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N.V. Pyrikova*, I.V. Osipova, I.G. Polyakova

Altai State Medical University, Department of faculty therapy and occupational diseases, Barnaul, Russia

Modern Aspects of the Clinic, Diagnosis and Treatment of Prediabetes

Abstract

Prediabetes is a common violation of carbohydrate metabolism, the medical and social relevance of which is due to the negative impact on the incidence of type 2 diabetes mellitus (DM) and cardiovascular disease (CVD). The analyzed literature emphasizes the presence of a close pathogenetic relationship between type 2 DM/prediabetes and CVD. This relationship becomes even more relevant, taking into account, on the one hand, the persistent upward trend in the prevalence of carbohydrate metabolism disorders in the population, and on the other hand, the fact that in patients with dysglycemia it is cardiovascular complications that are the main cause of death. However, while the significance of type 2 DM as a risk factor for CVD is widely known and its presence immediately stratifies most patients to a group of high or very high cardiovascular risk, the contribution of prediabetes to the development of CVD remains underestimated among the therapeutic and cardiological communities. The high prevalence of prediabetes creates prerequisites for a further increase in the incidence of type 2 DM and CVD in the Russian Federation, which requires doctors of various specialties to be wary of early detection of prediabetes, since timely preventive measures can significantly reduce the risk of type 2 DM and its complications in the future. Currently, the effectiveness of both non-drug and drug strategies in preventing the development of type 2 DM in people with prediabetes has been confirmed, more and more data are accumulating about the possibility of effective prevention of CVD in prediabetes. According to modern research, the primary role of measures to actively change lifestyle in the treatment and prevention of prediabetes is emphasized, at the same time, the effectiveness of these measures can be reduced due to insufficient commitment of the patients themselves to their independent long-term implementation. Therefore, the strategy of prescribing metformin for the prevention of type 2 diabetes is absolutely justified if the doctor and patient recognize the inefficiency or inability to follow the recommendations for active lifestyle changes for a long time. The article presents the data on the etiology, epidemiology, diagnosis, and approaches to the management of patients with prediabetes from the standpoint of modern recommendations.

Key words: *Prediabetes, diabetes mellitus, cardiovascular disease, metformin, fasting hyperglycemia, impaired glucose tolerance*

Conflict of interests

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BMI — body mass index, BP — blood pressure, CHD — coronary heart disease, CVD — cardiovascular diseases, DM — diabetes mellitus, FHG — fasting hyperglycemia, HbA1c — glycated hemoglobin, HDL — high density lipoproteins, IGT — impaired glucose tolerance, LDL — low density lipoproteins, MPO — myeloperoxidase, OGTT –oral glucose tolerance test, OR — odds ratio, PA — physical activity, RF — risk factor, RR — risk ratio

*Contacts: Natalia V. Pyrikova, e-mail: allinatali@mail.ru

ORCID ID: https://orcid.org/0000-0003-4387-7737

Prediabetes is a condition preceding type 2 diabetes mellitus (DM), with glycemia parameters exceeding the normal range but below the threshold to diagnose type 2 DM [1].

Epidemiology and Prognosis

As estimated by the International Diabetes Federation, in 2017, there were 451 million people with diabetes and more than 318 million people with prediabetes in the world. The total costs of their management amounted to 850 billion US dollars [2]. By 2040, the prevalence of prediabetes is expected to rise up to 482 million, along with global trends in obesity. It will increase dramatically in low- and middle-income countries due to rapidly changing urbanization and lifestyle [3].

Cohort studies have yielded information on the prevalence of prediabetes (Table 1 [6–14]).

