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PREDIABETES IN CARDIOLOGY PRACTICE

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The handbook presents data on the role of early carbohydrate metabolism disturbances in the development of cardiovascular diseases and diabetes mellitus. We analyzed methods for detecting and treating early carbohydrate metabolism disturbances on outpatient and inpatient levels. We present definition, criteria for prediabetes diagnosis, risk group stratification and preventive measures for cardiovascular diseases and diabetes. The supplement contains a scale on diabetes prediction and treatment algorithms for patients with prediabetes. The manual is intended for use by cardiologists, internists, family doctors, neurologists, endocrinologists and medical residents.

The handbook is approved by the Academic Council of the National Research Center for Preventive Medicine of the Health Ministry of Russia, Moscow, Russia

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Abbreviations

ADA	—American Diabetes Association
AH	—arterial hypertension
AMP	—adenosine monophosphate
AO	—abdominal obesity
ARIC	—Atherosclerosis Risk in Communities
BM	—body mass
BMI	—body mass index
CHD	—coronary heart disease
CVD	—cardiovascular disease
DBP	—diastolic blood pressure
DECODE	—Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe
DLP	—dyslipidemia
DM	—diabetes mellitus
DPP	—Diabetes Prevention Programm
DPP-4	—dipeptidyl-peptidase 4
EASD	—European Association for the Study of Diabetes
Euroheart	—Euro Heart Survey
FFA	—free fatty acids
FINDRISC	—The Finnish Diabetes Risk Score
GFL	—glucose fasting level
GDM	—gestational diabetes mellitus
GFR	—glomerular filtration rate
GLP-1	—glucagon-like peptide-1
GLUT-1	—glucose transporter 1
GLUT-4	—glucose transporter 2

HbA1c	—glycated hemoglobin
HDL	—high density lipoproteins
HR	—heart rate
HS CRP	—highly sensitive C reactive protein
IDF	—International Diabetes Federation
IFG	—impaired fasting glycemia
IGT	—impaired glucose tolerance
IR	—insulin resistance
LDL	—low density lipoproteins
LPA	—low physical activity
LVH	—Left ventricular hypertrophy
MI	—Myocardial infarction
MS	—metabolic syndrome
NCD	—non-communicable disease
NRDM	—National Register of Diabetes Mellitus
OGTT	—oral glucose tolerance test
PA	—physical activity
PH	—postprandial hyperglycemia
PPARa	—peroxisomal proliferator-activated alpha receptor
PPARg	—peroxisomal proliferator-activated receptor gamma
RF	—risk factors
RR	—risk ratio
SBP	—systolic blood pressure
SCORE	—Systematic Coronary Risk Evaluation
SGLT2	—sodium/glucose cotransporter 2
T2DM	—type 2 diabetes mellitus
TC	—total cholesterol
TG	—triglycerides
TNF-a	—tumor necrosis factor-a
UN	—United nations
WC	—waist circumference
WHO	—World Health Organization
2-hr PG	—2 hours after load plasma glucose level

Introduction

The number of patients with type 2 diabetes mellitus (T2DM) has been increasing over the last years. Diabetes is one of the most common non-communicable disease (NCD), in developed and developing countries. WHO experts consider diabetes as medical and social problem with enormous economic damage for civilization. According to official data, treatment of patients with diabetes costs as much that it may become an unbearable burden in future. Over 80% of costs are associated with the treatment of complications of diabetes mellitus (DM), outpatient medical care, hospital admission and other types of medical care.

Nowadays, it is important not only to prevent secondary micro- and macrovascular complications of DM, but also to diagnose prediabetes, assess risk factors of DM among adults and concentrate on primary prevention of DM. Prospective studies showed that such measures can reduce the risk of DM development and its complications.

The handbook presents data on the definition and classification of carbohydrate metabolism disorders, epidemiological studies and its association with other risk factors (RF). We analyzed the contribution of prediabetes to the development of cardiovascular diseases (CVD) and diabetes. The handbook present clinical research data based at the National Research Center for Preventive Medicine over the last years on the relationship between prediabetes and the risk cardiovascular complications development. We also present criteria for prediabetes diagnosis, risk groups stratification and preventive measures for CVD and diabetes that have practical value. The supplement contains scheme-algorithm for the treatment of patients with prediabetes that generalize clinical studies and international guidelines for its pharmacotherapy.

This handbook is intended for use by cardiologists, internists, family doctors, neurologists, endocrinologists and medical residents.

We will be grateful for the feedback and suggestions that can be sent to the email: mmamedov@mail.ru.

Chapter I
DEFINITION AND CLASSIFICATION OF CARBOHYDRATE METABOLISM DISORDERS

There are several types of carbohydrate metabolism disorders: hypoglycemia, hyperglycemia, glycogenosis, hexose- and pentosemia, aglycogenosis [27].

Hypoglycemia is a condition when blood glucose decreases below normal level. Hyperglycemia is a condition when blood glucose increases that can be explained by impaired absorption, synthesis and utilization of glucose. DM is the main carbohydrate metabolism disorder in endocrinological practice [36].

Nowadays diabetes can be defined as a group of metabolic disorders characterized by hyperglycemia due to impaired insulin synthesis and/or its biological effect [101]. Chronic increase of blood glucose leads to damage and dysfunction of various organ systems, including visual, nervous, urinary and cardiovascular.

There are four main etiological types of DM: type 1 diabetes, type 2 diabetes, «other specific types» and «gestational diabetes» (Table 1).

