Received: 29 August 2023 / Accepted: 24 October 2023 / Published online: 28 December 2023

DOI 10.34689/SH.2023.25.6.021

UDC 616-018-379-008.64

PARTICIPATION OF BIOMARKERS FABP4, ENDOCAN, PAI-1 TO THE DEVELOPMENT OF ENDOTHELIAL DYSFUNCTION IN PREDIABETES CONDITION

Viktoriya F. Parakhina[1], https://orcid.org/0000-0003-4250-6125

Yelena M. Laryushina[1], http://orcid.org/0000-0002-9590-690X

Olga A. Ponomareva[1], http://orcid.org/0000-0002-0222-5794

[1] NCJSC «Medical University of Karaganda», Karaganda, Republic of Kazakhstan.

Abstract

Introduction. The search of tools for the early detection of conditions associated with both carbohydrate metabolism disorders and the early development of endothelial dysfunction (ED), which subsequently leads to the development of cardiovascular events, continues currently. There are a large number of it for assessing these conditions, we settled on the most sensitive, reliable, economically low-cost methods: studying the biomarkers of endothelial dysfunction Endocan, FABP4, PAI-1 and ultrasound determination of intima media thickness in patients with prediabetes, risk of T2DM.

Aim. the participation and contribution of biomarkers: FABP4, Endocan, PAI-1 to study on the development of ED in patients with prediabetes.

Search strategy. This review primarily includes data from original studies, literature reviews found in Scopus, Web of Science, and Pubmed (Medline) databases, using appropriate keywords. The depth of the search was twenty years, due to the limited number of studies conducted on this topic and the relatively recent and growing interest of researchers in this field.

Results. All three biomarkers (FABP4, Endocan, PAI-1) appear in the early stages of endothelial dysfunction, when the development of cardiovascular events is reversible, which is the interest for the further research. Moreover, these biomarkers are responsible for different pathogenetic mechanisms of the development of endothelial dysfunction, and their combination allows one to immediately evaluate lipid metabolism disorders (FABP4), endothelial damage (Endocan), and increased thrombus formation (PAI-1). Thus, it is more accurate to establish the appearance of endothelial dysfunction in the early stages of carbohydrate metabolism disorder and prediabetes. It is worth noting that studies assessing the level of endothelial dysfunction biomarkers in patients with prediabetes and the risk T2DM have been poorly studied. And also their simultaneous association in conjunction with the study of intima media thickness in patients with prediabetes and the risk of T2DM has not been carried out at all.

Conclusions. It is scientific interest to study these markers of endothelial dysfunction at the prenosological stage, in the absence of vascular accidents manifested by diabetic micro - and macroangiopathies. Studying this issue will identify successful tools for future early detection and prevention of vascular injury and CVE.

Keywords: *endothelial dysfunction, biomarkers, prediabetes, cardiovascular events.*

Резюме

УЧАСТИЕ БИОМАРКЕРОВ FABP4, ENDOCAN, PAI-1 В РАЗВИТИИ ЭНДОТЕЛИАЛЬНОЙ ДИСФУНКЦИИ В УСЛОВИЯХ ПРЕДИАБЕТА

Виктория Ф. Парахина[1], https://orcid.org/0000-0003-4250-6125

Елена М. Ларюшина[1], http://orcid.org/0000-0002-9590-690X

Ольга А. Понамарева[1], http://orcid.org/0000-0002-0222-5794

[1] НАО «Медицинский Университет Караганды», г. Караганда, Республика Казахстан.

Введение. В настоящее время продолжается поиск инструментов для раннего выявления состояний, связанных как с нарушениями углеводного обмена, так и с ранним развитием эндотелиальной дисфункции (ЭД), приводящей в последующем к развитию кардиоваскулярных событий (КВС). Для оценки этих состояний существует большое количество методик, мы остановились на наиболее чувствительных, надежных, экономически недорогих методах: оценка биомаркеров эндотелиальной дисфункции Endocan, FABP4, PAI-1 и ультразвуковое определении толщины интимы-медиа у пациентов с преддиабетом, риском развития СД2.

Цель. Изучить участие и вклад биомаркеров: FABP4, Эндокан, PAI-1 в развитие эндотелиальной дисфункции у пациентов с предиабетом.

Стратегия поиска. В этот обзор в первую очередь включены данные оригинальных исследований, обзоров литературы, найденных в базах данных Scopus, Web of Science и Pubmed (Medline), с использованием соответствующих ключевых слов. Глубина поиска составила двадцатилетие из-за ограниченного количества исследований, проведенных по этой теме, а также относительно недавнего и растущего интереса исследователей в этой области.

Результаты. Все три биомаркера (FABP4, Эндокан, PAI-1) появляются на ранних стадиях ЭД, когда развитие КВС обратимо, что представляет интерес для дальнейших исследований и ранней диагностики эндотелиальных проблем и сосудистых катастроф. Более того, эти биомаркеры ответственны за разные патогенетические

механизмы развития эндотелиальной дисфункции, а их сочетание позволяет сразу оценить нарушения липидного обмена (FABP4), повреждение эндотелия (Endocan) и повышенное тромбообразование (PAI-1) и таким образом, точнее установить появление ЭД на ранних стадиях нарушения углеводного обмена и предиабета. Следует отметить, что исследования по оценке уровня биомаркеров эндотелиальной дисфункции у пациентов с предиабетом и риском СД2 не многочислены. Более того, одновременная оценка их взаимосвязи в комплексе с исследованием толщины интимы-медиа у пациентов с предиабетом и риском развития СД2 вообще не проводились.

Выводы. Научный интерес представляет изучение этих маркеров ЭД на донозологическом этапе, при отсутствии сосудистых катастроф, проявляющихся диабетическими микро- и макроангиопатиями. Изучение данного вопроса позволит выявить успешные инструменты для будущего раннего выявления и предотвращения повреждения эндотелия сосудов и ССВ.

Ключевые слова: *эндотелиальная дисфункция, биомаркеры, преддиабет, сердечно-сосудистые события.*

Түйіндеме

ПРЕДДИАБЕТ ЖАҒДАЙЫНДА ЭНДОТЕЛИАЛДЫ ДИСФУНКЦИЯ ДАМУЫНА FABP4, ENDOCAN, PAI-1 БИОМЕРКЕРЛЕРІНІҢ ҚАТЫСУЫ

Виктория Ф. Парахина[1], https://orcid.org/0000-0003-4250-6125

Елена М. Ларюшина[1], http://orcid.org/0000-0002-9590-690X

Ольга А. Понамарева[1], http://orcid.org/0000-0002-0222-5794

[1] «Қарағанды медицина университеті» КЕАҚ, Қарағанды қ., Қазақстан Республикасы.

Кіріспе. Қазіргі уақытта көмірсулар алмасуының бұзылуымен де, кейіннен кардиоваскулярлы оқиғаларының (КВО) дамуына әкелетін эндотелий дисфункциясының (ЭД) ерте дамуымен де байланысты жағдайларды ерте анықтау құралдарын іздеу жалғасуда. Бұл жағдайларды бағалаудың көптеген әдістері бар, біз ең сезімтал, сенімді және экономикалық тұрғыдан арзан әдістерге тоқтадық, олар: эндотелий дисфункциясының биомаркерлерін бағалау Endocan, FABP4, PAI-1 және 2 типті қант диабетінің даму қаупі бар, преддиабетпен ауыратын науқастарда интима-медиа қалыңдығын ультрадыбыстық анықтау.

Мақсаты. FABP4, Endocan, PAI-1 биомаркерлерінің преддиабетпен ауыратын науқастарда эндотелий дисфункциясының дамуына әсерін зерттеу.

Іздеу стратегиясы. Бұл шолуға, ең алдымен, сәйкес негізгі сөздерді пайдалана отырып, Scopus, Web of Science және Pubmed (Medline) дерекқорларында табылған түпнұсқа зерттеулерден, әдебиеттерге шолулардан алынған деректер кіреді. Бұл тақырып бойынша жүргізілген зерттеулердің шектеулі көлеміне және зерттеушілердің осы салаға деген салыстырмалы түрде жақында және өсіп келе жатқан қызығушылығына байланысты іздеу жиырма жыл тереңдікте жүргізілді.