Table 1. *Epidemiological data on prediabetes*

Authors, year	Design	Result
Andes L.J., Cheng Y.J., Rolka D.B. et al., 2019 [6]	Cross-sectional analysis of the base of the National Institute of Health and Nutrition for 2005–2016	Among young people, the prevalence of prediabetes is 24,0%, higher for men than for women (29,1% versus 18,8%), fasting hyperglycemia accounted for the largest share of prediabetes — 15,8%
Konnov M.V., Deev A.D., 2017 [7]	303 families were examined: probands (n=285; 79,2% after myocardial infarction) with early coronary artery disease, their spouses (n=216; 82,4% of women) and the children of probands (n=395; 55,2% of men) under the age of 38 years	Prediabetes was detected in 33 (14,1%) of 246 adult children aged 18-38 years and was associated with their own age (OR 1,15, 95% CI 1,06-1,24; p=0,001) and male gender (OR 2,72, 95% CI 1,24-5,97; p=0,013)
Lyu Y.S., Kim S.Y., Bae H.Y. et al., 2019 [8]	Data from the Korea National Institute of Health and Nutrition. Cross-sectional, nationwide representative survey, from 2014 to 2017, 4,442 healthy young people	The prevalence of undiagnosed prediabetes was 25,0%. Obesity was significant risk factor of prediabetes, regardless of gender (male: OR 9,808, 95% CI 1,619-59,412; female: OR 7,719, 95% CI 1,332-44,747)
Wang L., Gao P., Zhang M. et al., 2017 [9]	National representative cross-sectional survey in 2013 in China, 170,287 participants	The prevalence of overall diagnosed and undiagnosed prediabetes is 35,7% (95% CI 34,1-37,4). Under the age of 40 years — 28,8%
Younes N., Atallah M., Alam R. et al., 2019 [10]	A cross-sectional study in Beirut, from January 2016 to May 2018, 603 students aged 18 to 25.	The prevalence of prediabetes was 2,5%. HbA1c was not associated with eating habits or physical activity. Diastolic blood pressure was inversely associated with physical activity (p=0,002), systolic blood pressure was positively associated with fast food consumption (p=0,003)
Fazli G.S., Moineddin R., Bierman A.S. et al., 2019 [11]	Cohort of adults in Ontario (≥20 years), a unified database of a commercial laboratory (N=1772180), with normoglycemia, 2002-2011. Immigration data was used to determine ethnicity. The observation period is 8,0 years.	337,608 people developed prediabetes, the incidence of prediabetes was higher for immigrants compared with long-term residents of Canada (21,2% versus 16,0%, p<0,001) and almost two times higher among immigrants from South Asia than among Western Europeans (23,6% against 13,1%)
Dedov I.I., Shestakova M.V., Galstyan G.R., 2016 [12]	NATION study using questionnaire and screening determination of HbA1c	The prevalence of prediabetes in 19,26% of cases (20 million) in the age group of 20–70 years.
Breyer M.K., Ofenheimer A., Altziebler J. et al., 2020 [13]	Observational population cohort study of 11014 patients, Sweden	The prevalence of prediabetes was 20,2% (men — 23,6%; women — 17,1%)
Al Amri T., Bahijri S., Al-Raddadi R. et al., 2019 [14]	Cross-sectional study, stratified two-stage cluster sampling method, adults without diabetes ≥18 years of age from visitors to primary health care centers in Jeddah	It included 613 people, 32±11,8 years, of which 54,8% were women. Prediabetes was detected in 28,7%

However, the estimates vary depending on the thresholds used to diagnose prediabetes and the basic characteristics of the population [4, 5]. Recent studies conducted in the USA and UK revealed that the prevalence of prediabetes in adults is 38% and 35%, respectively [5]. Moreover, the prevalence of prediabetes in various ethnic groups in the UK nearly tripled between 2003 and 2011 [15]. A similar increase was recorded in Southeast and Eastern Asia, including Japan and China [9]. The NATION study conducted in the Russian Federation revealed that the prevalence of prediabetes in 19.26% of cases if estimated by the level of glycated hemoglobin (HbA1c) was 5.7–6.4% (a prediabetes criterion of the American Diabetes Association (ADA) [12].

The leading endocrinology organizations emphasize in their recommendations the significance of prediabetes as a condition that increases the risk of both type 2 DM and cardiovascular diseases (CVD) [16, 17], and overall mortality [18, 19]. Every year 11% of people with prediabetes develop type 2 DM; prediabetes is often associated with other risk factors (RF) of CVD, which results in microvascular changes [20] and is associated with a higher risk of stroke and coronary heart disease (CHD) in future (odds ratio (OR) 1.20, 95% CI 1.07–1.35) [18, 21]. Patients diagnosed with early-onset diabetes have a more unfavorable cardiovascular risk profile, which leads to premature death compared to those diagnosed with DM in the middle or older age [22]. Researchers found that during a 23-year follow-up period, older people with diabetes diagnosed before the age of 45 had a higher risk of mortality from CVD compared to individuals with normal glucose tolerance (risk ratio (RR) 1.76, 95% CI 1.04–2.98). However, the average age of the diabetic group was 12 years less than that of the healthy group [23].

During an 8-year follow-up period, it was found that patients with impaired glucose tolerance (IGT) or fasting hyperglycemia (FHG) were characterized by a significantly high risk of overall mortality compared with normoglycemic individuals [24]. It should be noted that health risk increases in individuals with a fasting glucose level of just 5.6 mmol/l or an HbA1c level of 39 mmol/mol [18]. A sub-analysis of the ARIC study published in 2017, with prospective follow-up for 10,844 individuals, included a comparison of different criteria for diagnosing prediabetes. It was found that HbA1c and FHG (6.1–6.9 mmol/l) have the highest specificity in identifying individuals who are at risk of adverse cardiovascular outcomes within 10 years. The HbA1c-based criteria demonstrated a small but statistically significant advantage over other risk discrimination criteria for a wide range of complications [25].

Along with the above-mentioned problem of the prevalence and prognostic significance of prediabetes, data obtained during the PARADIGM-FH study that revealed low vigilance among physicians regarding prediabetes should also be highlighted. Examination conducted before the beginning of this study additionally revealed 13% of patients with type 2 DM and 25% with prediabetes. Therefore, of the 38% of patients who survived until heart failure with left ventricular ejection fraction, ≤40% were not timely diagnosed with clinically significant carbohydrate metabolism disorders. At the same time, prediabetes significantly ($p < 0.001$) increased the risk of the endpoint (hospitalization for heart failure and cardiovascular mortality) by 27% compared to the group of patients with HbA1c < 6.0% [26].

Risk Factors and Association with Other Diseases

According to studies, RFs for impaired glucose metabolism include age, obesity and high consumption of carbonated drinks, hypertension, smoking, high-calorie diet and diabetes in family history [27]. Compared to individuals with normal glucose tolerance, adolescents and young people with prediabetes have a significantly higher level of low-density lipoproteins (LDL), systolic blood pressure (BP), central obesity and lower insulin sensitivity ($p < 0.05$ for all) [6].