Type 1 diabetes is characterized by the rapid destruction of pancreatic beta cells that causes decrease of insulin, and subsequently leads to absolute insulin deficiency. It is believed that type 1 diabetes is more likely to develop in asthenic young people and manifest by polyuria, thirst, weight loss and development of ketosis. It is also known that type 1 diabetes can develop at any age [101], have latent progression and develop into insulin deficiency over the years. Patients with type 1 diabetes produce antibodies to the proteins of pancreatic beta cells (including glutamate decarboxylase, tyrosine phosphatase, zinc and insulin

transporters) that can cause acute or slow diabetes manifestation. Autoantibodies to islet cells — marker of type 1 diabetes — are determined only in some patients and decrease over the years. This type of diabetes is more prevalent among Caucasian race [105].

Table 1. Etiological classification of diabetes mellitus

I. Type 1 diabetes (β-cell destruction, usually leading to absolute insulin deficiency)
A. Immune mediated
B. Idiopathic
II. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)
III. Other specific types
A. Genetic defects of β-cell function
1. Chromosome 12, HNF-1α (MODY3)
2. Chromosome 7, glucokinase (MODY2)
3. Chromosome 20, HNF-4α (MODY1)
4. Chromosome 13, insulin promoter factor-1 (IPF-1; MODY4)
5. Chromosome 17, HNF-1β (MODY5)
6. Chromosome 2, NeuroD1 (MODY6)
7. Mitochondrial DNA
8. Others
B. Genetic defects of insulin action
1. Type A insulin resistance
2. Leprechaunism
3. Rabson-Mendenhall syndrome
4. Lipoatrophic diabetes
5. Others
C. Diseases of exocrine pancreas
1. Pancreatitis
2. Trauma/pancreatectomy
3. Neoplasia
4. Cystic fibrosis
5. Hemochromatosis
6. Fibrocalculous pancreatopathy
7. Others
D. Endocrinopathies
1. Acromegaly

2. Cushing's syndrome
3. Glucagonoma
4. Pheochromocytoma
5. Hyperthyroidism
6. Somatostatinoma
7. Aldosteronoma
8. Others
E. Drug- or chemical-induced
1. Vacor
2. Pentamidine
3. Nicotinic acid
4. Glucocorticoids
5. Thyroid hormone
6. Diazoxide
7. β-adrenergic agonists
8. Thiazides
9. Dilantin
10. α-Interferon
11. Others
F. Infections
1. Congenital rubella
2. Cytomegalovirus
3. Others
G. Uncommon types of immune-mediated diabetes
1. «Stiff-man» syndrome
2. Anti –insulin receptor antibodies
3. Others
H. Other genetic syndromes associated with diabetes
1. Down syndrome
2. Klinefelter syndrome
3. Turner syndrome
4. Wolfram syndrome
5. Friedreich ataxia
6. Huntington chorea
7. Laurence-Moon-Biedl syndrome
8. Myotonic dystrophy
9. Porphyria
10. Prader-Willi syndrome
11. Others
IV. Gestational diabetes mellitus (GDM)

T2DM is characterized by insulin resistance (IR) and beta-cell deficiency associated with obesity (abdominal type) compared with type 1. At the early stage of type 2 diabetes, IR develops and insulin secretion impairs that leads to postprandial hyperglycemia (PH). Next stage is characterized by persistent hyperglycemia in response to insulin [2, 3]. T2DM usually affects older people, up to 90 % of all patients with DM are adults. But due to increase of obesity among European and non-European young population the frequency of type 2 diabetes is growing among younger patients [14]. Table 2 shows the difference between the types of DM.

Table 2. The main differences between types 1 and 2 of DM

Comparison of type 1 and 2 diabetes		
Feature	**Type 1 diabetes**	**Type 2 diabetes**
Onset	Sudden	Gradual
Age at onset	Any age (mostly yyong)	Mostly in adults
Body habitus	Thin or normal	Often obese
Ketoacidosis	Common	Rare
Autoantibodies	Usually present	Absent
Endogenous insulin	Low or absent	Normal, decreased or increased
Concordance in identical twins	50%	90%
Prevalence	Less prevalent	More prevalent -90 to 95 of U.S. diabetics

Gestational diabetes develops during pregnancy. Euglycemia usually returns after childbirth, but these women have higher risk of type 2 diabetes development. A meta-analysis showed that the development of type 2 diabetes is more common in women who had gestational diabetes [9, 10, 59]. According to a large Canadian study, the risk of type 2 diabetes was 4 % in the first 9 months after childbirth and 19 % in 9 years in women with gestational diabetes [31].

Other specific types of diabetes include: 1) single gene mutations that lead to rare types of diabetes, such as adolescent diabetes in young people; 2) secondary diabetes due to number of diseases (for example, pancreatitis, trauma or pancreatic surgery); 3) drug or chemically induced diabetes [45].

It is important to pay attention to diagnosis methods when glycemic data is interpreted. This includes both glucose and glycated hemoglobin levels (HbA1c) (Table 3).

Table 3. Algorithm for individualized selection of treatment targets according to HbA1c

	Age		
	Young	**Middle**	**Elderly and / or life expectancy <5 years**
No severe macrovascular complications and / or risk of severe hypoglycemia	<6,5 %	< 7,0 %	< 7,5 %
Severe macrovascular complications and / or risk of severe hypoglycemia	< 7,0 %	< 7,5 %	< 8,0 %
The following target values of pre- and postprandial plasma glucose levels will correspond to these target HbA1c levels			
HbA1c, %***	Fasting plasma glucose, mmol/L		Plasma glucose level on OGTT, mmol/L
< 6,5	< 6,5		< 8,0
< 7,0	< 7,0		< 9,0
< 7,5	< 7,5		< 10,0
< 8,0	< 8,0		< 11,0

Along with various types of diabetes, carbohydrate metabolism diseases also include prediabetes, which, according to the WHO definition, includes impaired fasting glycemia (IFG), impaired glucose tolerance (IGT), and a combination of IGT and IFG. Usually, prediabetes precedes type 2 diabetes [96]. But in some patients, it may act as an independent RF for CVD and other chronic non-infectious diseases [39, 42]. These aspects will be discussed in the following chapters of this handbook.