Нәтижелер. Барлық үш биомаркер (FABP4, Endocan, PAI-1) эндотелий дисфункциясының ерте кезеңдерінде, кардиоваскулярлы оқиғалардың дамуы қайтымды болған кезде пайда болады, бұл әрі қарай зерттеу және эндотелий проблемалары мен тамырлық апаттарды ерте диагностикалау үшін қызығушылық тудырады. Сонымен қатар, бұл биомаркерлер эндотелий дисфункциясы дамуының әртүрлі патогенетикалық механизмдеріне жауап береді және олардың комбинациясы липидтер алмасуының бұзылуын (FABP4), эндотелийдің зақымдалуын (Endocan) және тромб түзілуінің жоғарылауын (PAI-1) дереу бағалауға мүмкіндік береді. Осылайша, көмірсулар алмасуының бұзылуының және преддиабеттің ерте кезеңдерінде эндотелий дисфункциясының пайда болуын анықтау дәлірек болады. Айта кету керек, преддиабет және 2 типті қант диабеті қаупі бар науқастарда эндотелий дисфункциясының биомаркерлерінің деңгейін бағалайтын зерттеулер аз зерттелген. Сондай-ақ, преддиабетпен ауыратын науқастарда интима-медиа қалыңдығын және 2 типті қант диабетінің даму қаупін зерттеумен бірге олардың бір мезгілде байланысын бағалау мүлде жүргізілмеген.

Қорытынды. Диабеттік микро- және макроангиопатиямен көрінетін тамырлық апаттар болмаған кезде эндотелий дисфункциясының осы маркерлерін зерттеу ғылыми қызығушылық тудырады. Бұл мәселені зерттеу болашақта қан тамырларының зақымдануы мен жүрек-қан тамырлары оқиғаларын ерте анықтау және алдын алу үшін табысты құралдарды анықтайды.

Негізгі сөздер: *эндотелиалды дисфункция, биомаркерлер, преддиабет, жүрек-тамыр жағдайлары.*

Bibliographic citation:

Parakhina V.F., Laryushina Ye.M., Ponomareva O.A. Participation of biomarkers FABP4, Endocan, PAI-1 to the development of endothelial dysfunction in prediabetes condition // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2023, (Vol.25) 6, pp. 181-190. *doi 10.34689/SH.2023.25.6.021*

Парахина В.Ф., Ларюшина Е.М., Понамарева О.А. Участие биомаркеров FABP4, Endocan, PAI-1 в развитии эндотелиальной дисфункции в условиях предиабета // Наука и Здравоохранение. 2023. 6(Т.25). С. 181-190. *doi 10.34689/SH.2023.25.6.021*

Парахина В.Ф., Ларюшина Е.М., Понамарева О.А. Преддиабет жағдайында эндотелиалды дисфункция дамуына FABP4, Endocan, PAI-1 биомеркерлерінің қатысуы // Ғылым және Денсаулық сақтау. 2023. 6 (Т.25). Б. 181-190. *doi 10.34689/SH.2023.25.6.021*

Introduction

The mortality rate from cardiovascular diseases (CVD) exceed 17.9 million in 2019, It was 32% of all mortality around the globe [21,37,78]. In Kazakhstan, this mortality was 25.9% [72,76]**.** CVD still remain the leading ones. However, an equally significant non-infectious disease is type 2 diabetes mellitus (T2DM) makes an important contribution to the development of endothelial dysfunction. Diabetes is also on the rise from year to year, increasing morbidity and mortality from it. The prevalence of T2DM in the Republic of Kazakhstan increased by 44% from 2004 to 2017, and amounted to 305,160 people in 2015 [4,77]. Beyond diabetes, more than 352.1 million has prediabetes including impaired fasting glucose and impaired glucose tolerance. World health organization and International diabetes federation make prediction of prediabetes grown up to half a billion by 2045 [1,3,40]. This trend is caused by such modifiable risk factors of T2DM as overweight, obesity, unhealthy and junk food and sedentary habits. The global mortality from T2DM In 2016 reached 1.6 million. All carbohydrate metabolism disorders contributed to extra 2.2 million deaths, deteriorating the cardiovascular diseases (CVD) prevalence [2,40].

Prediabetes is a condition preceding T2DM, manifested by impaired carbohydrate metabolism in the form of fasting hyperglycemia, impaired glucose tolerance and euglycemic insulin resistance [9,61,67,71]. Furthermore, these risk factors lead not only to T2DM but also to development and progression of CVD [6,7,15,29,39,41,43,49,58,59,61,66,82]. According to a number of studies, an increase in the risk of cardiovascular complications and mortality from them is shown already at the stage of initial disorders of carbohydrate metabolism.

According to a study conducted by Wilson et al [75], the development of endothelial dysfunction and macrovascular complications in the form of adverse cardiovascular events may occur in the prediabetes stage. In a comparative study conducted by the DECODE Study Group, patients with IGT had a higher risk of death from all causes compared with controls without IGT. It was demonstrated that abnormal postprandial blood glucose levels were more significant than fasting glucose levels, and postprandial blood glucose levels were a predictor of all-cause, cardiovascular, and coronary artery disease mortality [28].

The search of tools for the early detection of conditions associated with both carbohydrate metabolism disorders and the early development of endothelial dysfunction, which subsequently leads to the development of cardiovascular events, continues currently. There are a large number of it for assessing these conditions, we settled on the most sensitive, reliable, economically low-cost methods: studying the biomarkers of endothelial dysfunction Endocan, FABP4, PAI-1 and ultrasound determination of intima media thickness in patients with prediabetes, risk of T2DM.

Such Biomarkers as Endocan, FABP4, PAI-1 [50,51,63] are early markers of endothelial dysfunction (ED), which launches insulin resistance (IR), subsequently various disorders of carbohydrate metabolism, including hyperglycemia, IGT. IR and hyperglycemia determined the development of oxidative stress, with the accumulation of reactive oxygen species, manifesting by decreased production of endothelium-relaxing factors. IR leads to increased liver release of FFAs due to lipolysis, leading to changes in the lipid profile with increased levels of triglycerides (TG), Very low density lipoproteins (VLDL) cholesterol, increased lipoprotein remnants, apolipoprotein B synthesis and small dense LDL particles, leading to atherogenic dyslipidemia.

Thus, these markers may reflect endothelial dysfunction in the early stages of the development T2DM, as well as cardiovascular diseases (CVD) reflecting early vascular remodeling, and atherosclerosis.

Aim. Is to investigate scientific literature about the impact of FABP4, Endocan, PAI-1 biomarkers on the endothelial dysfunction in patients with prediabetes.

A search strategy has been developed to conduct a literature review of participation of biomarkers FABP4, Endocan, PAI-1 to the development of endothelial dysfunction in prediabetes condition. Thus, this review primarily includes data from original studies, literature reviews found in Scopus, Web of Science, and Pubmed (Medline) databases, using appropriate keywords. The depth of the search was twenty years, 2001-2022 due to the limited number of studies conducted on this topic and the relatively recent and growing interest of researchers in this field. It was decided to expand the depth of the search due to the presence of earlier articles devoted to the level and location of biomarker formation under experimental conditions, which was basic knowledge that could not be ignored. These studies were experimental, have not lost their validity, and were carried out as closely as possible in accordance with modern standards of scientific research. These articles served as the basis for understanding the beginning of the synthesis of ED biomarkers. *Inclusion criteria:* data from randomized cohort studies conducted on large populations of subjects, meta-analyses, systematic reviews and full-length articles describing original studies were used. *Exclusion criteria:* articles describing isolated cases, conference abstracts, personal communications, and newspaper publications were excluded.