Few epidemiological projects regarding RFs of prediabetes have been carried out among the Russian population. One of these projects revealed that both type 2 DM and prediabetes were associated with weight gain and the age of subjects. The frequency of undetected type 2 DM and other carbohydrate metabolism disorders increased significantly, starting from the age of 40–45. The prevalence of carbohydrate metabolism disorders had no correlation with gender [12]. According to another analysis, prediabetes in children, adolescents, and young adults with early CHD in their parents' history is independently associated primarily with metabolic syndrome and its components [7].

A large population-based study of RFs associated with undetected IGT in healthy young people

(under 40 years old) was conducted in Korea. It demonstrated that obesity was significantly associated with the increased risk of undiagnosed prediabetes in young people. Family history of diabetes is only associated with the risk of undiagnosed diabetes in young women. Alcohol consumption is negatively associated with the risk of prediabetes in young women [8]. One Spanish study showed that the most sensitive RF for prediabetes was age, followed by fasting insulin, LDL cholesterol, body mass index (BMI), male gender and uric acid level. Researchers concluded that screening individuals with an assessment of selected RFs could help identify many people with prediabetes [28].

In another representative medical survey, participants with FHG were asked to undergo an oral glucose tolerance test (OGTT), fill out a prediabetes questionnaire, and measure weight, height and blood pressure. A positive association was obtained between adequate knowledge of prediabetes and such factors as female gender, non-smoking, and family history of diabetes. Despite their awareness, most participants were obese, had high blood pressure and dysglycemic status after OGTT [29]. Several studies have proven that progression from normoglycemia to prediabetes depends on ethnicity [30, 31].

A number of recent studies demonstrated that lipid metabolism disorders play an important role for individuals with prediabetes. One of these studies included 613 subjects aged 32 ± 11.8 years; 54.8% of the participants were women. Prediabetes was found in 28.7%, and dyslipidemia in 54.2% of the participants. After using an age correction factor, a relationship was found between a high level of LDL and prediabetes. After BMI correction, this relationship remained for any type of dyslipidemia and, in particular, for a high level of LDL. After age and BMI correction, a significant relationship was found only between a high LDL level and prediabetes (OR 1.50, 95% CI 1.02–2.19, p = 0.037) [14]. It is known that lipid metabolism disorders lead to atherosclerosis. Individuals with prediabetes are characterized by a higher prevalence of subclinical atherosclerosis than participants with HbA1c < 5.7% (70.4 vs. 67.5%, p = 0.017). This process in the population with prediabetes was found at the level of the carotid artery (p < 0.001), not in femoral arteries. Participants with prediabetes also had more localizations of atherosclerotic lesions (2 [1; 3] vs. 1 [0; 3], p = 0.002), demonstrating a positive correlation between HbA1c levels and the number of lesions (r = 0.068, p <0.001) [32]. Noninvasive magnetic resonance imaging in vivo revealed significant differences in the composition of plaques, with larger necrotic nuclei, and hemorrhage in carotid arteries compared with femoral arteries [33]. In 2017, Altin C. et al. showed that the total thickness of carotid — not femoral — intima was significantly greater in 113 patients with insulin resistance (homeostatic model assessment index > 2.5) without CVD compared to 112 normoglycemic individuals [34].

More aggressive coronary atherosclerosis in patients with prediabetes was confirmed by the study conducted by Acar B. et al. (2019), where 255 patients with the onset of acute coronary syndrome underwent coronary angiography with the assessment of the frequency of three-vessel disease and calculation of SYNTAX and Gensini indices. It was found that the value of each index and the frequency of multivascular lesion were significantly higher in groups with type 2 DM and prediabetes compared to the control group. At the same time, the severity of coronary atherosclerosis was comparable among patients with type 2 DM and prediabetes [35]. Researchers have demonstrated that active screening before coronary artery bypass grafting for dysglycemia can additionally help identify about 9% of patients with type 2 DM and 10% with prediabetes. Patients with prediabetes and type 2 DM have a comparable profile of hospital complications of coronary bypass surgery, the frequency of these complications was significantly higher than in the group without carbohydrate metabolism disorders [36].

The duration of prediabetes is significant for subclinical atherosclerosis [37] since many of atherogenic RFs are already present at the prediabetic stage [38]. Not only hyperglycemia in the non-diabetic range and the effect of insulin resistance contribute to CVD at the prediabetes stage, but also various metabolic changes, such as mild chronic inflammation, endothelial vasodilator and fibrinolytic dysfunction, and the atherogenic profile of lipoproteins [39].

However, according to the study that involved 6,434 asymptomatic patients from Korea, who underwent CT coronary angiography, prediabetes was not associated with an increased risk of subclinical coronary atherosclerosis [40]. In a study of the risk of coronary artery atherosclerosis in young adults, the risk ratio for the presence of calcified coronary artery plaque for each 5-year period of prediabetes is only 1.07 (1.01–1.13) [41]. This issue is of scientific and practical interest and requires further study [34].

