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Study of the spectrum of unsaturated fatty acids in the blood of men with diabetes mellitus in Novosibirsk (ESSE-RF3 in the Novosibirsk region)

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ABSTRACT

Aim. To study the content of unsaturated fatty acids (FAs) in blood plasma in men from Novosibirsk (*ESSE-RF3* in the Novosibirsk region) with established type 2 diabetes mellitus (DM2), newly diagnosed diabetes, and prediabetes, as well as to evaluate the associations of various types of FAs with the presence or absence of diabetes and fasting glucose levels.

Materials and methods. Within the framework of the multicenter, single-stage epidemiological ESSE-RF3 study in the Novosibirsk region, 1,200 residents of Novosibirsk (600 men, 600 women) aged 35–74 years were examined. The present study included 563 men with an average age of 54.4 ± 11.48 years, comprising: 61 individuals diagnosed with DM2 based on anamnestic data (Group I); 65 men with newly diagnosed diabetes (Group II); 46 men with conditional prediabetes (Group III); and 391 men without diabetes – (Group IV). The levels of unsaturated FAs in blood plasma were determined via high-performance liquid chromatography.

Results. An increase in omega-3, -6, and -9 FA levels was revealed in Group I compared to Group IV. An increase in the level of oleic acid ($p = 0.040$) was found in Group II compared to Group IV. The relative chance of DM2 is directly associated with an increase in the levels of omega-3 alpha-linolenic acid (odds ratio (OR) = 1.030, 95 confidence interval (CI) 1.002–1.058; $p = 0.034$) and omega-6 gamma-linolenic acid (OR = 1.026, 95 CI 1.001–1.051; $p = 0.044$). Newly diagnosed diabetes is inversely associated with the level of linoleic acid in blood plasma (OR = 0.545, 95 CI 0.301–0.996; $p = 0.048$), as well as directly associated with the level of oleic acid (OR = 1.961, 95 CI 1.054–3.648; $p = 0.034$). Prediabetes is inversely associated with the level of hexadecenoic acid (OR = 0.969, 95 CI 0.943–0.996; $p = 0.025$).

Conclusion. Detection of changes in the profile of unsaturated FAs in blood plasma can be used as an additional prognostic biomarker to identify patients at risk of developing DM.

Keywords: diabetes mellitus, fatty acids, blood, risk factors

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Conformity with the principles of ethics. All participants of the study signed an informed consent. The study was approved by the local Ethics committee of IIPM – Branch of IC&G SD of RAS (Protocol No. 69 of 29.09.2020).

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Исследование спектра ненасыщенных жирных кислот крови у мужчин с сахарным диабетом г. Новосибирска («ЭССЕ-РФ3» в Новосибирской области)

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РЕЗЮМЕ

Цель. Изучить содержание ненасыщенных жирных кислот (ЖК) плазмы крови у мужчин г. Новосибирска («ЭССЕ-РФ3» в Новосибирской области) с установленным сахарным диабетом 2-го типа (СД2), впервые диагностированным диабетом и «предиабетом», а также оценить ассоциации различных типов ЖК с наличием или отсутствием СД и уровнем глюкозы натощак.

Материалы и методы. В рамках многоцентрового одномоментного эпидемиологического исследования ЭССЕ-РФ3 по Новосибирской области были обследованы 1200 жителей г. Новосибирска (мужчин – 600, женщин – 600) в возрасте 35–74 лет. В исследование были включены 563 мужчины (средний возраст 54,4 ± 11,48 лет), из них: 61 человек с диагнозом СД2 на основании анамнестических данных – группа (I); 65 мужчин с впервые выявленным диабетом – группа (II); 46 мужчин с условным «предиабетом» – группа (III); 391 человек без СД – группа (IV). В плазме крови всем определяли уровень ненасыщенных ЖК методом высокоэффективной жидкостной хроматографии.