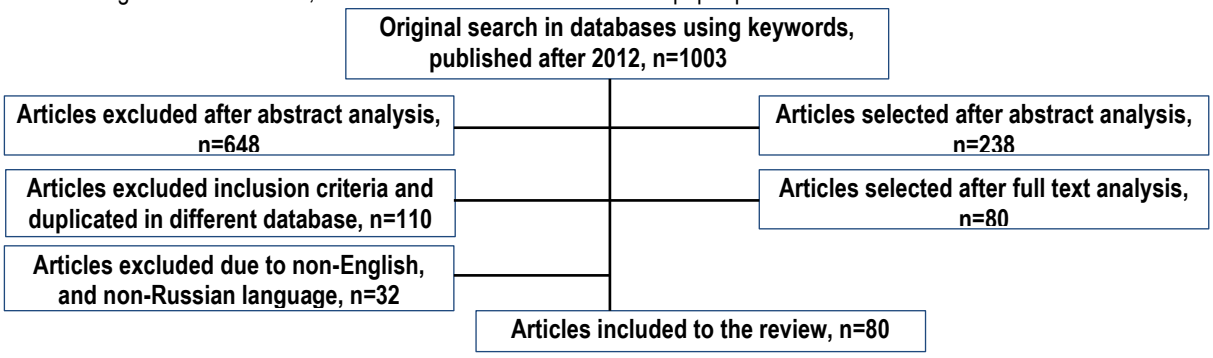


Figure 1. Search algorithm.

Endothelial dysfunction biomarkers in a different carbohydrate metabolism disorder.

Fatty acid binding protein 4 (FABP4)

Plasma fatty acid binding proteins (FABPs) belong to a family of proteins with a tissue-specific distribution. It is biological role is in the cellular uptake and transport of fatty acids, along with the organization of metabolic and inflammatory pathways and the regulation of gene expression [38].

FABP4 manly produced by adipose tissue and macrophages; huge amount of it is synthesized in mature adipocytes [54] and has been detected by standard plasma immune essay [79,80]. Investigation of FABP4 expression provides controversial results. Drolet R. et al. revealed that FABP4 is produced in a various types of adipose tissue [30]. Fisher RM et al. found that FABP4 is more produced by subcutaneous adipose tissue than visceral, regardless of the presence or absence of the obesity [35]. However, Clemente-Postigo M. and et. did not identify significant differences in FABP4 concentrations in subcutaneous and visceral adipose tissue [25].

Despite that role of FABP4 is not completely investigated, researchers have found its link with insulin sensitivity, participation in lipid metabolism and inflammation [14]. Nowadays, researchers test the hypothesis of FABP4 as a main signaling biochemical mediator of interaction between adipocytes and macrophages in adipose tissue. In the experimental study on mice strains with neutralized FABP4 proteins, researchers revealed reducing obesity-induced IR, IGT and atherosclerosis, moreover, mice's adipocytes perfomed reduced efficiency of lipolysis [55]. A decrease in plasma concentrations of FABP4 and apoliporoprotein E in experimental mice showed a slowdown in the development of atherosclerotic plaque [55]. Numerous studies found association between FABP4 plasma concentration and metabolic syndrome, diabetes, familial combined hyperlipidemia and CVD [12,17,18,19,20,26]. The strong correlation between FABP4 and obesity, metabolic syndrome and high cardiovascular risk were illustrated by the study conducted by *Koh J.H et al.* [46]. It can be argued that FABP4 is a powerful and early biomarker of metabolic risk in individuals with metabolic syndrome and T2DM in other prospective studies [70,73]. Accordingly, the role of FABP4 can be scaled to estimation of CVD. 51.

In a study was conducted by Laryushina et al. was investigated link between high concentration of FABP4 and risks of T2DM and cardiovascular events [51].

The main mechanism of endothelial damage when studying the FABP4 biomarker is atherogenic dyslipidemia, launch development of atherosclerosis, endothelial dysfunction and adverse cardiovascular events [16]. *Yeung D.C.Y et al.* [81] found direct link between of increasing FABP4 concentration and thickness of carotid intima-media.

As a result, the studies hold promise for using plasma FABP4 as marker of inflammation in adipose tissue that mediate the development of insulin resistance, T2DM, and atherosclerosis. In addition, this FABP4 biomarker may become a potential target for the treatment of metabolic disorders and both metabolic and cardiovascular diseases caused by them [36].

Endocan (endothelin-1 molecule)

The Endocan biomarker is also involved in the development of endothelial dysfunction, and may be a new potential marker of immunoinflammatory processes associated with cardiometabolic risk. Endocan (endothelin-1 molecule) is an endothelial cell-specific molecule, a vasopressor agent, whose structure is a proteoglycan secreted by the endothelium. With the help of glycan domains, it can bind to hepatocyte growth factor and increase mitogenic activity in the lumen of the vessels, in the organs most specific for this marker, such as the lungs and kidneys [68].

A genetic study on the expression of the Endocan mRNA marker [68] revealed that its work is regulated by the following cytokines: TNFα, IL-1β and IFNγ. Endocan has been shown to contribute to the inhibition of spontaneous leukocyte adhesion to the endothelium or the random migration of leukocytes into the blood through the vessel wall, and thus participates in critical tissue-specific, leukocyte-endothelial cell interactions.

Prospective studies have revealed a relationship between increased Endocan concentrations and CVD, including arterial hypertension, coronary heart disease, and episodes of acute myocardial infarction [11,47,48,65]. A positive association has been established between the level of this biomarker of endothelial dysfunction and intima-media thickness and subclinical atherosclerosis [53]. These studies indicate the presence of endothelial dysfunction in this category of patients, which is reflected by a high concentration of it.

The results of scientific work on the relationship between metabolic disorders, risks of T2DM and Endocan levels are few. An increase in the level of the Endocan biomarker was detected in patients with verified T2DM, in a patients with control hyperglucemia [8], and in individuals with T2DM in uncontrolled hyperglycemia conditions [24]. An increase concentration of the Endocan biomarker was recorded predominantly in patients with T2DM, in a pilot study non-alcoholic fatty liver disease [27]. However, the results of these studies only allowed us to establish a fait accompli of ED, and indicate a predictable result in the form of an increase in the Endocan biomarker and the presence of ED as a result of diabetes. No relationship has been established regarding the appearance of the Endocan biomarker as a manifestation of early ED in patients at the stage of prediabetes.

Plasminogen activator inhibitor-1 (PAI-1)

The Plasminogen activator inhibitor-1 (PAI-1) is a coronary artery disease biomarker whose significance is in a fast-acting inhibition of fibrinolysis [10]. In the number of studies, PAI-1 is believed as one of the risk factors initiates atherosclerotic process [32,74].

It is known that PAI-1 is not only secreted by endothelial and smooth muscle cells, but also produces in adipose tissue cells, including preadipocytes, mature adipocytes, and macrophages that was proved in several studies [13,62]. There is literature evidence that hyperglycemia can affect PAI-1 levels. Chen Y-Q et al [23], demonstrated that hyperglycemia may activate PAI-1 gene promoter in vascular smooth muscle cells in a mice strains. It can be assumed that PAI-1 has similar atherothrombotic effect in prediabetic patients. In experiments on mice, the lowering

of PAI-1 was identified under diet control and hypoglycemic agents, that led to normalization of insulin sensitivity.

In parallel with atherogenesis PAI-1 may serve as a predictor of the development of T2DM [33,34,69, 50]. In a study was conducted by *Laryushina Ye.M. et al*. was investigated interrelations between high PAI-1 concentrations and adverse cardiovascular events development among prediabetic patients [50]. Andreas *Festa A. et al.* in a prospective study revealed the role of PAI-1 as a biomarker of IR along with such standard risk factors as BMI, waist circumference, gender, age, and smoking. In this study, T2DM was found in 16.6% of participants after a 5-year follow-up period [33].

However, there is a research gap in the knowledge of atherosclerotic plaque formation under the influence of elevated PAI-1 concentration.