Researchers have proven the relationship between prediabetes and psychosocial factors and sexual disorders. This study included four groups of apparently healthy men (25–50 years old) comparable in age and weight: with FHG (n = 16), with IGT (n = 17), with FHG + IGT (n = 16), as well as men with normal glucose tolerance (n = 18). All participants completed questionnaires to assess male sexual function (IIEF-15) and to assess the presence and severity of depressive symptoms (Beck Depression Inventory-Second Edition — BDI-II). As a result, men with both FHG and IGT had lower levels erectile function, sexual desire and overall satisfaction, and a higher overall BDI-II score. Individuals with isolated IGT and FHG were characterized by a lower level of sexual desire only. In all study groups, the level of erectile function correlated with the BDI-II score, while the level of erectile function and sexual desire correlated with the level of insulin resistance. Results obtained indicate that prediabetes can affect sexual function in young men [42].

The second study included four groups of women: with FHG (group A; n = 19), with IGT (group B; n = 18), with FHG + IGT (group C; n = 18), as well as healthy individuals (group D; n = 19). All participants completed questionnaires to assess sexual function (Female Sexual Function Index — FSFI), and BDI-II. Total FSFI and BDI-II scores were lower in group C than in the other groups of women, while the total FSFI score was lower in groups A and B than in group D. Scores in all areas (sexual desire, arousal, orgasm, sexual satisfaction, and dyspareunia) were lower in patients with FHG and IGT. Compared to group D, group A had lower levels of sexual desire and sexual satisfaction, and group B had lower levels of desire, arousal and orgasm. In all groups of women with prediabetes, the total FSFI score negatively correlated with the level of insulin resistance and had a weak correlation with the total BDI-II score. Researchers concluded that impaired fasting glucose levels and IGT can interfere with sexual function and cause depressive symptoms in women [43].

Socially active individuals are less likely to develop abnormal glucose regulation. It was proven that low social support at a young age is associated with high fasting glucose levels and prediabetes in middle-aged women, not in men [44]. Another study demonstrated that participation in social events reduced the risk of prediabetes in women, while marriage or living with a partner reduced the risk of prediabetes only in men [45].

Information obtained for 2009–2016 in the NHANES study showed that the prevalence of arthritis in adults with prediabetes is 32.0% (26 million). The prevalence of sufficient physical activity (PA) among adults with arthritis or prediabetes is 56.5% (95% CI 51.3–61.5) and 50.1% (95% CI 46.5–53,6), respectively. Approximately 50% of adults with prediabetes or arthritis either have no physical activity or are obese, further increasing the risk of type 2 DM [4]. The profile of concomitant diseases in men and women with prediabetes differs significantly: women are more likely to have arrhythmias, non-coronary heart diseases, osteoporosis, increased levels of systemic inflammatory biomarkers and depression; men with prediabetes are more likely to have angina, myocardial infarction, and atherosclerosis [13].

Challenges in Prediabetes Diagnosis

Currently, prediabetes is generally detected by chance, as part of routine clinical examinations of the population or targeted examination of a patient for confirmation/exclusion of carbohydrate metabolism disorders, primarily type 2 DM. Prediabetes is characterized by the absence of definite clinical symptoms, primarily due to insignificant glycosuria and continued energy supply to organs and tissues. In rare cases, patients cite decreased working capacity, increased fatigue, and slow healing of wounds. In most cases, overweight or obesity, AH and pathologies of the cardiovascular system come to the fore. In connection with existing insulin resistance, pronounced clinical manifestations of non-alcoholic fatty liver disease, gouty arthritis, and hyperuricemia can be observed [20].

Any individual aged over 45 years, or with BMI ≥ 25 kg/m² and at least one RF from the following (family history of diabetes, gestational diabetes or delivery of a large fetus, AH, low PA, high density lipoprotein cholesterol (HDL) ≤ 0.9 mmol/l and/or triglyceride level ≥ 2.82 mmol/l, polycystic ovary syndrome, CVD) or with ≥12 points on the FINDRISC scale should be referred for screening aimed at diagnosing possible carbohydrate metabolism disorders. If the patient is diagnosed with prediabetes, re-examination should be done every year, and if there is no prediabetes — once in 3 years [1].

There is currently no consensus on the diagnostic criteria for prediabetes. All expert societies and

associations consider such conditions as FHG and IGT as prediabetes [1]. However, FHG is interpreted by different associations in different ways. According to ADA criteria, FHG is fasting plasma glucose level of 5.6–6.9 mmol/l [16], while according to the IDF (International Diabetes Federation), RAE (Russian Association of Endocrinologists), NICE (the National Institute for Health and Care Excellence, UK), Diabetes Canada it is 6.1–6.9 mmol/l [46, 17, 47, 48]. Studies revealed that fasting glucose level at the upper limit of normal was associated with an increased risk of prediabetes (OR 2.74, 95% CI 1.78–4.23 and 3.08, 95% CI 1.69–5.58) among adults with normal weight and overweight/obesity, respectively, compared with low fasting glucose level [49].