Результаты. В группе (I) выявлено увеличение содержания омега-3, -6, -9 ЖК при сравнении с группой (IV). В группе (II) установлено увеличение уровня олеиновой ЖК ($p = 0,040$) при сравнении с группой (IV). Наличие СД2 прямо ассоциировано с повышением уровня омега-3 альфа-линоленовой (отношение шансов (ОШ) = 1,030; 95-й доверительный интервал (ДИ) 1,002–1,058; $p = 0,034$) и омега-6 гамма-линоленовой ЖК (ОШ = 1,026; 95-й ДИ 1,001–1,051; $p = 0,044$). Наличие впервые выявленного СД обратно ассоциировано с содержанием в плазме крови линолевой кислоты (ОШ = 0,545; 95-й ДИ 0,301–0,996; $p = 0,048$) и прямо ассоциировано с уровнем олеиновой ЖК (ОШ = 1,961; 95-й ДИ 1,054–3,648; $p = 0,034$). Наличие «предиабета» обратно ассоциировано с содержанием гексадеценовой кислоты (ОШ = 0,969; 95-й ДИ 0,943–0,996; $p = 0,025$).

Заключение. Выявление изменений профиля ненасыщенных ЖК в плазме крови может использоваться в качестве дополнительного прогностического биомаркера для выявления пациентов с риском развития СД.

Ключевые слова: сахарный диабет, жирные кислоты, кровь, факторы риска

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Соответствие принципам этики. Все участники исследования подписали информированное согласие. Исследование одобрено локальным этическим комитетом НИИТПМ – филиал ИЦиГ СО РАН (протокол № 69 от 29.09.2020).

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INTRODUCTION

According to the International Diabetes Federation, by 2021 there were about 537 million patients with diabetes mellitus (DM) in the world, and by 2045 their number is expected to increase to 783 million [1]. At the same time, type 2 DM (DM2) accounts for 90–95% of all cases of diabetes [2]. DM2 poses a significant risk to people's health and life expectancy. For example, the average life expectancy of a 50-year-old person with DM2 is six years shorter compared to people without DM2 [3].

According to the hypothesis of lipotoxicity, chronically elevated levels of free fatty acids (FA) may cause dysfunction of pancreatic β-cells and, thereby, disrupt insulin secretion, accelerating two major defects underlying the pathophysiology of DM2 [4]. However, the data on the association between different types of FA (omega-3 /-6 /-9) and the risk of developing DM2 are quite contradictory. For example, in the study by J. Shanta et al. [5], a direct effect of arachidonic acid (20 : 4, omega-6), and not its metabolites, was noted on the regulation of insulin secretion by β-cells. In the study by M.A.Lankinen et al. [6] levels of digomo-γ-linolenic acid (20 : 3, omega-6) in phospholipids and cholesterol esters, but not in triglycerides, were positively associated with the risk of developing DM2. In contrast, according to a recent meta-analysis, higher intake of linoleic acid (18 : 2, omega-6) and its higher concentrations in adipose tissue and blood are associated with a decrease in the risk of developing DM2 [7].

In experimental studies, with regard to supplements and/or a diet high in omega-3 polyunsaturated fats (PUFA), it has been shown that omega-3 FA (in particular, α-linolenic acid 18 : 3) can increase fasting glucose levels [8] and is directly associated with the risk of developing DM2 [9]. However, in a number of meta-analyses, the level of docosahexaenoic acid (20 : 3, omega-3) was lower in patients with DM2 compared with the control group of healthy subjects [10]. In total, it can be said that the composition of FA, rather than their total level, has a greater effect on insulin-glucose homeostasis.

The aim of the study was to study the levels of unsaturated FA in blood plasma in men from Novosibirsk (Epidemiology of Cardiovascular Diseases and Their Risk Factors in the Regions of the Russian Federation (ESSE–RF3) in the Novosibirsk region) with an established DM2 diagnosis, newly diagnosed diabetes, and prediabetes, as well as to evaluate the associations of various types of unsaturated FA with the presence/absence of DM and fasting glucose levels.