Jung R.G et al. in the meta-analysis taken from 38 relevant articles [45] have identified relationships between PAI-1 and adverse cardiovascular events. Increasing of PAI-1 level was associated with myocardial infarction and stroke among 11557 patients included in meta-analysis PAI-1. However, the prediction model which was used in meta-analysis did not take into account the parameters of carbohydrate metabolism disorder. The prediction model estimating the impact of PAI-1 adverse cardiovascular events in prediabetic patients might be the future scientific interest.

As a result, the future is needed to evaluate the common impact of biomarkers Endocan, FABP4, PAI-1 and ED and further risk of averse cardiovascular events in patients with prediabetes.

Intima Media Thickness and biomarkers (FABP4, Endocan, PAI-1).

An increase of intima media thickness (IMT) to be considered as a preclinical stage of atherosclerosis base on ultrasound investigation [42,44,60]. There are few studies that have found that IMT is influenced by glucose levels [31], glycemic variability in patients with type 1 diabetes [22], and glycemic fluctuations in patients with type 2 diabetes [52, 63].

A weak but statistically significant relationship was found between IMT and the level of postprandial glycemia, according to a meta-analysis [31]. Both parameters were associated with a cardiovascular event [58]; the higher the glycemia (from normoglycemic patients with IGT to patients with diabetes), the higher the odds of cardiovascular events [83].

However, studies assessing the level of the FABP4, Endocan, PAI-1 biomarkers and its effect on IMT in patients with prediabetes, risk of T2DM have not been conducted.

Endothelial dysfunction and it biomarkers (FABP4, Endocan, PAI-1) in insulin resistance conditions and prediabetes.

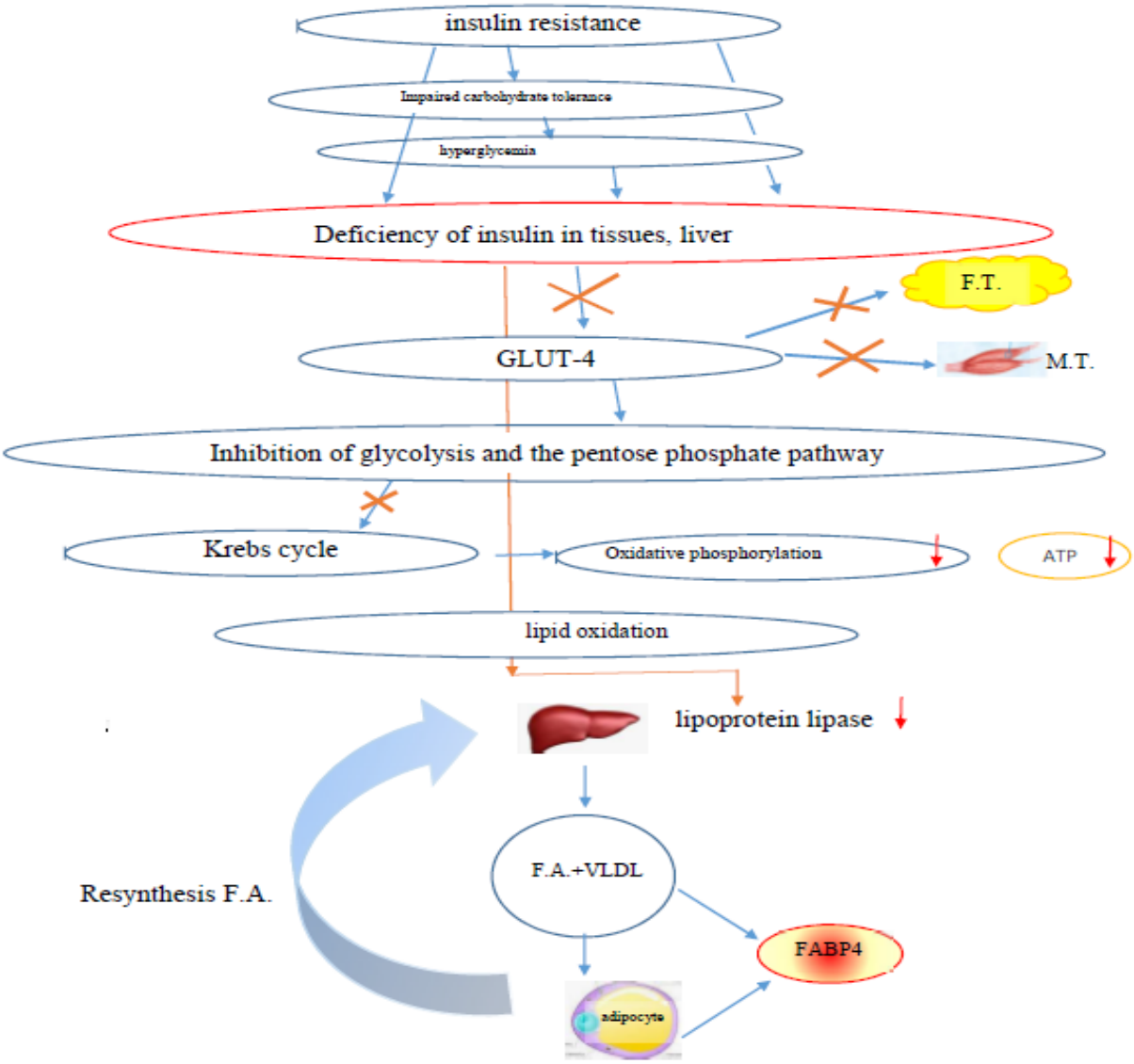
The pathogenesis of endothelial dysfunction has a similar mechanism in patients with prediabetes as same as T2DM. Obesity develops in conditions where the supply of nutrients exceeds the body's expenditure, under certain conditions, as a result of an increased intake of foods containing easily digestible carbohydrates.

An important role in this pathogenesis is played by a hereditary factor, which ultimately leads to insulin resistance (IR) and impaired tolerance to carbohydrates. Glucose utilization decreases by peripheral tissues, which in turn increases glucose production by the liver, under IR conditions.

Hyperglycemia stimulates even greater insulin secretion, causing hyperinsulinemia (HI) [9,66]. This condition causes dysfunction of pancreatic β cells, and high levels of free fatty acids further impair tissue glucose uptake, increasing IR and HI, leading to the phenomenon of lipotoxicity (decreased insulin production in the pancreas, against the background of high levels of free fatty acids) [40]. Thus, this condition leads to insulin deficiency in the tissues and liver. The translocation of GLUT-4, a glucose transport protein, into tissues, in particular muscle and adipose tissue, is disrupted. Next, glycolysis and the pentose phosphate pathway are inhibited, the Krebs cycle is disrupted, oxidative phosphorylation slows down accordingly, and as a result, energy deficiency occurs (NADPH2↓), in the form of the final product of the Krebs cycle - ATP deficiency. Ultimately, hyperglycemia develops. The energy deficit is replenished via an alternative pathway due to lipid oxidation in this category of patients. The enzyme lipoprotein lipase, in the absence of insulin resistance in a normally functioning body, promotes the transfer of fatty acids in very low density lipoproteins (VLDL) from the liver to adipose tissue (adipocytes). And when insulin resistance develops, lipoproteinase activity decreases, which leads to the accumulation of fatty acids and VLDL in the blood, their oversaturation of adipocytes, and their resynthesis in the liver, which ultimately leads to fatty hepatosis. At this stage of excess fatty acids and VLDL in the bloodstream, the activity of the studied biomarker FABP4 increases; a high level of this marker indicates an early phase of endothelial dysfunction and atherosclerosis (Figure 1).