Chapter II
EPIDEMIOLOGICAL ASPECTS OF DM AND EARLY CARBOHYDRATE METABOLISM DISORDERS

The prevalence of early carbohydrate metabolism disorders and diabetes became pandemic over the last years in both developed and developing countries [43]. The number of patients with diabetes in the world doubled over the last 10 years and reached 415 million people by the end of 2015 [44]. According to the forecasts of the International Diabetes Federation (IDF) 642 million people will suffer from diabetes in 2040 (Fig. 1) [44]. This led to the adoption of 61/225 UN Resolution from 12/20/2006 on diabetes mellitus, UN Political Declaration in 2011 that was addressed to national health systems and required the use of multidisciplinary strategies for the prevention and control of noncommunicable diseases, especially diabetes — one of the leading causes of disability and mortality [88].

The prevalence of diabetes also significantly increased in the Russian Federation (RF) over the last years. According to the federal register by the end of 2016, 4.35 million people (3.0 % of the population) had diabetes, 92 % of which (4 million) had type 2 diabetes, 6 % (255 thousand) — type 1 diabetes and 2 % (75 thousand) — other types of diabetes [87]. However, these data underestimate the real number of patients, since they consider only detected and registered cases. The results of a large-scale Russian epidemiological study (NATION) showed that only 50 % of type 2 diabetes cases are diagnosed. Thus, the actual number of patients with DM in the RF is over 8–9 million people (about 6 % of the population), which is an extreme threat in long-term prospect since a significant part of patients

Fig. 1. The prevalence of DM in the world from 2015 to 2040 (million people), according to the IDF for people aged 20 to 79

remain undiagnosed, do not receive treatment and have high risk of vascular complications [46].

T2DM is the most common type of diabetes and the number of patients is increasing due to cultural and social changes [64, 67, 75]. Almost 91 % of cases of type 2 diabetes are detected in high-income countries. The number of people suffering from diabetes is expected to reach 642 million by 2040 according to general upward trend. The problem is that over 50 % of patients with DM remain undiagnosed in developing countries. According to IDF, approximately 193 million people with early carbohydrate metabolism disorders remain undiagnosed [81].

An IDF epidemiological review showed that 22 million people had DM in Africa in 2014 (5.1 %). The highest prevalence was recorded on Reunion Island (15.4 % of the population), the Seychelles (12.1 %), Gabon (10.7 %) and Zimbabwe (9.7 %). In these regions type 1 diabetes remain undiagnosed among children and even in case of early diagnosis, these patients are unable to maintain appropriate monitoring and insulin therapy which leads to high incidence of early mortality. This fact explains relatively low prevalence of type 1 diabetes in Africa. Mortality due to diabetes in this region is 8.6 %, and 76.4 % of deaths among people aged under 60 years. The mortality rate in women is almost 2 times higher compared with men.

In Europe, epidemiological indicators vary among countries. The total number of patients with DM is 52 million people (33.1 % of undiagnosed patients), which is 1 case per 13 adults. Turkey has the highest rate of diabetes — 14.8 %, and Russia, due to large population, has the largest number of patients with DM (10.9 million people). The largest number of patients with DM differs significantly from the data of the National Register of Diabetes Mellitus (NRDM) that ended in 2012. Age is considered as one of the main risk factors of DM, since the proportion of the population over 50 years exceeds 37 %. It is proposed to increase to 44 % in 2035. In addition, the largest number of children with type 1 diabetes among all IDF regions (about 129,300 children) is in Europe with the frequency of new cases about 20,000 per year. The leading countries by the number of children with type 1 diabetes are Germany, the United Kingdom and Russia. According to the data from 2013, 1 of 10 deaths is due to diabetes complications (total number — 619 thousand). It is also remarkable that women have higher mortality rate [12, 16, 24, 32, 39, 46].

The prevalence of diabetes in Middle East and Northern Africa countries is 9.7 % of the adult population or 37 million patients, and it is proposed to double (up to 68 million people) by 2035. This fact can be explained by the rapid economic development of several countries and the aging of the population. About 25 million women suffer from gestational diabetes, which increase the risk of type 2 diabetes developing. Saudi Arabia has the highest number of type 1 diabetes patients. Mortality due to diabetes was 368 thousand cases in 2013, with about 50 % of the cases in patients aged under 60 [43, 76].

Caribbean of North America countries share second place in the world by the number of patients with DM — 39 million. Prevalence is 11.4 % among adult population. The number of patients is proposed to increase to 50.4 million people by 2035. The highest prevalence of diabetes is in Brazil (15.9 %), Guyana (15.9 %) and Curacao (14.5 %), while the highest number of patients with diabetes is in the USA (24.4 million people) and Mexico [43].

The Multicenter European DECODE study revealed some patterns of DM prevalence between various populations [24]. The prevalence of DM increases with age, regardless of gender among Europeans. DM is detected in <10 % of population under 60 years, 10–20 % — from 60 to 69 years, 15–20 % — over 70 years. Screening revealed the same number of patients with asymptomatic diabetes. This means that the risk of «getting» diabetes is 30–40 % on average among European population [9].

According to published data, average blood sugar level 2 hours after eating increase with age, especially after 50 years among Europeans. PH is significantly

higher in women compared with men, especially after the age of 70 years (this may be explained by shorter life expectancy in men). Average fasting plasma glucose concentrations slightly increase with age. Men have higher concentrations compared with women at the age of 30–69 while women have higher concentrations compared with men after 70 years. The frequency of DM is less than 10 % at the age of 60, 10–20 % — at the age of 60–69 and 15–20 % — at senile age (asymptomatic diabetes has the same percentage). These data indicate that a lifetime risk of DM development is 30–40 % among European population [1, 6, 12, 18].