Also, there is no consensus on adding HbA1c to the diagnostic criteria for prediabetes. According to the recommendations of ADA, NICE and Diabetes Canada, HbA1c is on the list of tests for prediabetes, albeit with a different diagnostic range: 5.7–6.4% and 6.0–6.4% according to the criteria of ADA and NICE, and Diabetes Canada, respectively. Meanwhile, IDF and RAE guidelines do not currently consider HbA1c as an independent diagnostic criterion for prediabetes. Benefits associated with using the HbA1c level as a prediabetes criterion include the following: no fasting period, no daily changes during illness or stress, higher preanalytical stability. Also, prediabetes diagnosis with the help of HbA1c is more specific and improves the assessment of CVD risk and other clinical complications compared with determination based on fasting plasma glucose level [50, 51]. This is confirmed by data: the study included 817 participants with prediabetes (HbA1c 5.7–6.4% (39–47 mmol/mol). Their glycemic status during follow-up was classified as "diagnosed with diabetes" (diagnosis by a physician or taking an antidiabetic drug), "undiagnosed diabetes" (HbA1c ≥ 6.5% (≥48 mmol/mol), "prediabetes and normoglycemia" (HbA1c < 5.7% (<39 mmol/mol). During median follow-up (12 years), 33.8% of participants returned to normoglycemia, 7.2% progressed to undiagnosed diabetes, 12.8% progressed to diagnosed diabetes, and 46.2% remained prediabetic [52].

It should be noted that blood test for HbA1c should be performed using the HbA1c determination method certified according to the National Glycohemoglobin Standardization Program (NGSP) or the International Federation of Clinical Chemists (IFCC) and standardized according to the reference values accepted in the Diabetes Control and Complications Trial (DCCT) [1].

IGT is a combination of FHG and insulin response to 75 g of glucose per 200–300 ml of water that is insufficient in strength and activity. IGT is found when plasma glucose level during OGTT after 120 min (2 hours) is 7.8–11.0 mmol/l, and fasting glycemia is < 7.0 mmol/l [20].

According to the latest data, glucose level in saliva can be used as a reliable non-invasive test for screening and diagnosis of prediabetes. A comparative study was conducted that included 204 adults in 3 groups (104 patients with type 2 DM, 50 individuals with prediabetes, 50 control patients without diabetes) aged 18–65 years. The median glucose level in saliva was 23.40 ± 12.755 mg/dl in the control group, 42.68 ± 20.830 mg/dl in the prediabetic group and 59.32 ± 19.147 mg/dl in the diabetic group, with a significant difference between the three groups (p-value < 0.001). Salivary glucose can help differentiate non-diabetic patients from individuals with prediabetes with sensitivity of 94.2% and specificity of 62% [53].

Prediabetes is a chronic inflammatory disease. Therefore, there is an intensive search for the corresponding screening markers. It is known that myeloperoxidase (MPO) is a leukocyte-derived enzyme, which is associated with both oxidative stress and inflammation and is touted as a possible mediator of atherosclerosis. A group of researchers set the goal of evaluating the MPO level in patients with prediabetes and comparing it with other CVD risk factors. A crossover study involved 400 subjects, 200 with prediabetes and 200 in the control group, comparable in age and gender. BP, weight, height, waist circumference, hip circumference and lipid parameters, and MPO level were measured for each subject. MPO level was significantly increased in individuals with prediabetes compared with the control group. Results of correlation analysis revealed that MPO reliably and positively correlates with all RFs of CVD, such as age, BMI, waist-to-hip ratio, BP, lipid parameters, except for HDL, which showed a negative correlation. Therefore, the MPO level can be used to evaluate cardiovascular risk in prediabetic patients. It can also be an early biomarker of oxidative stress and inflammation in such cases [54].

Another study included 400 subjects, 200 with prediabetes, 200 in the control group, comparable in age and gender. Blood samples were taken from all participants; they were tested for

8-hydroxy-2'-deoxyguanosine (8-OHdG), malondialdehyde (MDA), reduced glutathione (GSH) and high-sensitivity C-reactive protein (hs-CRP). It was found that oxidative stress markers, i.e., 8-OHdG and MDA, were significantly increased in subjects with prediabetes compared to control subjects, except for GSH, which was significantly reduced in prediabetic individuals. In the same way, hs-CRP was significantly increased in prediabetic subjects compared with the control group. Correlation analysis demonstrated that 8-OHdG, MDA, and hs-CRP significantly and positively correlated with IGT in prediabetic subjects, while GSH showed a significant negative correlation with IGT [55].

A number of studies attempted to evaluate the possible relationship between serum creatinine level and impaired fasting glucose. It was found that serum creatinine level negatively correlates with impaired fasting glycemia in men (RR 0.98; 95% CI 0.96–0.99; p = 0.008) and women (RR 0.94; 95% CI 0.91–0.97; p < 0.001). Low creatinine levels may be associated with impaired fasting glycemia [56].

Another study named CORDIOPREV aimed to detect changes in the level of circulating miRNAs associated with type 2 DM or prediabetic status and the possibility of using it as a biomarker for assessing the risk of disease. At the start, the study enrolled 462 patients without type 2 DM. After follow-up during 60 months, 107 patients developed type 2 DM, and 253 patients developed prediabetes. Plasma levels of four miRNAs associated with insulin signaling and beta-cell function were measured by reverse transcription polymerase chain reaction. The relationship between miRNA levels and signaling and insulin release parameters were analyzed at the baseline and after the follow-up period. This study revealed that unregulated plasma levels of miR-150, miR-30a-5p, miR-15a and miR-375 were detected one year before the onset of type 2 DM and prediabetes and can be used to assess the risk of disease [57].