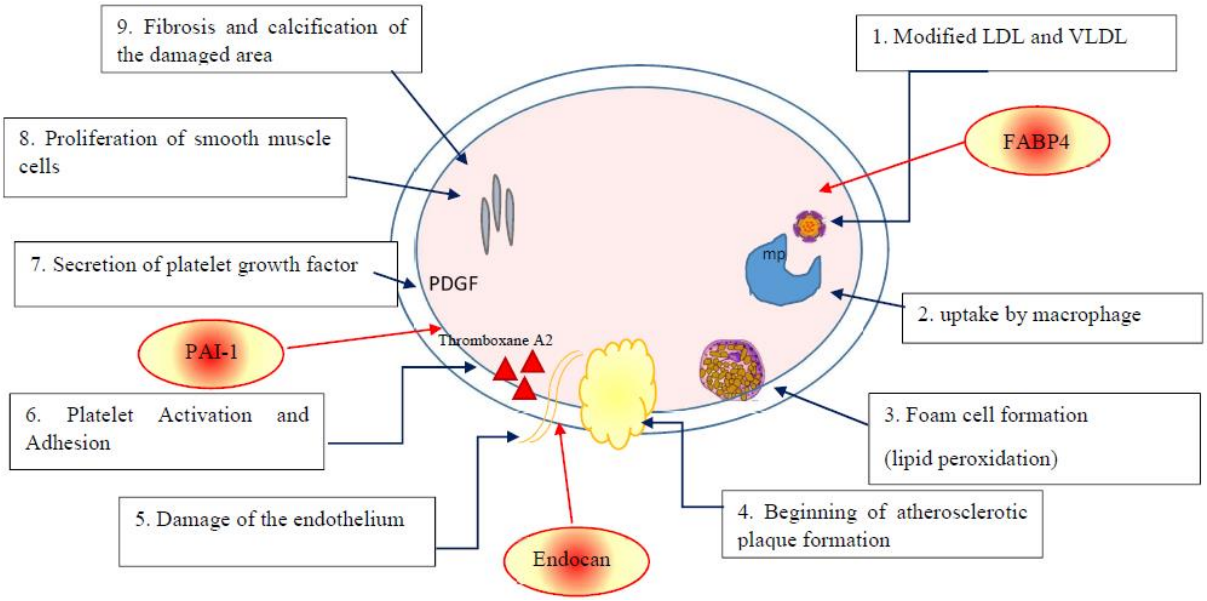
Changes in the conformation of LP occur under conditions of excess and circulation of LDL, VLDL against the background of hyperglycemia, they can glycosylate, aggregate, become peroxidized under the influence of free radicals, and finally become immunogenically active and form complexes with antibodies. As a result of lipid peroxidation, such a modified lipid (LDL, VLDL) is recognized by the macrophage as foreign, captured by it, excess amounts of cholesterol, forcing the latter to absorb excessive amounts of cholesterol, then the macrophages turn into foam cells. Foam cells can invade the subendothelial space causing endothelial damage.

The key, initial process of endothelial dysfunction and atherosclerosis is damage to the endothelium as a result of lipid peroxidation by foam cells. At this stage, the next biomarker Endocan appears, reflecting early endothelial dysfunction, even at the stage of atherosclerotic plaque formation. Subsequently, platelets are activated and aggregated, which secrete thromboxane A2. At the same time, the last studied biomarker PAI-1 is synthesized, which, along with platelets, leads to the formation of a blood clot. Next, platelet-derived growth factor is formed, which triggers the proliferation of smooth muscle cells. Thus, the atherosclerotic plaque receives a fibrous capsule, becomes denser, and a capsule is formed. In the final stages, the plaque grows with collagen and elastin, is saturated with Ca+ salts and becomes denser. At the last stage of the formation of an atherosclerotic plaque, repeated thrombosis and inflammation are possible, with a decrease in the lumen of the coronary vessel and the development of fatal and non-fatal cardiovascular events (Figure 2).



Abbreviations: F.T. - *Fat tissue,* ***M.T.*** *– muscle tissue,* ***F.A.*** *- fatty acids,* ***VLDL*** *- very low density lipoproteins,* ***ATP*** *- adenosine triphosphate.*

Figure 2. Scheme of endothelial dysfunction development in conditions of insulin resistance.



Abbreviations: VLDL *- very low density lipoproteins,* ***LDL*** *- low density lipoproteins,* ***MP*** *– macrophage.*

Figure 3. Scheme of endothelial dysfunction development in conditions of insulin resistance. Continuation.

All three biomarkers (FABP4, Endocan, PAI-1) appear in the early stages of endothelial dysfunction, when the development of adverse cardiovascular events is reversible, which is the interest for the further research. Moreover, these biomarkers are responsible for different pathogenetic mechanisms of the development of endothelial dysfunction, and their combination allows one to immediately evaluate lipid metabolism disorders (FABP4), endothelial damage (Endocan), and increased thrombus formation (PAI-1). Thus, it is more accurate to establish the appearance of endothelial dysfunction in the early stages of carbohydrate metabolism disorder and prediabetes.

Conclusion.

In conclusion, it is necessary to note that there are a sufficient number of theories explaining the increase in the concentration of endothelial dysfunction biomarkers in various pathological conditions, such as obesity, hyperglycemia, and insulin resistance.

It is worth noting that studies assessing the level of endothelial dysfunction biomarkers in patients with prediabetes and the risk T2DM have been poorly studied. And also their simultaneous association in conjunction with the study of intima media thickness in patients with prediabetes and the risk of T2DM has not been carried out at all. It is scientific interest to study these markers of endothelial dysfunction at the prenosological stage, in the absence of vascular accidents manifested by diabetic micro- and macroangiopathies. Considering insulin resistance as the most important link in the pathogenesis of T2DM, it should be noted that currently there is a need to conduct research in the field of endothelial problems at the stage of prediabetes. Studying this issue will identify successful tools for future early detection and prevention of vascular injury and CVE.

Conflict of interest: *The authors declare no conflicts of interest.*

Funding: *No*

Authors contributed. *All authors contributed equally.*

Publication details: *The authors assure that the review has not been published anywhere else and is not under review in another journal.*

Literature:

1. *Атлас диабета. IDF* (International Diabetes Federation). Седьмое издание, Брюссель, Бельгия. 2015 год. С. 90-94

2. Всемирная организация здравоохранения. Информационный бюллетень. Диабет. Ноябрь 2016. http://www.who.int/mediacentre/factsheets/fs312/ru/ (Дата обращения: 1.12.2023)

3. Всемирная Организация Здравоохранения. Профили сахарного диабета в странах, 2016. Женева, Швейцария, 2016. http://who.int/diabetes/country-profiles/kaz_ru.pdf (Дата обращения: 1.12.2023)

4. Здоровье населения Республики Казахстан и деятельность организаций здравоохранения в 2015 году: Стат. сборн. - Астана, 2016. 358 с. http://www.mzsr.gov.kz/sites/default/files/sbornik_za_2015_dlya_razmeshcheniya_na_sayte.pdf (Дата обращения: 1.12.2023)

5. *Иванов В.В., Шахристова Е.В., Степовая Е.А., Носарева О.Л.* Окислительный стресс: Влияние на секрецию инсулина, рецепцию гормона адипоцитами и липолиз в жировой ткани // Бюллетень сибирской медицины, 2014, Т.13, №3, С. 32–39.

6. *Калашникова М.Ф., Буденная И.Ю., Учамприна В.А.* Предиабет: современные критерии диагностики и перспективы лечения // Вестник Репродуктивного Здоровья, Март, 2009. 2-5. С. 6-13.

7. *Мельникова Ю.С., Макарова Т.П.* Эндотелиальная дисфункция как центральное звено патогенеза хронических болезней // Казанский медицинский журнал. 2015, Т. 96. №4, С. 659-660.

8. *Перцева Н.О.* Состояние эндотелиальной функции у больных сахарным диабетом 2 типа с артериальной гипертонией в условиях хорошей компенсации гипергликемии // Российский медико-биологический вестник имени академика И.П. Павлова, 2014. №4, С.88-91.