Even though type 1 diabetes is less common compared with type 2, the number of patients still increase about 3 % annually, especially in children. Approximately 86,000 children develop type 1 diabetes annually [53]. The issue of dynamic growth, medical and social significance of diabetes is essential today, especially due to an increase of type 2 diabetes among children and teenagers. The main RFs of type 2 diabetes include: overweight, excessive calorie intake, lack of exercise, which interact with periods of changes in endocrine system (prepubertal and puberty), and family history [15, 29, 50, 51, 79, 84, 108].

Thus, the prevalence of early carbohydrate metabolism disorders is important due to high risk of DM and cardiovascular complications development. Many large epidemiological studies have been performed to assess the frequency of early carbohydrate metabolism disorders over the past 15 years (Fig. 2).

Fig. 2. The prevalence of prediabetes worldwide from 20 to 79 years of age, 2015

According to IDF, 318 million people worldwide (6.7 % of adults) have IGT, and 69.2 % of them live in low- and middle-income countries [61, 72, 82, 83]. IGT is expected to reach 482 million (7.8 % of the adult population) by 2040 (Fig. 3). 50.1 % of these people under 50 years (159 million people) have high risk of type 2 diabetes development. This age group will continue to have the highest number of IGT patients (Fig. 4).

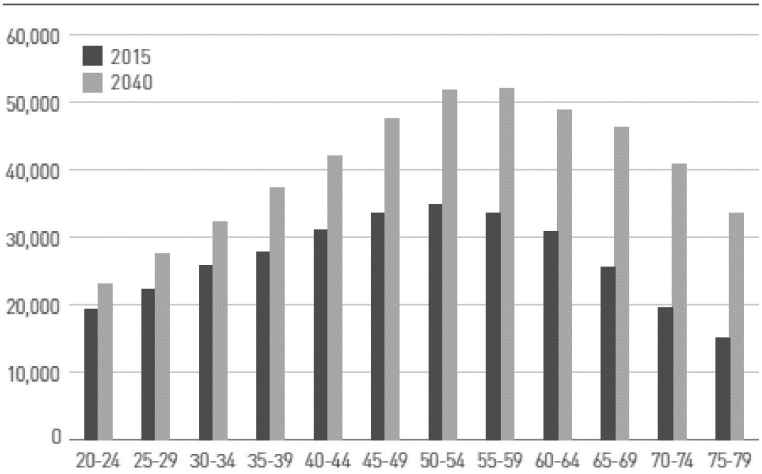


Fig. 3. The number IGT patients by age groups in 2015 and 2040

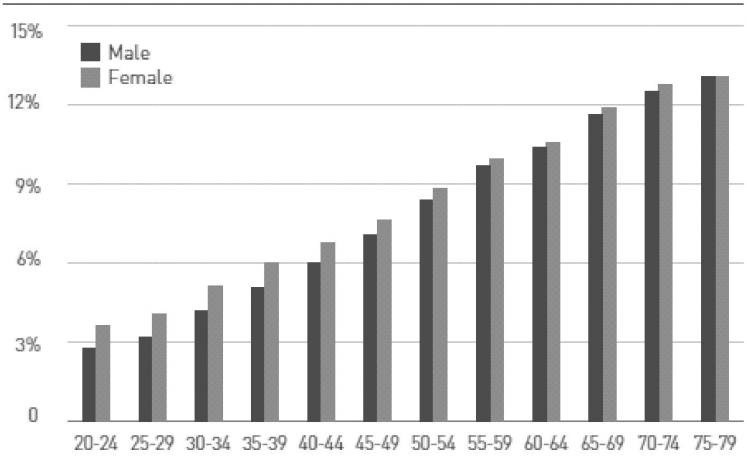


Fig. 4. Prevalence (%) by age (20–79 years) and gender in 2015

The number of patients with T2DM is expected to reach 209 million by 2040 among this age group. According to IDF, the highest prevalence of IGT is in Caribbean and North America — 15.0 %, while the lowest is in Europe — 4.8 % (Table 4).

Table 4. The number of people with IGT in ten countries of the world aged 20–79 years in 2015 and in 2040

Rank	Country/ territory	2015 Number people with impaired glucose tolerance	Rank	Country/ territory	2040 Number people with impaired glucose tolerance
1	India	36.5 million	1	India	63.6 million
2	United States of America	35.8 million	2	United States of America	42.8 million
3	Indonesia	29.0 million	3	Indonesia	36.8 million
4	China	26.7 million	4	China	34.6 million
5	Japan	11.9 million	5	Mexico	18.0 million
6	Brazil	11.0 million	6	Brazil	16.7 million
7	Mexico	10.7 million	7	Pakistan	15.1 million
8	Pakistan	7.9 million	8	Nigeria	12.9 million
9	Nigeria	6.3 million	9	Japan	10.7 million
10	Republic of Korea	5.2 million	10	Ethiopia	10.6 million

IDF Diabetes Atlas – Seventh Edition

A meta-analysis of 8 large population studies showed that about 300 million people worldwide suffer from IGT, which is twice higher than the number of patients with T2DM.

The prevalence of patients with IGT is 10–25 % higher compared with patients with IFG in Western countries. Epidemiological studies show the correlation between type 2 diabetes development and IGT, age, race, obesity, which averages up to 5 % per year [55, 83, 85, 103].