MATERIALS AND METHODS

The recruitment and examination of participants took place within the framework of the multicenter single-stage epidemiological *ESSE-RF3* study in 2020–2022. The study was approved by the Independent Ethics Committee of the National Medical Research Center for Therapy and Preventive Medicine [11]. Within the framework of this study, 1,200 residents of the Novosibirsk region aged 35–74 years (600 men, 600 women) were examined at the premises of the IIPM – Branch of IC&G SB RAS.

The diagnosis of DM2 was established on the basis of anamnestic data and included the study participants who positively answered the questions: "Has your doctor ever told you that you have/had the following diseases – diabetes mellitus?" and "Is the type of diabetes mellitus type 2?". The individuals with fasting glucose levels in plasma of ≥ 7.0 mmol/l, without a previous history of diabetes, and who were not taking hypoglycemic drugs were classified as patients with newly diagnosed diabetes. The respondents who answered positively to the question: "Has a doctor or other medical professional told you that you have an elevated sugar level in blood?", but whose blood glucose level at the moment of screening was < 7.0 mmol/l and who were not taking hypoglycemic drugs, were classified as patients with conditional prediabetes.

The blood samples for laboratory tests (namely, levels of total cholesterol, cholesterol, high-density and low-density lipoprotein cholesterol, triglycerides, and glucose) were collected from all participants under fasting conditions by venipuncture from the cubital vein. The tests were performed in the laboratory of the National Medical Research Center for Therapy and Preventive Medicine (Moscow) [12]. The levels of the parameters in blood serum were determined using an Abbot Architect c8000 biochemical analyzer (USA) and diagnostic kits from Abbot Diagnostic (USA). Recalculation of serum glucose into plasma glucose was carried out using The European Association for the Study of Diabetes (2005) formula: plasma glucose (mmol/l) = –0.137 + 1.047 × serum glucose (mmol/l).

Additionally, the following levels of omega-3 PUFA were determined in the blood plasma: alpha-linolenic acid (C 18 :3), eicosapentaenoic acid (C 20 : 5), docosahexaenoic acid (C 22 : 6); omega-6 PUFA: linoleic acid (C 18 : 2), gamma-linolenic acid (C 18 : 3), dihomo-gamma-linolenic acid (C 20 : 3), arachidonic acid (C 20 : 4), docosatetraenoic acid (C 22 : 4), docosapentaenoic acid (C 22 : 5); omega-9 FA: hexadecenoic acid (C 16 : 1), oleic acid (C 18 : 1), mead acid (C 20 : 3), nervonic acid (C 24 : 1). These levels were determined by the method of high-performance liquid chromatography at the premises of the IIPM – Branch of IC&G SB RAS (Novosibirsk).

The values obtained during the study were statistically processed using the SPSS 13.0 statistical software package. The Kolmogorov – Smirnov test was used to assess the distribution of features. Due to their abnormal distribution, descriptive statistics for continuous features is presented in the form of *Me* [25%; 75%]. The nonparametric Mann – Whitney *U*-test was used to compare the groups. The Pearson Criterion ($\chi 2$) was used to determine the statistical significance of differences in qualitative characteristics. The associations of FA with DM/newly diagnosed DM/prediabetes were studied using a multifactorial logistic regression model (with standardization by age, body mass index (BMI), and plasma glucose levels). The results are presented as the odds ratio (OR) and 95% confidence interval (CI). The differences were considered statistically significant at $p < 0.05$.

RESULTS

The present study included 563 men, with an average age of 54.4 ± 11.48 years. The study participants were divided into four groups, depending on the presence/absence of a DM2 diagnosis and fasting glucose levels above/below 7.0 mmol/l: group (I) – 61 men with an established diagnosis of DM2; group (II) – 65 men with newly diagnosed diabetes; group (III) – 46 men with conditional prediabetes; group (IV) – 391 people without diabetes. Table 1 shows the distribution of blood plasma FA by groups.