Today, individuals at high risk of carbohydrate metabolism disorders can undergo any of the following tests: FHG, IGT, or HbA1c. However, according to current Russian recommendations, patients are diagnosed with prediabetes only based on FHG and/or IGT. An HbA1c level of 6.0–6.4% is not yet an independent diagnostic criterion and should be confirmed with FHG and/or IGT. Nevertheless, patients with HbA1c in the range of 6.0–6.4% belong to the group with the highest risk of type 2 DM [1].

Treatment Approaches

Educating the population on healthy eating and lifestyle are crucial for curbing prediabetes. These measures aim to reduce body weight by 5–7% from the baseline by maintaining a moderately hypocaloric diet, primarily with limited consumption of fats and simple carbohydrates and regular moderate PA. Researchers proved that the greatest effect on preventing type 2 DM was observed only in individuals with high adherence to lifestyle changes, who achieved the recommended weight loss [16, 17, 46–48].

We should mention a number of recent studies regarding lifestyle changes and eating habits. One of these studies included women with prediabetes, aged 18–55 years, from among 190 participants; they were randomized to a group with 3-month individual intensive lifestyle modification (test group, n = 95) or a group with standard treatment (control group, n = 95). The participants completed questionnaires about their diet and PA. Blood samples were taken at the beginning of the study and then after 3 and 6 months. A total of 123 individuals completed this study (74 from test group (age 40.6 ± 9.8 years; BMI 31.2 ± 7.0 kg/m²) and 49 from the control group (age 40.6 ± 12.7 years; BMI 32.3 ± 5.4 kg/m²). HbA1c (primary endpoint) significantly improved in test group after 6 months compared with the control group (p < 0.001). A comparative analysis of the groups revealed lower dietary calories and total cholesterol and increased HDL in the test group (p-values < 0.001, 0.04 and < 0.001, respectively), while BMI and weight changes were not clinically significant between both groups [58].

A longer follow-up (23 years) performed during the Da Qing Diabetes Prevention Study (n = 577) demonstrated that active lifestyle changes over 6 years significantly reduce the risk of cardiovascular mortality, general mortality, and type 2 diabetes compared with the control group by 41%, 29%, and 45%, respectively [59].

It is known that healthy eating is an issue of concern for the prevention and treatment of prediabetes: weight loss of 1 kg in patients with IGT leads to a progressive decrease in the risk of type 2 DM by 16%. A learning resource with video instructions and pre- and post-questionnaires was developed and tested online among 156 participants (17 with pre-diabetes and type 2 DM, 118 interested individuals and 21 health professionals). The high motivation of

these individuals to study nutrition issues through simple, visual, practical and culturally acceptable online educational resources was revealed. After using the learning resource, the accuracy of determining products that increase blood glucose concentration improved by 17.4% (p = 0.013) in people with type 2 DM and prediabetes, and by 12.8% (p = 0.003) in health professionals (p < 0.001) [19].

Another study regarding diet was conducted as follows: adults (n = 34) with HbA1c > 6.0% and increased body weight were randomized into two groups: the first group — with a ketogenic diet and very low carbohydrates (n = 16), and the second group — with a moderate-carbohydrate diet and low fat content (n = 18). In 12 months, subjects from the first group showed a greater decrease in HbA1c levels (from 6.6 to 6.1%) than subjects from the second group (from 6.9 to 6.7%, p = 0.007). Patients in the first group lost more weight (from 99.9 to 92.0 kg) than in the second group (from 97.5 to 95.8 kg, p <0.001) and reduced use of diabetes-related drugs; 6 out of 10 patients stopped taking these drugs (p = 0.005) [60].

Higher intake of total protein was proven to be associated with a lower level of prediabetes (OR 0.49, 95% CI 0.28–0.83), while the primary determining factor is the intake of plant protein (OR 0.53, 95% CI 0.36–0.76). Replacing 2 protein energy percent (E%) with carbohydrates revealed an increased risk of prediabetes (OR 1.09, 95% CI 1.01–1.18) [61].

There are a number of studies on the effectiveness of the Mediterranean diet. One study included a sample of 42 patients with prediabetes and BMI > 25 kg/m², who were recommended a Mediterranean diet by nutritionists during group sessions every 2 weeks for 4 months. Information on calorie and macronutrient intake was obtained using a diary for 7 days; adherence to the diet was studied using the PREvención con DIeta MEDiterránea (PREDIMED) questionnaire. No recommendations were given to patients regarding calorie restriction and PA. Each subject underwent anthropometric, metabolic and nutritional evaluation at the beginning and the end of this study. Approximately 40.5% of subjects achieved restoration of normal glucose tolerance by the end of the study. Fasting plasma glucose level, HbA1C, BMI, waist circumference, BP, visceral obesity index, triglycerides, total cholesterol, and LDL level were significantly reduced, while the HDL level was significantly increased by the end of the study. Individuals with prediabetes showed significantly increased adherence to the Mediterranean diet as assessed during follow-up in accordance with the PREDIMED questionnaire. A decrease in the prevalence of metabolic syndrome was also reported [62].

