001$) [10].

The CD14 receptor may play a significant role in the impact of LPS on endothelial function and the progression of atherosclerotic changes. Based on the literature, levels of soluble CD14 (sCD14) have been shown to directly correlate with the formation of atheromatous plaques in carotid arteries, as well as with measures of aortic stiffness [14]. It is thought that CD14 is not expressed on endothelial cells, and the primary interaction with LPS occurs through sCD14 [15]. However, there have been reports of CD14 expression *in vitro* in endothelial cells from human umbilical veins [16], as well as on the surfaces of smooth muscle cells in coronary arteries [17].

A study has also found a possible association between serum LBP levels and carotid intimal thickness, which is a common marker of atherosclerosis disease. This suggests that serum LBP may play a role in the development of this condition [18]. Other studies have indicated that infections with a low LBP/CD14 ratio are also linked to the development of atherosclerosis [15]. Additionally, a previous study found that a low LBP/CD14 ratio is linked to activation of smooth muscle and endothelial cells in human coronary arteries [17].

However, CD14 is not the sole mediator of LPS effects on vascular cells. A study found that LPS effects on dermal microvascular endothelial cells were mediated by TLR4, which was expressed on these cells [19]. Atherosclerotic plaques, studied in various animal models and in humans, confirmed TLR4 expression, particularly on inflammatory macrophages and endothelial cells [20]. Furthermore, studies have demonstrated that TLR4 is expressed on both smooth muscle and endothelial cells in human coronary arteries and saphenous veins [21].

TABLE 1

CHARACTERISTICS OF THE PATIENTS INCLUDED IN THE STUDY

Signs	DM1 ($n = 92$) 1
Sex — Male abs. (%)	45 (48.91)
Sex — Male abs. (%)	47 (51.09)
Age (full years) Me [Q1;Q3]	34,5 [23.0; 47.0]
BMI, kg/m^2 Me [Q1;Q3]	23.0 [21.0; 26.7]
Achievement of target HbA1c levels, abs. (%)	16 (18.0)
Achievement of LDL target levels, abs. (%)	20 (21.7)
IHD: angina pectoris, abs. (%)	6 (6.52)
Angiopathy of the lower extremities, abs. (%)	38 (41.3)
AG, abs. (%)	32 (34.78)
Nephropathy, abs. (%)	73 (79.3)
Retinopathy, abs. (%)	68 (73.9)
Polyneuropathy, abs. (%)	66 (71.7)
Duration of illness (in full years) Me [Q1, Q3]	9.0 [4.0; 19.0]
Statins intake, abs. (%)	3 (3.3)
Angiotensin-converting enzyme inhibitor use, abs. (%)	15 (16.3)
Calcium antagonist intake, abs. (%)	7 (7.6)
Diuretic intake, abs. (%)	11 (12.0)
Beta-blocker intake, abs. (%)	7 (7.6)

Note. BMI – body mass index, IHD – ischemic heart disease, AG – arterial hypertension.

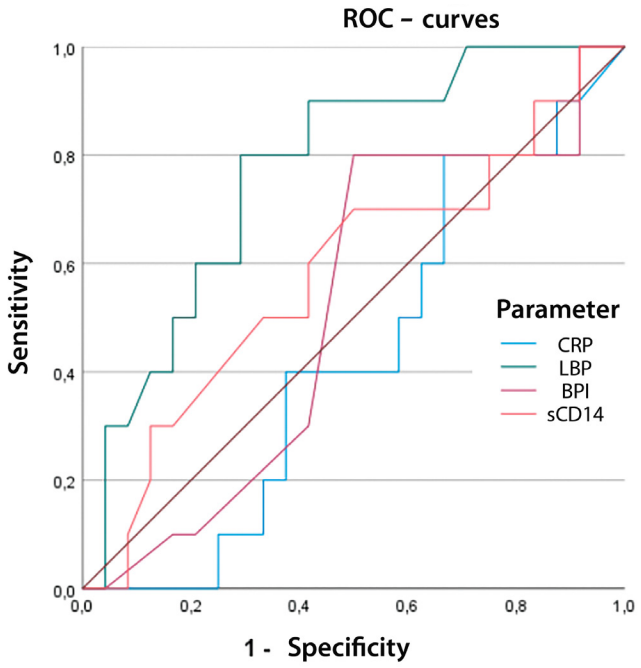

FIG. 1.
ROC-curves of the dependence of the risk of arterial hypertension on the level of lipopolysaccharide-binding systems

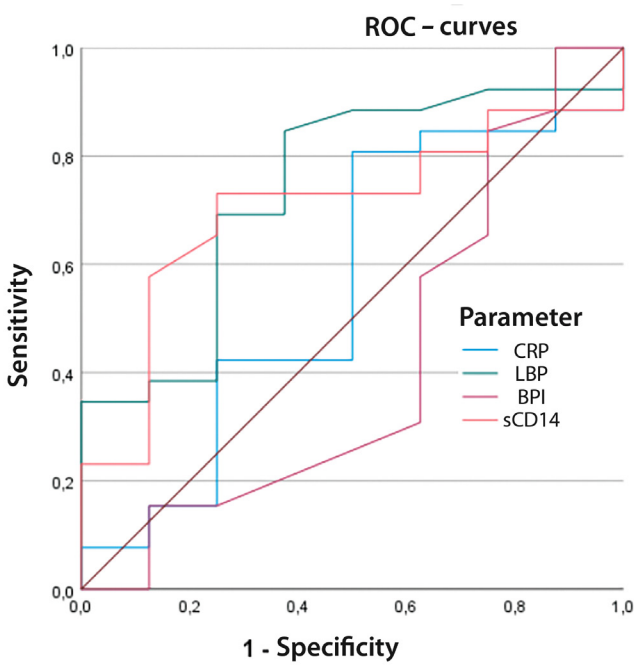

FIG. 2.
ROC-curves of the dependence of the risk of diabetic nephropathy on the level of lipopolysaccharide-binding systems

It has been postulated that LBP in combination with high-density lipoprotein (HDL) interacts with stabilin to mediate a series of metabolic reactions resulting in the inactivation and breakdown of LPS [22]. However, the exact physiological pathway and participants in these processes have not yet been fully established. This hypothesis is further supported by evidence of HDL dysfunction in patients with DM1, indicating that the LBP-HDL complex may lack the necessary anti-inflammatory properties. There is also evidence of increased intestinal permeability in individuals with CD14 deficiency, which could lead to increased LPS translocation into the portal and systemic circulations, increasing LPS concentrations and potentially damaging vascular endothelium [23].

In our view, patients with DM1 experience a "depletion" or imbalance in LPS-binding systems, which lead to reduced clearance and elimination of LPS, resulting in direct vascular damage associated with LPS. This phenomenon of "depletion", on the one hand, may be a consequence of increased concentrations of circulating LPS in the bloodstream of patients with DM1 and excessive consumption of LPS-binding system components. On the other hand, prolonged hyperglycemia in these patients can lead to protein glycation, disrupting its conformation and functional activity, potentially affecting LPS and sCD14 [24].

CONCLUSION

We have found a statistically significant impact of LPS and sCD14 levels on the development of vascular complications in patients with DM1. Reduced levels of the primary LPS-binding proteins are associated with an increased risk of hypertension and respiratory dysfunction. Gram-negative lipopolysaccharide plays a crucial role in the pathogenesis of complications in this condition, primarily due to its specific effects under conditions of elevated glucose levels and impaired normal responses to LPS, including protective mechanisms and subsequent clearance of LPS.

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Conflicts of interest

No potential conflict of interest relevant to this article reported.

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