Table 1

The content of FA in blood plasma in men of the study groups

Fatty acid	Group (I), $n = 61$	Group (II), $n = 65$	Group (III), $n = 46$	Group (IV), $n = 391$	p_{I-IV}	p_{II-IV}	p_{III-IV}
Alpha-linolenic acid 18 : 3 omega-3	86.0 [64.5; 114.5]	69.0 [55.5; 92.0]	74.0 [52.0; 94.25]	68.0 [54.0; 92.0]	0.001	0.581	0.955
Eicosapentaenoic acid 20 : 5 omega-3	40.0 [24.5; 62.0]	31.0 [22.0; 52.5]	32.0 [19.75; 62.75]	30.0 [19.0; 48.0]	0.002	0.169	0.270
Docosahexaenoic acid 22 : 6 omega-3	124.5 [80.0; 171.5]	124.0 [55.5; 178.5]	96.5 [52.25; 176.0]	10.0 [53.0; 159.0]	0.040	0.230	0.899
Linoleic acid * 18 : 2 omega-6	3.52 [3.07; 3.8]	3.13 [1.94; 3.72]	3.14 [1.6; 3.98]	3.22 [1.89; 3.76]	0.021	0.823	0.738
Gamma-linolenic acid 18 : 3 omega-6	88.0 [48.5; 112.0]	64.0 [37.5; 98.0]	48.0 [27.75; 101.5]	59.0 [33.0; 86.0]	0.001	0.480	0.786
Dihomo-gamma-linolenic acid 20 : 3 omega-6	139.0 [74.0; 216.5]	98.0 [54.5; 153.0]	111.0 [49.0; 190.25]	91.0 [53.0; 155.0]	0.001	0.712	0.805
Arachidonic acid * 20 : 4 omega-6	1.13 [0.72; 1.33]	1.06 [0.42; 1.3]	0.90 [0.35; 1.32]	0.97 [0.41; 1.26]	0.015	0.374	0.783
Docosatetraenoic acid 22 : 4 omega-6	27.5 [19.5; 32.75]	27.0 [19.0; 34.0]	21.0 [12.75; 33.0]	25.0 [14.0; 33.0]	0.086	0.118	0.499
Docosapentaenoic acid 22 : 5 omega-6	32.0 [20.0; 44.0]	28.0 [8.0; 43.5]	24.0 [7.75; 41.25]	26.0 [8.0; 40.0]	0.041	0.427	0.839
Hexadecenoic acid 16 : 1 omega-9	46.0 [29.5; 75.0]	40.0 [19.0; 58.0]	32.0 [17.0; 59.25]	39.0 [19.0; 62.0]	0.004	0.994	0.330
Oleic acid * 18 : 1 omega-9	2.09 [1.63; 2.88]	2.14 [1.19; 3.04]	1.44 [0.77; 2.51]	1.66 [0.96; 2.64]	0.007	0.040	0.204
Mead acid 20 : 3 omega-9	25.0 [12.5; 33.0]	23.0 [5.5; 34.0]	12.5 [4.0; 30.0]	18.0 [4.0; 29.0]	0.017	0.072	0.664
Nervonic acid 24 : 1 omega-9	73.0 [56.0; 95.5]	67.0 [43.5; 94.5]	60.0 [42.75; 95.25]	63.0 [46.0; 89.0]	0.025	0.602	0.845

* units of measurement for FA in μmol/ml.

In group (I) of men with established DM2, an increase in the relative content of omega-3 PUFA was revealed: alpha-linoleic acid by 26% (p = 0.001), eicosapentaenoic acid by 33% (p = 0.002), docosahexaenoic acid by 17% (p = 0.040); omega-6 PUFA: linoleic acid by 9% (p = 0.021), gamma-linolenic acid by 49% (p = 0.001), dihomo-gamma-linolenic acid by 52% (p = 0.001), arachidonic acid by 16% (p = 0.015), docosapentaenoic acid by 23% (p = 0.041); and omega-9 FA: hexadecenoic acid by 18% (p = 0.004), oleic acid by 26% (p = 0.007), mead acid by 38% (p = 0.017), nervonic acid by 15% (p = 0.040), when compared with group (IV) of men without diabetes (Table 1).