The latest information relates to eating habits, such as drinking coffee. Lower risk of prediabetes (OR 0.73, 95% CI 0.62–0.86) was observed in subjects who drank coffee compared with those who did not. Higher consumption of caffeine (≥152 compared with <65 mg/day) was accompanied by a borderline (p = 0.053) decrease in the risk of prediabetes (OR 0.45, 95% CI 0.19–1.00) [63].

Projects aimed at increasing PA demonstrated good effect. A randomized controlled trial was conducted to compare the effect of low-intensity PA with high-intensity interval PA on HbA1c and fasting blood glucose levels in young people with overweight and prediabetes (60 subjects). Statistically significant effects on HbA1c and fasting blood glucose levels were obtained from both exercises (p < 0.05), but high-intensity PA led to a greater decrease in HbA1c (26.07 vs. 14.50%) and fasting glucose (17.80 vs. 13.22%), respectively [64].

Another study proved the effectiveness of home workouts using video aids compared to standard physical exercises (for example, treadmill, cycling) and a control group of subjects with an increased HbA1c level (prediabetes group). At week 12, HbA1c level in patients from the test group decreased by an average of 2% compared with a 0.6% decrease in the standard and control groups (p = 0.04 and 0.03). Participants demonstrated a decrease in LDL (p = 0.05), and trends indicating a decrease in body fat (p = 0.10) suggested higher PA and motivation compared to other participants [65].

Results of the National Health and Nutrition Examination Survey 2011–2014 (NHANES) conducted in the USA were used to determine predictors of insufficient PA in a large sample of adults with prediabetes, aged at least 20 years (n = 2,536). Extrapolation to more than 45 million adults in the United States aged 20 years with prediabetes revealed that 42.7% had insufficient PA.

It was proved that recommendations on PA for people with low activity and other restrictions should be personalized as part of a special exercise program in order to account for their specific restrictions [66, 67]. However, lifestyle changes tested in clinical trials were poorly implemented at the primary care stage due to the growing number of individuals

with prediabetes and limitations in infrastructure, resources and coordination of efforts for preventing diabetes [68]. Healthcare systems, especially in developing countries, may have limited economic and technical resources. Also, most subjects of clinical trials later gained weight again [1].

Large-scale studies on using pharmaceuticals to prevent type 2 DM have been completed along with non-drug approaches.

Different pharmaceutical agents showed their efficacy in reducing the risk of type 2 DM: metformin, α-glucosidase inhibitors, orlistat, glucagon-like peptide-1 (GLP-1) receptor agonists and thiazolidinediones. However, metformin plays a leading role in terms of the efficacy/safety ratio, as proven in long-term studies (follow-up of more than 15 years), among the medications recommended for use in patients with prediabetes for the prevention of type 2 DM in cases when measures on lifestyle changes are ineffective [16, 17, 48].

Patients with prediabetes, primarily with IGT, were included in metformin studies. The average follow-up period was 2.5–3 years; the average dose of the drug was 1,500–1,700 mg. The decrease in the progression of prediabetes into type 2 DM was observed in 25–40% of cases on average. However, compared with non-drug methods in young patients with obesity, the efficacy of metformin was higher and comparable with that in the group of intensive lifestyle changes [20].

A major study of the efficacy of metformin in patients with prediabetes, DPPOS [69], was conducted to establish a long-term evaluation of diabetes prevention measures, assess microvascular and neuropathic outcomes and RFs for CVD. Phase II of the DPPOS (last report as of January 2014) revealed that the risk of diabetes decreased by 27% in the group of lifestyle changes and by 18% in the group treated with metformin, which also indicates decreased adherence of patients to the activities aimed at lifestyle changes over time. At the same time, it demonstrates a steadily decreasing risk of diabetes in the metformin group. Moreover, this study demonstrated a more significant decrease in fasting glycemia level and less frequent use of glucose-lowering drugs in the metformin group. Together with pharmacoeconomic calculations, this information enables to recommend metformin for treating prediabetic patients [70]. It is crucial that metformin, along with its hypoglycemic properties, has an additional cardioprotective effect, reduces the levels of C-reactive protein and tissue plasminogen activator (t-PA) [71], lipid peroxidation products [72], and also improves endothelial function and lipid profile [71]. For patients with prediabetes, metformin also proved to be effective in reducing systolic BP (especially in individuals with IGT and obesity) [73] and reducing left ventricular myocardial hypertrophy [72]; an anti-atherogenic effect was revealed, which was independent of demographic, anthropometric or metabolic factors or treatment with statins [74].

Alpha-glucosidase inhibitors reduce glucose absorption in the intestines and, consequently, blood glucose levels. In the STOP-NIDDM study that included 1,429 patients with IGT, treatment with acarbose reduced the relative risk of diabetes by 25% after 3.3 years of follow-up compared with the placebo group. Unfortunately, non-life-threatening gastrointestinal side effects (flatulence and diarrhea) of these drugs are poorly tolerated by patients in real clinical practice, significantly hindering their widespread use [16, 46].

Orlistat is a gastrointestinal lipase inhibitor. It is used to treat obesity because it inhibits the absorption of dietary fat (by about 30%), thereby significantly reducing total caloric value. Positive results were obtained during the large-scale controlled XENDOS study: using orlistat for 4 years reduced the risk of type 2 DM by 37%. Therefore, orlistat can be considered for patients with obesity and prediabetes. It allows reducing not only their body weight but also the risk of type 2 DM [47].