European experts presented data where the prevalence of IGT ranged from 10 % to 25 % and showed the prevalence of DM and IGT according to the results of PH (Fig. 5). Thus, men had higher incidence of type 2 diabetes compared with women, while women had higher incidence of IFG, DM frequency was the same in patients with IGT and IFG. The frequency of new cases of type 2 diabetes is higher in patients with IGT compared with IFG (Fig. 5) [33].

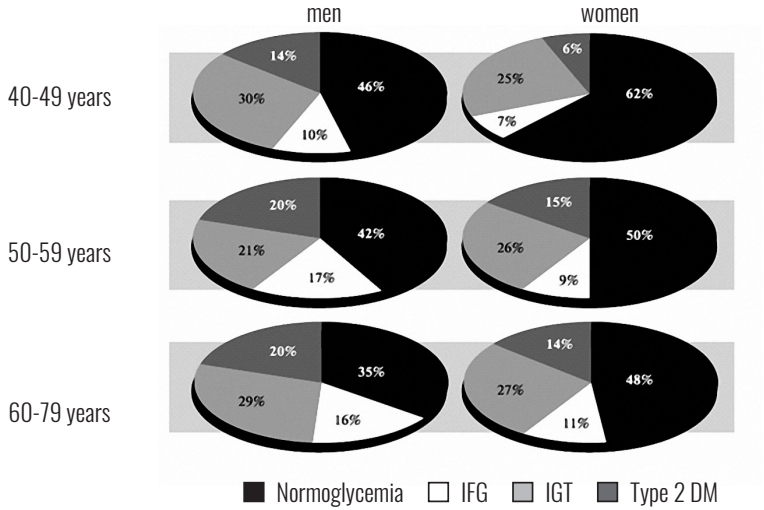


Fig. 5. The prevalence of carbohydrate metabolism disorders in population

Fasting and 2 hours after 75 g of glucose load blood sugar levels were determined during multicenter epidemiological study (in 7 major cities of the Russian Federation, with 10,000 randomly selected respondents) to identify 20 CVD risk factors [62]. According to the data of completed study in the city of Volga Federal District (Cheboksary, 1800 people, random sample aged 30–69 years), fasting hyperglycemia was detected in 3.9 % of cases, while hyperglycemia after load was detected in 2.5 % of cases. This study examined the age-related features of fasting and after 2 hours after load hyperglycemia. Carbohydrate metabolism disorders were not detected in a random sample aged 30–39 years.

Both types of hyperglycemia occurred with the same frequency among patients aged from 40 to 49 years (2.4–2.6 %) (Fig. 6). The frequency of hyperglycemia, especially during fasting, increased in older age groups (twice as much as hyperglycemia after load) [62].

Table 5 presents the average fasting and 2 hours after load sugar blood level that shows a significant increase of fasting sugar blood level in men and with age.

The average after load (during OGTT) blood glucose level was higher compared with the fasting level. It also increases significantly and proportionally with age. This tendency was detected among both men and women. A comparative analysis of fasting and after load blood glucose levels between men and women did not reveal any significant differences (Table 6).

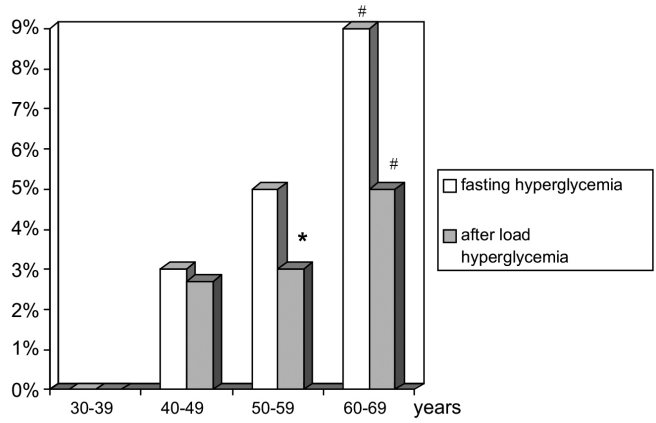


Fig. 6. The frequency of hyperglycemia among various age groups

*p <0.05 statistically significant differences between fasting and after load hyperglycemia;

#p <0.05 statistically significant differences compared with 40–49 years age group

Table 5. Age distribution of mean and absolute values of fasting sugar blood level

Glycemia	Men				Women			
	30–39	40–49	50–59	60–69	30–39	40–49	50–59	60–69
Average value	4.32 + 0.06	4.48+ 0.07	4.56+ 0.06*	4.71+ 0.11**	4.31+ 0.05	4.55+ 0.06**	4.75+ 0.07***##	4.87+ 0.09***##
Absolute value	3.0–5.8	3.0–14.0	3.3–12.3	3.0–12.0	1.1–5.8	3.0–12.5	3.2–16.4	3.2–13.0

*p <0.05, ** p <0.01, *** p <0.001 statistically significant differences compared with 30-39 years age group; ##p <0.01 statistically significant differences compared with 40–49 years age group.

Table 6. Age distribution of average and absolute values of blood sugar level during OGTT

Glycemia	Men				Women			
	30–39	40–49	50–59	60–69	30–39	40–49	50–59	60–69
Average value	5.17+ 0.08	5.5+ 0.1**	5.5+ 0.08***	5.82+ 0.15****	5.22+ 0.07	5.47+ 0.08*	5.83+ 0.1***###	6.03+ 0.14***###
Absolute value	3.5–7.3	3.5–16.4	3.3–14.2	3.8–13.0	3.3–7.8	3.8–15.6	3.0–21.3	3.8–18.4

* p <0.05, ** p <0.01, *** p <0.001, **** p <0.0001 statistically significant differences compared with 30–39 years age group, ###p <0.001 statistically significant differences compared with 40–49 years age group.