In group (II) of men with newly diagnosed diabetes, an increase in the relative content of only omega-9 oleic acid by 29% (p = 0.040) was found, when compared with group (IV) of men without diabetes (Table 1).

The levels of unsaturated FA in men with conditional prediabetes (group III) were similar to the levels in samples obtained from men of the same age without diabetes (group IV). When comparing groups III and IV, no significant difference was found (Table 1).

Table 2

The results of a multifactorial logistic regression analysis of DM2 association depending on the level of FA, μmol/ml

Fatty acid	OR (95% CI for OR), p
Alpha-linolenic acid, 18 : 3 omega-3	1.030 (1.002–1.058), 0.034
Eicosapentaenoic acid, 20 : 5 omega-3	0.993 (0.962–1.025), 0.685
Docosahexaenoic acid, 22 : 6 omega-3	0.986 (0.967–1.006), 0,.60
Linoleic acid, 18 : 2 omega-6	0.639 (0.287–1.422), 0.272
Gamma-linolenic acid, 18 : 3 omega-6	1.026 (1.001–1.051), 0.044
Dihomo-gamma-linolenic acid, 20 : 3 omega-6	1.003 (0.990–1.015), 0.680
Arachidonic acid, 20 : 4 omega-6	1.002 (0.999–1.005), 0.300
Docosatetraenoic acid, 22 : 4 omega-6	0.956 (0.874–1.045), 0.319
Docosapentaenoic acid, 22 : 5 omega-6	1.019 (0.971–1.068), 0.447
Hexadecenoic acid, 16 : 1 omega-9	1.007 (0.971–1.045), 0.694
Oleic acid, 18 : 1 omega-9	1.848 (0.691–4.940), 0.221
Mead acid, 20 : 3 omega-9	0.943 (0.861–1.032), 0.200
Nervonic acid, 24 : 1 omega-9	0.998 (0.973–1.023), 0.885

Note: CI – confidence interval; OR – odds ratio.

Then, the probability of having DM2 was estimated via the Model 1 of multivariate logistic regression analysis (Table 2). The dichotomous parameter – the presence or absence of DM2 (according to the anamnestic data) was used as a dependent variable; the studied unsaturated FA were used as independent variables. The analysis of Model 1 was carried out with standardization by age, BMI, and plasma glucose content.

According to the results, the relative odds of having DM2 are directly associated with an increase in the levels of omega-3 alpha-linolenic acid (OR = 1.030, 95% CI 1.002–1.058; p = 0.034) and omega-6 gamma-linolenic acid (OR = 1.026, 95% CI 1.001–1.051; p = 0.044). With an increase in their level by 1 nmol/ml, the probability of having DM2 in men increases by 3 and 2.6%, respectively.

The subsequent stepwise multivariate logistic regression analysis showed independent associations of some of the FA studied with the odds of having newly diagnosed diabetes (Model 2), with standardization by age and BMI (Table 3).

Table 3

The results of a multivariate logistic regression analysis of associations of newly diagnosed diabetes depending on the level of FA, μmol/ml