Glucagon-like peptide-1 (GLP-1) receptor agonists increase the secretion of insulin and glucagon, suppress glucose production in the liver, slow down gastric emptying, and reduce appetite, thereby contributing to weight loss in obese individuals. Exenatide and liraglutide demonstrated long-term efficacy in terms of sustained weight loss in obese patients. In experimental studies, they also showed the ability to reduce the incidence of diabetes and prediabetes. However, this effect is yet to be confirmed by controlled randomized clinical trials. The most common side effects of this class of drugs are nausea and vomiting, which can significantly reduce patients' adherence to treatment. The limited clinical use of such drugs is also associated with their relatively high cost and parenteral administration [16, 48].

Like metformin, thiazolidinediones increase the absorption and utilization of glucose in peripheral organs and reduce gluconeogenesis in the liver, thereby reducing insulin resistance. In the DREAM

study, rosiglitazone reduced the incidence of type 2 DM by 60% in 3 years. However, its administration was associated with significant side effects, such as weight gain (on average 2.2 kg in the test group compared with the control group), increased risk of heart failure (0.5% vs. 0.1%), and overall frequency of cardiovascular events (2.9% vs. 2.1%). A later Canadian study — CANOE — demonstrated the efficacy of combining rosiglitazone and metformin in low doses in reducing the incidence of type 2 DM with low risk of side effects. The frequency of new diabetes cases in the active treatment group was 14%, and 39% in the placebo group. In general, thiazolidinediones, despite their significant preventive effect, cannot be recommended for patients with prediabetes for safety reasons. This is because these drugs contribute to weight gain, are hepatotoxic, increase the incidence of cardiovascular complications, and, possibly, urinary bladder cancer [47, 48].

Probiotic biotherapy for maintaining appropriate intestinal flora is widely discussed now. It can be an effective early measure in hyperglycemia treatment. There is a study designed to determine the hypoglycemic effect and safety of administering bifidobacteria and berberine to newly diagnosed prediabetic patients. It revealed decreased fasting plasma glucose level compared with the baseline after 16 weeks of treatment [75].

A study was conducted on the effect of normalization of intestinal microflora as a method of preventing and treating prediabetes. Measures include encapsulated Lactobacillus rhamnosus HN001 (6 × 109 colony forming units/day) (A) and cereals containing 4 g of β-glucan (B), placebo capsules (O1), and low-calorie porridge (O2). Participants of this study underwent six-month measures in the following groups: AB, AO1, BO2, and O1O2. The primary outcome was HbA1c level in 6 months; follow-up in 9 months will help to evaluate the long-term effect of these measures [76].

Researchers proved that abscisic acid can improve glucose homeostasis and reduce inflammation in mammals by activating lanthionine synthetase C-like 2 (LANCL2). This study was focused on two fig fruit extracts (FFE) with different abscisic acid concentration: the FFE-10X extract contained ≥300 ppm of abscisic acid, and the FFE-50X extract contained ≥50 ppm of abscisic acid. Four beverages were used: 1) 100 mg FFE-50X, 2) 200 mg FFE-50X, 3) 600 mg FFE-10X, and 4) 1,200 mg FFE-10X. In a randomized, double-blind crossover study, ten healthy adults drank four test beverages. The glycemic index (GI) and insulinemic index (II) were then evaluated. The test beverages containing 200 mg of FFE-50X and 1,200 mg of FFE-10X significantly reduced GI by 25% ($p = 0.001$) and 24% ($p = 0.002$), respectively. Adding FFE to a glucose solution significantly reduced values II at all dosages and showed an apparent decrease in the dose-effect: FFE-50X at 100 mg and 200 mg (–14% ($p < 0.05$) and –24% ($p = 0.01$), respectively) and FFE-10X at the doses of 600 and 1,200 mg (–16% ($p < 0.05$) and –24% ($p = 0.01$), respectively). Therefore, FFE supplements are a promising measure for the correction of postprandial glucose level and insulin homeostasis and offer possible additional treatment for chronic metabolic disorders, such as prediabetes [77].

Another study included patients with prediabetes who were injected with coenzyme Q10. It showed a significant decrease in the HOMA-IR insulin resistance index. This suggested that coenzyme Q10 in patients with IGT may slow down the progression from prediabetes to overt diabetes [78].

Therefore, prediabetes, especially in young and middle-aged people, is an important medical and social problem. However, the abovementioned methods for the correction of carbohydrate metabolism disorders do not currently have a sufficient evidence base. The corresponding trials are being conducted, and the efficacy and safety of drugs used are being studied. The development of an array of targeted measures for the prevention, early detection and timely beginning of treatment of prediabetes remains an urgent issue and is of academic and practical interest.

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Pyrikova N.V. (ORCID ID: https://orcid.org/0000-0003-4387-7737): development of the concept and design, justification and writing of the manuscript, final approval for the publication of the manuscript, responsible for all aspects of the work

Osipova I.V. (ORCID ID: https://orcid.org/0000-0002-6845-6173): verification of critical intellectual content

Polyakova I.G. (ORCID ID: https://orcid.org/0000-0001-5575-2451): substantiation and writing of the manuscript

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