Thus, the frequency of diabetes and early carbohydrate metabolism disorders is growing rapidly. Prediabetes occurs 1.5–2 times more often compared with DM. According to the forecast, this tendency will maintain over the next 20 years. The Russian Federation refers to regions with high risk of DM its complications. However, early carbohydrate metabolism disorders have not been studied yet in our country.

Chapter III
CONTINUUM OF THE DEVELOPMENT OF CARBOHYDRATE METABOLISM DISORDERS

DM has rather long pathogenesis or continuum. Scientists pay great attention to prediabetes that reflects the progression from normoglycemia to type 2 diabetes in order to find effective preventive measures and early markers of DM. This condition is characterized by fluctuations of blood glucose levels [2].

According to prospective studies, the early stage of carbohydrate metabolism disorders lasts from 5 to 10 years on average (Fig. 7).

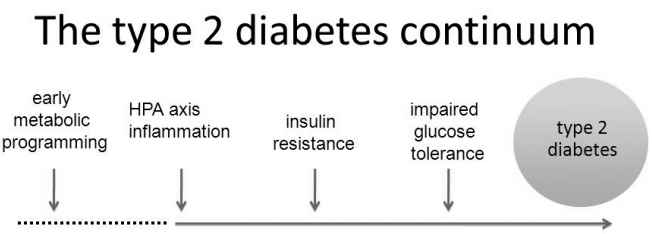


Fig. 7. The type 2 diabetes continuum

The pathogenesis of DM has four stages, and intervention during early stages prevents or slows down the development of this pathology [9].

The development of hyperglycemia is based on three mechanisms:

1) decreased insulin-stimulated glucose utilization by peripheral tissues (skeletal muscle, adipose tissue and liver) or IR;

2) increased glucose production by liver;

3) impaired synthesis and secretion of insulin by pancreatic β-cells.

Today, the prevailing opinion is that type 2 diabetes is based on genetically determined and saved during evolution IR.

IR induced the accumulation of energy in the form of fat deposition in omentum, mesentery and retroperitoneal space. These fat deposits contributed to the survival of primitive people in case of hunger. Nowadays, people live sedentary lifestyle, consume a lot of fat and refined carbohydrates that in combination with genetic memory of IR and energy accumulation, lead to abdominal obesity.

The continuum of diabetes has 4 stages [2]:

- IR and compensatory hyperinsulinemia without clinical manifestation of carbohydrate metabolism disorder;
- IGT manifested by increased level of glucose at least 2–3 hours after eating;
- the initial stage of DM caused by decreased basal insulin secretion;
- DM decompensation caused by pronounced decrease of insulin secretion.

The conversion of IGT to type 2 diabetes has many reasons: the presence of CVD and diabetes RF, lifestyle, social status. Conducted prospective studies show that the annual conversion of IGT to type 2 diabetes in various countries ranges from 1.5 % to 7.3 % (Fig. 8) [34, 36].

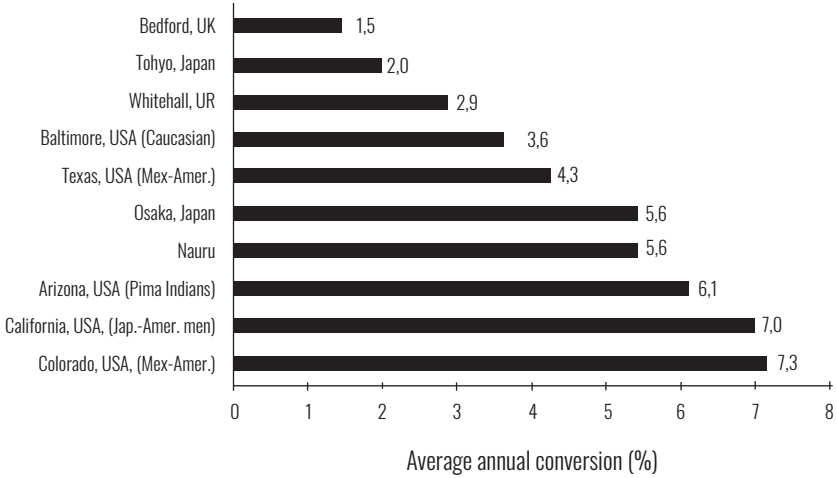


Fig. 8. Annual conversion of IGT to type 2 diabetes

Meta-analysis data of prospective studies (Fig. 9) showed that patients with a combination of IGT and IFG have the highest risk of DM development in the next 5 years [100].

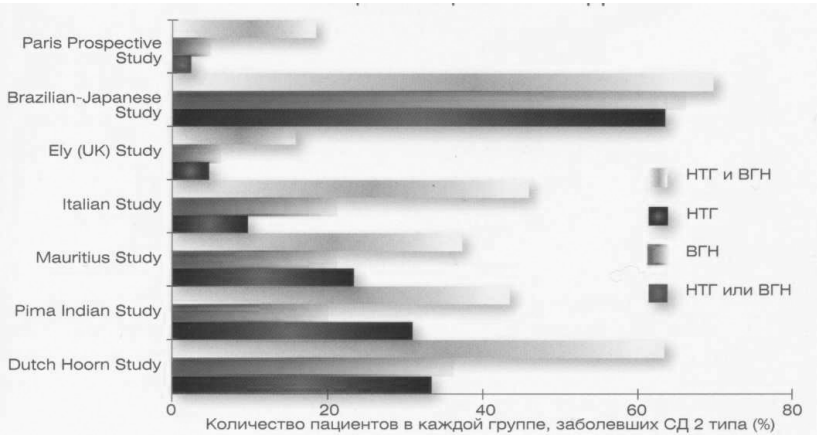


Fig. 9. Prediabetes is associated with increased risk of type 2 diabetes

However, another review showed that regardless of fasting glycemia level patients with IGT had 50 % higher risk of DM development compared with patients with normal glycemia during OGTT (Table 7). On the other hand, blood glucose level during fasting and 2 hours after load had positive correlation.