Fatty acid	OR (95% CI for OR), p
Alpha-linolenic acid, 18 : 3 omega-3	1.013 (0.995—1.031), 0.161
Eicosapentaenoic acid, 20 : 5 omega-3	0.987 (0.961—1.014), 0.342
Docosahexaenoic acid, 22 : 6 omega-3	1.004 (0.990—1.019), 0.553
Linoleic acid, 18 : 2 omega-6	0.545 (0.301—0.996), 0.048
Gamma-linolenic acid, 18 : 3 omega-6	1.004 (0.989—1.020), 0.590
Dihomo-gamma-linolenic acid, 20 : 3 omega-6	0.998 (0.989—1.008), 0.744
Arachidonic acid, 20 : 4 omega-6	1.431 (0.147—3.896), 0.757
Docosatetraenoic acid, 22 : 4 omega-6	1.001 (0.937—1.069), 0.979
Docosapentaenoic acid, 22 : 5 omega-6	0.994 (0.958—1.032), 0.760
Hexadecenoic acid, 16 : 1 omega-9	0.988 (0.962—1.016), 0.401
Oleic acid, 18 : 1 omega-9	1.961 (1.054—3.648), 0.034
Mead acid, 20 : 3 omega-9	0.998 (0.939—1.061), 0.949
Nervonic acid, 24 : 1 omega-9	1.002 (0.985—1.019), 0.841

Note: CI – confidence interval; OR – odds ratio.

Newly diagnosed diabetes in men aged 35–74 years is inversely associated with the level of linoleic acid in blood plasma (OR = 0.545, 95% CI 0.301–0.996; p = 0.048), as well as directly associated with the level of oleic acid (OR = 1.961, 95% CI 1.054–3.648; p = 0.034). Thus, with a decrease in the concentration of omega-6 linoleic PUFA by 1 μmol/ml, the chance of having newly diagnosed diabetes increases by 45%; with an increase in the level of omega-9 oleic acid by 1 μmol / ml, the chance of having newly diagnosed diabetes is 1.96 times higher.

In the Model 3 of multivariate logistic regression analysis, the probability of having prediabetes depending on the level of the studied unsaturated FA was estimated (Table 4). The analysis of Model 3 was carried out with standardization by age and BMI.

Table 4

The results of a multivariate logistic regression analysis of associations of prediabetes depending on the level of FA, μmol / ml

Fatty acid	OR (95% CI for OR), p
Alpha-linolenic acid, 18 : 3 omega-3	1.001 (0.984—1.019), 0.887
Eicosapentaenoic acid, 20 : 5 omega-3	1.023 (0.997—1.049), 0.080
Docosahexaenoic acid, 22 : 6 omega-3	1.007 (0.994—1.020), 0.278
Linoleic acid, 18 : 2 omega-6	1.042 (0.606—1.793), 0.881
Gamma-linolenic acid, 18 : 3 omega-6	1.004 (0.990—1.017), 0.592
Dihomo-gamma-linolenic acid, 20 : 3 omega-6	1.002 (0.994—1.011), 0.579
Arachidonic acid, 20 : 4 omega-6	0.814 (0.102—3.510), 0.846
Docosatetraenoic acid, 22 : 4 omega-6	0.951 (0.895—1.010), 0.100
Docosapentaenoic acid, 22 : 5 omega-6	0.996 (0.962—1.031), 0.827
Hexadecenoic acid, 16 : 1 omega-9	0.969 (0.943—0.996), 0.025
Oleic acid, 18 : 1 omega-9	0.657 (0.344—1.256), 0.204
Mead acid, 20 : 3 omega-9	1.007 (0.953—1.064), 0.801
Nervonic acid, 24 : 1 omega-9	1.008 (0.992—1.024), 0.334

Note: CI – confidence interval; OR – odds ratio.

When studying the results, it was found that prediabetes, regardless of age and BMI, was inversely associated with the level of hexadecenoic acid (OR = 0.969, 95% CI 0.943–0.996; p = 0.025). A decrease in the level of omega-9 hexadecenoic FA by 1 nmol / ml increases the chance of having prediabetes by 3.1%.

DISCUSSION

Presently, almost one in eleven people between the ages of 20 and 79 years suffers from diabetes [1]. Moreover, diabetes often remains undiagnosed for a long time, since an increase in blood glucose levels develops gradually. In addition, clinical manifestations in the early stages are often not severe enough for the patient to notice the classic symptoms of diabetes. Nevertheless, even undiagnosed patients have an increased risk of developing macro- and microvascular complications [2]. This, in turn, stresses the expediency of conducting an early diagnostic examination to detect diabetes, as well as timely initiation of drug treatment to reduce the risk of complications.