9. *Таратухин Е.О.* Рекомендации по диабету, предиабету и сердечно-сосудистым заболеваниям EASD / ESC // Российский кардиологический журнал 2014. №3, С.19-20

10. *Adly A.A., Elbarbary N.S., Ismail E.A., Hassan S.R.* Plasminogen activator inhibitor-1 (PAI-1) in children and adolescents with type 1 diabetes mellitus: relation to diabetic micro-vascular complications and carotid intima media thickness // J Diabetes Complications. 2014. May-Jun. 28(3):340-7.

11. *Balta S., Mikhailidis D.P., Demirkol S., Ozturk C.* Endocan-a novel inflammatory indicator in newly diagnosed patients with hypertension: a pilot study // Angiology. 2014 Oct., 65(9):773-7.

12. *Bao Y., Lu Z., Zhou M., Li H., Wang Y. et al.* Serum levels of adipocyte fatty acid-binding protein are associated with the severity of coronary artery disease in Chinese women // PLoS One. 2010. 6(4): e19115.

13. *Bastelica D., Morange P., Berthet B., Bordhi H., Lacroix O., Grino M., Juhan-Vague I., Alessi M.C.* Stromal cells are the main plasminogen activator inhibitor-1-producing cells in human fat: evidence of differences between visceral and subcutaneous deposits // Arteriosclerosis, Thrombosis, and Vascular Biology, 2002. Vol. 22, no. 1, pp.173–178/

14. *Boord J.B., Maeda K., Makowski L., Babaev V.R.* Adipocyte fatty acid binding protein, aP2, alters late atherosclerotic lesion formation in severe hypercholesterolemia // Arterioscler Thromb Vas Biol. 2002. 22: 1686–1691.

15. *Brown A.E., Walker M.* Genetics of Insulin Resistance and the Metabolic Syndrome // Curr Cardiol Rep. 2016 Aug. 18(8):75. doi: 10.1007/s11886-016-0755-4. PMID: 27312935; PMCID: PMC4911377.

16. *Cabre A., Babio N., Lázaro I.* FABP4 predicts atherogenic dyslipidemia development. The PREDIMED study // Atherosclerosis. 2012 May. 222(1):229-34

17. *Cabre A., Lazaro I., Cofan M., Jarauta E.* FABP4 plasma levels are increased in familial combined hyperlipidemia // J Lipid Res. 2009. 51(5):1173–8.

18. *Cabre A., Lazaro I., Girona J., Manzanares J.M.* Fatty acid binding protein 4 is increased in metabolic syndrome and with thiazolidinedione treatment in diabetic patients // Atherosclerosis. 2007. 195:e150–8.

19. *Cabre A., Lazaro I., Girona J., Manzanares J.M.* Plasma fatty acid-binding protein 4 increases with renal

dysfunction in type 2 diabetic patients without microalbuminuria // Clin Chem. 2008. 54: 181–7.

20. *Cabre A., Lazaro I., Girona J., Manzanares J.M., Marimo´n F. et al*. Plasma fatty acid-binding protein 4 is associated with atherogenic dyslipidemia in diabetes // J Lipid Res. 2008. 49: 1746–51.

21. *Cardiovascular deseases. WHO. Key facts.* June 2021. Available from: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds) (Дата обращения: 1.12.2023)

22. *Cesana F., Giannattasio C., Nava S., Soriano F., Brambilla G., Baroni M., et al.* Impact of blood glucose variability on carotid artery intima media thickness and distensibility in type 1 diabetes mellitus // Blood Press. 2013. 22:355–61.

23. *Chen Y.-Q., Su M., Raja Walia R., Hao Q., Cowington J.W., Vaughan D.E.* Sp1 sites mediate activation of the plasminogen activator inhibitor-1 promoter by glucose in vascular smooth muscle cells // J Biol Chem. 2002. 273: 8225–8231.

24. *Cikrikcioglu M.A., Erturk Z., Kilic E.* Endocan and albuminuria in type 2 diabetes mellitus // Ren Fail. 2016, Nov. 38(10):1647-1653.

25. *Clemente-Postigo M., Queipo-Ortun˜o M.I., Fernandez-Garcia D.* Adipose tissue gene expression of factors related to lipid processing in obesity // PLoS One 6(9): (2011) e24783.

26. *Coll B., Cabre A., Alonso-Villaverde C., Lazaro I., Aragone´s G. et al.* The fatty acid binding protein-4 (FABP4) is a strong biomarker of metabolic syndrome and lipodystrophy in HIV-infected patients // Atherosclerosis. 2008. 199: 147–53.

27. *Dallio M., Masarone M., Caprio G.G.* Endocan Serum Levels in Patients with Non-Alcoholic Fatty Liver Disease with or without Type 2 Diabetes Mellitus: A Pilot Study // J Gastrointestin Liver Dis. 2017 Sep. 26(3).

28. DECODE Study Group, the European Diabetes Epidemiology Group. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria // Arch Intern Med. 2001 Feb 12. 161(3):397-405.

29. *Del Turco S., Gaggini M., Daniele G., Basta G., Folli F., Sicari R., Gastaldelli A.* Insulin resistance and endothelial dysfunction: a mutual relationship in cardiometabolic risk // Curr Pharm Des. 2013. 19(13):2420-31.

30. *Drolet R., Richard C., Sniderman A.D., Mailloux J., Fortier M. et al*. Hypertrophy and hyperplasia of abdominal adipose tissues in women // Int J Obes (Lond). 2008. 32(2): 283–291.

31. *Einarson T.R., Hunchuck J., Hemels M.* Relationship between blood glucose and carotid intima media thickness: a meta-analysis // Cardiovasc Diabetol. 2010. 9:37.

32. *Erzen B., Sabovic M.* In young post-myocardial infarction male patients elevated plasminogen activator inhibitor-1 correlates with insulin resistance and endothelial dysfunction // Heart Vessels. 2013. 28: 570–577.

33. *Festa A., D'Agostino R.Jr., Tracy R.P., Haffner S.M.* Elevated levels of acute-phase proteins and plasminogen activator inhibitor-1 predict the development of type 2 diabetes: the insulin resistance atherosclerosis study // Diabetes. 2002 Apr. 51(4):1131-7.

34. *Festa A., Williams K., Tracy R.P., Wagenknecht L.E., Haffner S.M.* Progression of plasminogen activator inhibitor-1 and fibrinogen levels in relation to incident type 2 diabetes // Circulation. 2006 Apr 11. 113(14):1753-9.

35. *Fisher R.M., Eriksson P., Hoffstedt J., Hotamisligil G.S., Thorne A. et al.* Fatty acid binding protein expression in different adipose tissue depots from lean and obese individuals // Diabetologia. 2001. 44(10): 1268–1273.

36. *Furuhashi M., Hotamisligil G.S.* Fatty acid-binding proteins: role in metabolic diseases and potential as drug targets/ // Nat Rev Drug Discov 7: 2008 489–503.

37. Heart Disease and Stroke Statistics—2019 Update: A Report From the American Heart Association // Circulation, march, 2019. V. 139(10), p.56-528.

38. *Hertzel A.V., Bernlohr D.A.* The mammalian fatty acid-binding protein multigene family: molecular and genetic insights into function // Trends Endocrinol Metab. 2000. 11: 175–180.

39. *Hill M.A., Yang Y., Zhang L., Sun Z., Jia G., Parrish A.R., Sowers J.R.* Insulin resistance, cardiovascular stiffening and cardiovascular disease // Metabolism. 2021 Jun. 119:154766.

40. *International Diabetes Federation.* IDF Diabetes Atlas, 8th edition. Brussels, Belgium: International Diabetes Federation, 2017. Available from: http://www.diabetesatlas.org; last accessed on 23 January, 2019 (Дата обращения: 1.12.2023)

41. *Incalza M.A., D'Oria R., Natalicchio A., Perrini S., Laviola L., Giorgino F.* Oxidative stress and reactive oxygen species in endothelial dysfunction associated with cardiovascular and metabolic diseases // Vascul Pharmacol. 2018 Jan. 100:1-19.

42. *Iana S.* Intima-media thickness: appropriate evaluation and proper measurement // the e-Journal of Cardiology Practice. Vol. 13, N° 21 - 05 May 2015.