Table 7. Continuity of IGT as a predictor of type 2 diabetes development compared with IFG (ADA 2004)

Fasting glucose (mmol/L)	Glycemic status during OGTT	Risk of developing type 2 diabetes in the next 8 years
<5,6	Normal tolerance IGT	2,4 19,1
5,6–6,0	Normal tolerance IGT	9,6 31,1
6,1–6,9	Normal tolerance IGT	28,6 59,8

The problem of DM prevention takes national scale as screening of high-risk groups today is not enough. We need to create screening and prevention programs at the federal and regional levels based on systematic population-based approach. Detection and correction of early carbohydrate metabolism disorders has medical and social significance.

Chapter IV
THE ASSOCIATION BETWEEN PREDIABETES AND OTHER RISK FACTORS FOR CHRONIC NONCOMMUNICABLE DISEASES

It is known that most NCDs including CVDs, diabetes, osteoporosis, chronic obstructive pulmonary disease have common risk factors. Today we know over 200 RF, that can be classified into modifiable and non-modifiable, environmental, biological, social, behavioral etc. [49, 70, 107].

The results of prospective studies showed that the same RF can contribute to the development of several chronic NCDs. Table 8 reflects the relationship between 8 major RF and CVD, DM, oncological and respiratory diseases [23, 25, 30].

RFs can be combined according to the principle of causation (obesity and impaired carbohydrate metabolism), pathogenetic interaction (metabolic syndrome) and mechanical combination (arterial hypertension and hypercholesterolemia) [40, 41].

A number of studies showed that early carbohydrate metabolism disorders are not only the initial stage of DM development, but also an independent RF of CVDs and other chronic NCDs. There are several groups of biological and behavioral RF of early carbohydrate metabolism disorders. It is also remarkable that early carbohydrate metabolism disorders are usually detected among people with cardiovascular RF. Thus, screening methods of patients with cardiovascular risk is the priority for DM primary prevention [49, 52, 65].

Table 8. RF for major chronic non-communicable diseases

Risk factors	Cardiovascular diseases	Diabetes mellitus	Oncological diseases	Respiratory diseases
Smoking	+	+	+	+
Excess alcohol consumption	+		+	
Nutrition disorders	+	+	+	+
Lack of physical activity	+	+	+	+
Obesity	+	+	+	+
Increased blood pressure above 140/90 mm Hg.	+	+		
High blood glucose> 5.6 mmol/L	+	+	+	
High blood cholesterol> 5.0 mmol/L	+	+	+	

Interest to early carbohydrate metabolism disorders has grown significantly over the last years due to the development of diagnostic criteria for metabolic syndrome (MS), which includes prediabetes as one of main components. According to the Russian population-based PRIMA study, 40 % of patients with MS have early impairment of carbohydrate metabolism. OGTT is necessary during MS diagnosis, since 60 % of patients with IGT has normal level of fasting blood glucose [65].

British scientists claim that only 39 % of patients with AH have normal glucose tolerance — 10 % have IFG, and 22 % have IGT [95, 100].

Table 9 presents data on the frequency of carbohydrate metabolism disorders in patients with FR and CHD.

Table 9. The frequency of the carbohydrate metabolism disorders in patients with RF and CHD

RF	AH	Dyslipidemia	CHD
Normoglycemia	39 %	44,4 %	43 %
IGT	22 %	17,7 %	31 %
IFG	10 %	8,3 %	6 %
DM	15 %	29,7 %	20 %

According to many sources patients with the following RF have high risk of DM: low physical activity (LPA), abdominal obesity (AO), family history of DM (first-degree relatives suffering from DM), dyslipidemia (high TG level, low HDL level), AH, fatty liver disease, polycystic ovary syndrome in women, erectile dysfunction in men, atherosclerosis manifestations (CHD, stroke, intermittent claudication), recurrent skin infections and unexplained fatigue [104].

The MRFIT study showed that AH is associated with a 23-fold increase of cardiovascular mortality risk in patients with type 2 diabetes compared with patients without DM. Cardiovascular and renal complications in patients with DM in 35–75 % of cases are associated with increased blood pressure. The same results were obtained during the HOT study. The risk of cardiovascular complications and mortality was 2–3 times higher in patients with DM and target DBP level of 90 mm Hg compared with 80 mm Hg [93, 100].

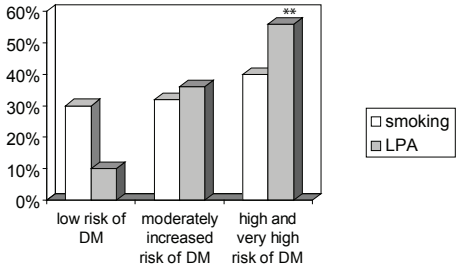
It is also remarkable that AH is one of the most common reasons of primary visit to health care facilities. During the study based on the National Research Center for Preventive Medicine, 37 % of patients with AH had IGT and 32 % of them had MS.

The assessment of the association between RF and high risk of DM

Increased risk of CVD in patients with DM a can only partially be explained by hyperglycemia. The risk of CVD in patients with prediabetes and DM also increases due to concomitant RF, including AO, AH, dyslipidemia, smoking, etc [47, 77].

During series of studies conducted on the base of National Research Center for Preventive Medicine we examined the number of basic and metabolic RFs of CVD in a cohort of patients with different risk levels of DM. We analyzed smoking and LPA rates in groups of men with different risk levels of DM. Smoking is one of the main CVD RF that cause about 4 million deaths every year, and this number will increase according to forecast [5, 63]. 77 % of men smoked during study, and smoking rates in DM risk groups were comparable. About 30 % of smokers have low or moderately increased risk of DM, while 41.1 % have high and very high risk. (Fig. 1).