There is evidence that DM is closely associated with lipid metabolism disorders, especially with the involvement of free FA. Increased levels of free FA in blood can cause insulin resistance, disruption of insulin signaling pathways, and destruction of β-cells. However, different types of FA have different and even opposite effects during the development and course of insulin resistance and DM2 [4]. Therefore, studying the relationship between specific types of FA and DM is more important than studying the general level of FA.

Linoleic acid (18 : 2) belongs to the family of essential omega-6 PUFAs. It is found in significant amounts in vegetable oils and nuts [13]. It is known that linoleic PUFA is a biochemical precursor of pro-inflammatory metabolites, especially eicosanoids and endocannabinoids. Therefore, it is generally accepted that its excess in the diet is directly or indirectly associated with markers of inflammation and metabolic diseases (such as obesity). However, pro-inflammatory effects may depend on the complex interaction of metabolic factors and have not been definitively proven [14].

Similar contradictions are also observed in the studies of linoleic acid as a biomarker. Some studies show that higher 18 : 2 levels in blood or adipose tissue are associated with a lower risk of developing DM2 [15, 16]. Other studies do not show any significant association, or contain contradictory data about the association between linoleic acid in blood and DM2 [17, 18]. In this study, in men aged 35–74 years, the level of linoleic acid was inversely associated with newly diagnosed diabetes and was significantly higher in the group with an established diagnosis of DM2 (based on anamnestic data). According to a meta-analysis of prospective studies by S.M. Mousavi et al. [7], each 5% increase in linoleic PUFA intake is associated with a 10% decrease in the risk of developing DM2, while a 15% decrease in the risk of developing diabetes is observed with an increase in the 18 : 2 level as a biomarker. The results of the EPIC-InterAct Case-Cohort Study [15] also provide convincing evidence of a strong inverse association between linoleic FA levels in blood and DM2. In this study, we only analyzed linoleic acid levels at baseline and did not assess changes over time from newly diagnosed to established diabetes, which could have led to these differences. In addition, it is necessary to take into account the total amount of dietary intake of linoleic PUFA, which was not evaluated in this study and needs further confirmation.

Gamma-linolenic PUFA (18 : 3, omega-6) belongs to the class of essential omega-6 FA. It usually gets to the human body as part of dietary supplements. Due to the rapid conversion to omega-6, dihomo-gamma-linolenic PUFA is found in low concentrations in blood and tissues [19]. Therefore, the increased content of gamma-linolenic acid cannot be associated with high food consumption. In a prospective study by Z. Miao et al. [17], it was found that baseline levels of 18 : 3 (omega-6) in erythrocytes were positively associated with DM2, regardless of BMI and other potential factors influencing the result. The authors suggested that high levels of circulating gamma-linolenic acid may be a risk factor for developing DM2.

As part of the Kuopio Ischaemic Heart Disease Risk Factor Study [20], it was also found that higher concentrations of gamma-linolenic and dihomo-gamma-linolenic PUFA may be associated with a higher risk of developing DM2. In this study, the levels of gamma-linolenic acid were the highest in people with an established diagnosis of DM2. In addition, regardless of risk factors (age, BMI, plasma glucose levels), direct associations were found between gamma-linolenic acid and DM2, which may indicate the importance of this PUFA in the development of the disease.

Alpha-linolenic acid (18 : 3, omega-3) is the most common PUFA of omega-3 class. However, the human body cannot synthesize this PUFA; therefore, it must be obtained from food [13]. Among the well–known edible oils, linseed oil has the highest content of alpha-linolenic acid and is an excellent source of supplements. In experimental animal studies, it has been shown that alpha-linolenic acid intake can improve the lipid profile, treat diabetes and reduce complications caused by diabetes, as well as reduce the risk of developing diseases of the circulatory system [21]. However, one large systematic review registered on PROSPERO found no evidence that alpha-linolenic PUFA alters glucose metabolism or affects the risk of developing diabetes [8].