43. *Janus A., Szahidewicz-Krupska E., Mazur G., Doroszko A.* Insulin Resistance and Endothelial Dysfunction Constitute a Common Therapeutic Target in Cardiometabolic Disorders // Hindawi Publishing Corporation Mediators of Inflammation Volume 2016, Article ID 3634948, 10 p.

44. *Joseph F. Polak, Quenna Wong, W. Craig Johnson, David A. Bluemke, Anita Harrington, Daniel H. O'Leary, N. David Yanez.* Associations of cardiovascular risk factors, carotid intima-media thickness and left ventricular mass with inter-adventitial diameters of the common carotid artery: the Multi-Ethnic Study of Atherosclerosis (MESA) Atherosclerosis. 2011 October. 218(2): 344–349.

45. *Jung R.G., Motazedian P., Ramirez F.D., Simard T., Santo P.D., Visintini S., Faraz M.A., Labinaz A., Jung Y., Hibbert B. et al.* Association between plasminogen activator inhibitor-1 and cardiovascular events: a systematic review and meta-analysis // Thrombosis Journal. 2018. 16:12.

46. *Koh J.H., Shin Y.G., Nam S.M., Lee M.Y., Chung C.H. et al.* Serum adipocyte fatty acid-binding protein levels are associated with nonalcoholic fatty liver disease in type 2 diabetic patients // Diabetes Care. 2009. 32: 147–15.

47. *Kundi H., Gok M., Kiziltunc E., Topcuoglu C.* The Relationship Between Serum Endocan Levels With the Presence of Slow Coronary Flow: A Cross-Sectional Study // Clin Appl Thromb Hemost. 2017 Jul. 23(5):472-477.

48. *Kundi H., Balun A., Cicekcioglu H.* Admission Endocan Level may be a Useful Predictor for In-Hospital Mortality and Coronary Severity Index in Patients With ST-Segment Elevation Myocardial Infarction // Angiology. 2017 Jan. 68(1):46-51.

49. *Lalic K., Nedeljkovic M., Jotic A., Babic R., Rajkovic N., Popovic L., Lukic L., Milicic T., Lukac S.S., Stosic L., Macesic M., Rasulic I., Gajovic J.S., Lalic N.M.* Endothelial dysfunction of coronary arteries in subjects without diabetes: an association with both insulin resistance and impaired insulin secretion response // Diabetes Res Clin Pract. 2018 May.139:179-187.

50. *Laryushina Y., Parakhina V., Turgunova L., Sheryazdanova D., Dosmagambetova R., Turmukhambetova A., Ponamareva O., Orbetzova M.* Association of Plasminogen Activator Inhibitor-1 and Cardiovascular Events Development in Patients with Prediabetes // Macedonian Journal of Medical Sciences. 2021 Aug.81 28. 9(B):726-33. Available from: https://oamjms.eu/index.php/mjms/article/view/6825 (Дата обращения: 1.12.2023)

51. *Laryushina Y., Parakhina V., Turmukhambetova A., Turgunova L., Ibraeva L., Amirkhanova D., Nildibayeva F.* The Relationship Between the Level Fabp4, Risks of Type 2 Diabetes Mellitus, and Cardiovascular Events // Macedonian Journal of Medical Sciences. 2020 Oct 10; 8(B):762-768. https://doi.org/10.3889/oamjms.2020.4678. eISSN: 1857-9655 (Дата обращения: 1.12.2023)

52. *Liu M., Ao L., Hu X., Ma J., Bao K., Gu Y. et al.* Infuence of blood glucose fuc tuation, C-peptide level and conventional risk factors on carotid artery intima-media thickness in Chinese Han patients with type 2 diabetes mellitus // Eur J Med Res. 2019. 24:13.

53. *Lv Y.*, *Zhang Y., Shi W.* The Association Between Endocan Levels and Subclinical Atherosclerosis in Patients With Type 2 Diabetes Mellitus // Am J Med Sci. 2017 May. 353(5):433-438.

54. *Maeda K., Cao H., Kono K., Gorgun C.Z., Furuhashi M.* Adipocyte/ macrophage fatty acid binding proteins control integrated metabolic responses in obesity and diabetes // Cell Metab. 2005. 1: 107–119.

55. *Makowski L., Boord J.B., Maeda K., Babaev V.R.* Lack of macrophage fatty-acid-binding protein aP2 protects mice deficient in apolipoprotein E against atherosclerosis // Nat Med. 2001. 7: 699–705.

56. *Maria G., Isaac S., David A., Rafel R., Xavier B., Ruth M., Eric de G., Roman J.A., Jaume M., Nino K., Roberto E.* Carotid intima-media thickness in the Spanish population: reference ranges and association with cardiovascular risk factors // Rev Esp Cardiol (Engl Ed). 2012 Dec. 65(12):1086-93.doi: 10.1016/j.recesp.2012.04.026. Epub 2012 Sep 28.

57. *Makowski L., Hotamisligil G.S.* Fatty acid binding-proteins-the evolutionary crossroads of inflammatory and metabolic responses // J Nutr. 2004. 134: 2464S–2468S.

58. *Moore K.J., Shah R.* Introduction to the Obesity, Metabolic Syndrome, and CVD Compendium // Circ Res. 2020 May 22. 126(11):1475-1476.

59. *Muniyappa R., Sowers J.R.* Role of insulin resistance in endothelial dysfunction // Rev Endocr Metab Disord. 2013. Mar.14(1):5-12.

60. *Novo S., Peritore A., Trovato R.L., Guarneri F.P., Di Lisi D., Muratori I. et al.* Preclinical atherosclerosis and metabolic syndrome increase cardio- and cerebrovascular events rate: a 20-year follow up // Cardiovasc Diabetol. 2013. 12:155.

61. *Odegaard A.O., Jacobs D.R., Sanchez O.A., Goff D.C., Reiner A.P., Gross M.D.* Oxidative stress, inflammation, endothelial dysfunction and incidence of type 2 diabetes // Cardiovasc Diabetol. 2016, Mar 24.15:51.

62. *Pandolfi A., Cetrullo D., Polishuck R., Alberta M.M., Calafiore A., Pellegrini G., Vitacolonna E., Capani F., Consoli A.* Plasminogen Activator Inhibitor Type 1 Is Increased in the Arterial Wall of Type II Diabetic Subjects // Arteriosclerosis, Thrombosis, and Vascular Biology. 2001, 1 August. Volume 21, Issue 8, p.1378-1382.

63. *Parakhina V., Laryushina Y., Ponamareva O.* Association between Endocan, PAI-1 and intima media thickness in patients with high diabetes risk // Bulletin of the Karaganda University; Byology, Medicine, Geography. 2022. № 2(106) pp143-144.

64. *Prieto D., Contreras C., Sánchez A.* Endothelial dysfunction, obesity and insulin resistance // Curr Vasc Pharmacol. 2014 May. 12(3):412-26.

65. *Qiu C.R., Fu Q., Sui J., Zhang Q.* Serum Endothelial Cell-Specific Molecule 1 (Endocan) Levels in Patients With Acute Myocardial Infarction and Its Clinical Significance // Angiology. 2017 Apr; 68(4):354-359.

66. *Qiu Q.Y., Zhang B.L., Zhang M.Z.* Combined Influence of Insulin Resistance and Inflammatory Biomarkers on Type 2 Diabetes: A Population-based Prospective Cohort Study of Inner Mongolians in China // Biomed Environ Sci. 2018. Apr. 31(4):300-305.

67. *Ryden L.* ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD // Grant European Heart Journal. 2013. 34, 3035–3087.

68. *Scherpereel A., Gentina T., Grigoriu B.* Overexpression of endocan induces tumor formation // Cancer Res. 2003 Sep 15. 63(18):6084-9.

69. *Somodi S., Seres I., Lőrincz H., Harangi M., Fülöp P., Paragh G.* Plasminogen Activator Inhibitor-1 Level Correlates with Lipoprotein Subfractions in Obese Nondiabetic Subjects // Int J Endocrinol. 2018 May 30. 2018:9596054.

70. *Stejskal D., Karpisek M.* Adypocite fatty acid binding protein in Caucasian population: a new marker of metabolic syndrome? // Eur J Clin Invest 2006. 36: 621–625.

71. *Sun D., Man W., Zhang L.* Roles of Insulin Resistance, Endothelial Dysfunction and Lifestyle Changes in the Development of Cardiovascular Disease in Diabetic Patients // Curr Drug Targets. 2017. 18(15):1792-1799.

72. The National Register of the Republic of Kazakhstan; 2021. Available from: http://www.rcrz.kz/files/sbornik/sbornik_2020-converted.pdf (Дата обращения: 1.12.2023)

73. *Tso A., Xu A.W., Sham P., Wat N.M., Wang Y. et al.* Serum adipocyte fatty acid-binding protein as a new biomarker predicting the development of type 2 diabetes // Diabetes Care, 2007. 30: 2667–2672.

74. *Tretjakovs P., Jurka A., Bormane I., Mikelsone I., et al.* Circulating adhesion molecules, matrix metalloproteinase-9, plasminogen activator inhibitor-1, and

myeloperoxidase in coronary artery disease patients with stable and unstable angina // Clinica Chimica Acta. 2012; 413: 25–29

75. *Wilson P.W., D'Agostino R.B., Parise H. et al.* Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus // Circulation. 2005. 112:3066–3072.

76. World Health Organization, Health of the Population of the Republic of Kazakhstan and the Activities of Health Organizations in 2017/Stat, p. 354, World Health Organization, Astana, Kazakhstan, 2018.

77. World Health Organization. Global action plan for the prevention and control of noncommunicable diseases 2013-2020. http://apps.who.int/iris/bitstream/10665/94384/5/9789244506233_rus.pdf?ua=1 (Дата обращения: 1.12.2023)

78. *Wilkins E., Wilson L., Wickramasinghe K., Bhatnagar P., Leal J., Luengo-Fernandez R., Burns R., Rayner M., Townsend N.* European Cardiovascular Disease Statistics 2017. European Heart Network, Brussels. file:///C:/Users/User/OneDrive/%D0%A0%D0%B0%D0%B1%D0%BE%D1%87%D0%B8%D0%B9%20%D1%81%D1%82%D0%BE%D0%BB/European%20cardiovascular%20disease%20statistics%202017.pdf (Дата обращения: 1.12.2023)

79. *Xu A., Tso A.W., Cheung B.M., Wang Y.* Circulating adipocyte-fatty acid binding protein levels predict the development of the metabolic syndrome: a 5-year prospective study // Circulation, 2007. 115: 1537–1543.

80. *Xu A., Wang Y., Yu S.J., Stejskal D., Tam S.* Adypocite fatty acidbinding protein is a plasma biomarker associated with obesity and Metabolic Syndrome // Clin Chem. 2006. 52: 405–413.

81. *Yeung D.C.Y., Xu A., Cheung C.W.S.* Serum Adipocyte Fatty Acid-Binding Protein Levels Were Independently Associated With Carotid Atherosclerosis // Arterioscler Thromb Vasc Biol. 2007. 27:1796-1802.

82. *Yilmaz M.I., Romano M., Basarali M.K., Elzagallaai A., Karaman M., Demir Z., Demir M.F., Akcay F., Seyrek M., Haksever N., Piskin D., Cimaz R., Rieder M.J., Demirkaya E.* The Effect of Corrected Inflammation, Oxidative Stress and Endothelial Dysfunction on Fmd Levels in Patients with Selected Chronic Diseases: A Quasi-Experimental Study // Sci Rep. 2020 Jun 2. 10(1):9018.

83. *Yuan-Yuan Z., Hong-Mei Q., Ying Y., Yuan-Yuan H.* Analysis of risk factors for carotid intima-media thickness in patients with type 2 diabetes mellitus in Western China assessed by logistic regression combined with a decision tree model // Diabetol Metab Syndr. 2020. Jan 28.12:8.

References: [1-9]

1. *Atlas diabeta IDF* (International Diabetes Federation) Sed'moe izdanie [IDF DIABETES ATLAS Seventh Edition]. Brussels, Belgium. 2015, pp 90-94.

2. *Vsemirnaya organizatsiya zdravookhraneniya. Informatsionnyi byulleten'* [World Health Organization. News bulletin. Diabetes]. November 2016. http://www.who.int/mediacentre/factsheets/fs312/ru/ (accessed: 1.12.2023) [in Russian]

3. *Vsemirnaya Organizatsiya Zdravookhraneniya. Profili sakharnogo diabeta v stranakh* [World Health Organization. Country profiles of diabetes mellitus], http://who.int/diabetes/country-profiles/kaz_ru.pdf, 2016. Geneva, Switzerland, 2016. (accessed: 1.12.2023) [in Russian]

4. *Zdorov'e naseleniya Respubliki Kazakhstan i deyatel'nost' organizatsii zdravookhraneniya v 2015 godu: Stat. sborn.* [Health of the population of the Republic of Kazakhstan and the activities of healthcare organizations in 2015: Stat. collection]. Astana, 2016. 358 p. http://www.mzsr.gov.kz/sites/default/files/sbornik_za_2015_dlya_razmeshcheniya_na_sayte.pdf. (accessed: 1.12.2023) [in Russian]

5. Ivanov V.V., Shahristova E.V., Stepovaya E.A., Nosareva O.L. Okislitel'nyi stress: Vliyanie na sekretsiyu insulina, retseptsiyu gormona adipotsitami i lipoliz v zhirovoi tkani [Oxidative stress: Effect on insulin secretion, hormone reception by adipocytes and lipolysis in adipose tissue]. Byulleten' sibirskoi meditsiny [Bulletin of Siberian Medicine]. 2014, V.13, №3, pp. 32–39. [in Russian]

6. Kalashnikova M.F., Budennaya I.Yu., Uchamprina V.A.. Prediabet: sovremennye kriterii diagnostiki i perspektivy lecheniya [Prediabetes: modern diagnostic criteria and treatment prospects]. *Vestnik Reproduktivnogo Zdorov'ya* [Newsletter of reproduction health], 2009. Mart, 2-5. pp 6-13 [in Russian]

7. Mel'nikova Yu.S., Makarova T.P. Endotelial'naya disfunkctsya kak tsentral'noe zveno patogeneza khronicheskikh boleznei [Endothelial dysfunction as a central link in the pathogenesis of chronic diseases]. *Kazanskii meditsinskii zhurnal* [Kazan Medical Journal]. 2015, T.96, №4. pp. 659-660. [in Russian]

8. Pertseva N.O. Sostoyanie endotelial'noi funktsii u bol'nykh sakharnym diabetom 2 tipa s arterial'noi gipertoniei v usloviyakh khoroshei kompensatsii giperglikemii [The state of endothelial function in patients with type 2 diabetes mellitus with arterial hypertension in conditions of good compensation for hyperglycemia]. *Rossiiskii mediko-biologicheskii vestnik imeni akademika I.P. Pavlova* [Russian Medical and Biological Bulletin named after Academician I.P. Pavlova]. 2014, №4, pp.88-91. [in Russian]

9. Taratuhin E.O. Rekomendatsii po diabetu, prediabetu i serdechno-sosudistym zabolevaniyam EASD/ESC [Recommendations for diabetes, prediabetes and cardiovascular diseases EASD/ESC]. Rossiiskii kardiologicheskii zhurnal [Russian Journal of Cardiology]. 2014, №3, pp.19-20. [in Russian]

Corresponding author:
Parakhina Viktoriya - PhD student, (Specialty Medicine) NCJSC «Medical University of Karaganda», Karaganda, Republic of Kazakhstan.
Address: Republic of Kazakhstan, 100000, Karaganda, Gogol street, 40.
E-mail: Parahina@qmu.kz
Phone: +7 708 526 52 81