According to 20 prospective cohort studies (https://force.nutrition.tufts.edu/), the levels of alpha-linolenic acid in blood/adipose tissue (of plant origin) also were not significantly associated with DM2 [22]. However, some of the data presented in large meta-analyses on the effects of alpha-linolenic acid are either limited or of low quality. We established a higher level of alpha-linolenic PUFA in the group of men with DM2 (based on anamnestic data), and in Model-1 of the regression analysis it was a significant indicator affecting the presence of diabetes, which contradicts most literature data and, of course, requires further study.

Oleic acid (18 : 1) is one of the most common omega-9 monounsaturated FA (MUFA), found in both animal and vegetable oils. It accounts for approximately 80% of MUFA in the composition of total plasma lipids [13]. It is believed that oleic acid can stimulate the secretion of glucagon-like peptide-1, thereby showing its protective effect in patients with DM2 [23]. Moreover, it can increase insulin sensitivity by suppressing the production of reactive oxygen species and regulating the activity of matrix metalloproteinases-2 [24]. In contrast, a large prospective cohort study [25] did not show any significant overall association between circulating oleic acid and diabetes. The study by T. Plotz et al. [26] records the toxicity of oleic acid and its inability to neutralize the toxic effects of palmitic acid. A cross-sectional study by M. Kang et al. [27] found that an increase in 18 : 1 and desaturase activity can lead to impaired metabolism of FA (including MUFA) and dysfunction of adipose tissue. Consequently, this promotes hypersecretion of proatherogenic, proinflammatory, and prodiabetic adipocytokines that contribute to the development of DM2. In this study, higher levels of oleic acid in men with established and newly diagnosed diabetes, as well as direct associations with the chance of having newly diagnosed diabetes are probably associated with the characteristic accumulation of fat in the anterior abdominal wall and viscerally, which is often found in men.

Hexadecenoic FA (16 : 1 omega-9) is another omega-9 MUFA that can be produced by partial β-oxidation of oleic acid. It is mainly found in neutral lipids (triglycerides and cholesterol esters) and monocytes [28]. Very little information is available about the hexadecenoic FA. This MUFA is either barely mentioned in studies or occurs in epidemiological articles, where FA are simply indicated as a secondary component of certain tissues, without taking into account possible biological or biochemical phenomena [29]. Recent studies have shown that omega-9 hexadecenoic FA exhibits a strong anti-inflammatory effect *in vitro* and *in vivo*, which differs from the effect of omega-7 palmitoleic acid (16 : 1), and is comparable in magnitude to the effect of omega-3 PUFA [29]. In our case, the concentrations of hexadecenoic MUFA did not differ in the studied groups, however, in the Model-3 regression analysis, an inverse association with prediabetes was revealed. Despite the fact that we did not evaluate the activity of this omega-9 MUFA, the results obtained can be used in new areas of research.

CONCLUSION

In the course of the comparative study, it was shown that the levels of unsaturated FA in the blood plasma of men with established DM2 significantly differ from the levels of FA in individuals with newly diagnosed DM, prediabetes, and without diabetes. In men aged 35–74 years, DM2 is directly associated with the level of alpha-linolenic and gamma-linolenic PUFA in blood plasma. Newly diagnosed DM is inversely associated with the level of linoleic acid and directly associated with the level of oleic acid. Prediabetes is inversely associated with the content of hexadecenoic acid. Thus, detection of changes in the profile of unsaturated FA can be used as an additional prognostic biomarker for identifying patients at risk of developing DM.

Limitations. Insulin sensitivity and secretion, which are important mechanisms contributing to the risk of developing DM2 and/or worsening glycaemia, were not assessed.

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V.S. Shramko – concept and design development; data analysis and interpretation; writing the article. Simonova G.I., Afanasieva A.D. – revisions to the manuscript to improve the scientific value of the article. Shcherbakova L.V. – data analysis and interpretation.

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