Increased risk of DM is associated with LPA [8, 36]. Men with LPA have low risk of DM in 10.8 % of cases and have moderately increased or increased risk in 33.5 %. 55.7 % of men with LPA have a high and very high risk of DM. Thus, every second man with LPA has a high or very high risk of DM, which is significantly higher compared with low-risk group of DM.



** p <0.01, statistically significant differences between the groups with low, high and very high risk of DM

Fig. 10. The risk of DM in smokers and people with LPA

The prevalence of AH in the studied groups vary greatly: every fifth patient with hypertension and cardiovascular RF has low risk of DM, every third — moderately increased risk and every second — high or very high risk. Left ventricular hypertrophy (LVH), determined by ECG, had similar tendency.

Table 10 presents the average values of anthropometric and hemodynamic parameters (waist circumference (WC), BMI, SBP, DBP and heart rate (HR)) among people with different risk levels of DM.

Table 10. Instrumental parameters of CVD RF

Instrumental parameters	Low risk of DM	Moderately increased risk of DM	High and very high risk of DM
WC, cm	88,6±6,0	96,8±5,5	100,5±5,6
BMI, kg/m^2	24,7±1,7	27,3±2,5	28,7±2,2
SBP, mm Hg.	136,7±17,7	144,5±17,4	154,8±16,0
DBP, mm Hg	85,7±11,2	89,8±8,0	94,1±8,5
HR, b/min	73,6±6,4	75,4±6,5	75,5±7,6

According to the data obtained, average indicators of anthropometric (WC and BMI) and hemodynamic (SBP, DBP and HR) parameters did not differ significantly between the groups, despite slight tendency to increase with the growth of DM risk. This tendency refers to WC, BMI and BP parameters.

We also performed frequency analysis to identify the relationship between anthropometric and hemodynamic parameters and different risk levels of DM (Table 11). Abdominal and general obesity are the important RF not only for the development of CVDs but also for type 2 diabetes [15, 16]. WC and BMI also are important parameters for the estimation DM risk [17–19]. We analyzed the frequency of these RF in groups of men with different risk levels of DM. The main

question of the study was: How often abdominal and general obesity is associated with DM risk in a cohort of men with different cardiovascular risk levels? Obviously, average WC increases with the risk of DM. Less than 5 % of men with AO has low risk of DM, while 36 % has moderately increased risk of DM. Every second patient with AO has high or very high risk of DM. Obesity estimated by BMI has similar tendency. LPA is one of the main reasons of abdominal and general obesity [20, 21]. Only 10.8 % of patients with LPA has a low risk of DM, while 33.5 % has moderately increased risk. Thus, over 55 % of patients with a sedentary lifestyle have high or very high risk of DM. Thus, only some patients with a high or very high risk of DM have abdominal and general obesity as well as patients with moderately increased risk.

Table 11. DM risk in men with various anthropometric and hemodynamic RF

Instrumental parameters	Low risk of DM	Moderately increased risk of DM	High and very high risk of DM
Abdominal obesity	4,3 %	36 %*	59,7 %**#
Overweight	21,9 %	36,8 %	41,3 %*
Obesity	0 %	29,6 %*	70,4 %**#
AH	20,7 %	32,6 %	50,3 %**#
Tachycardia	22,9 %	30 %	37,1 %
LVH by ECG	27,4 %	25,2 %	47,4 %*#

* p <0.05, ** p <0.01, statistically significant differences between the groups of low, moderately increased, high and very high risk of DM;
# p <0.05, statistically significant differences between the groups of low, moderately increased, high and very high risk of DM.

There are no patients with low risk of DM among patients with AO, and every third patient has a moderately increased risk of DM [98, 109]. 60 % of patients with AO have high and very high risk of DM. This difference is statistically significant between groups. Increased BM is also associated with higher risk of DM. Every fifth patient with increased BM has a low risk of DM, and 41.3 % of patients have high or very high risk. It is remarkable that the frequency of obesity varies significantly between groups. About 70 % of patients with obesity have high or very high risk of DM and there are no patients with low risk. The frequency of AH differs significantly between groups with different DM risk levels. Every second patient with AH and cardiovascular RF has a high or very high risk of DM, every third patient-moderately increased risk and about 20 % — low risk. LVH determined by ECG has similar tendency. The frequency of tachycardia did not differ significantly between groups.

Dyslipidemia is one of the most common disorders in patients with DM. According to clinical studies, most patients with type 2 diabetes have high TG, low HDL and PH. The level of total cholesterol and LDL are the same as in patients without DM. LDL has pronounced atherogenic effect [40,50,104]. Even though TC and LDL levels in patients with type 2 diabetes are similar to patients without DM, they are RF of CVD [102]. The UKPDS study showed that 1 mmol/L (or 38.7 mg/dL) increase of LDL cholesterol increase the rate of cardiovascular complications by 57%. The level of HDL also plays an important role: its increase by 0.1 mmol/L (4 mg/dL) reduce cardiovascular risk by 15% [95]. It is difficult to estimate the prognostic value of TG and other lipoproteins using mathematical methods, including multivariate regression analysis, due to its complex interaction and variability of concentrations. Meta-analysis of population cohort studies showed that cardiovascular risk increases by 32% in men and 76% in women with the increase of TG by 1 mmol/L (89 mg/dL). Adjusted for the level of HDL, cardiovascular risk decreased by half (37% in women and 14% in men) and still was statistically significant. Large 7-year cohort study showed that patients with type 2 diabetes, high level of TG and low level of HDL had high risk of cardiovascular complications and coronary death [100].

Hypercholesterinemia was detected in three groups of patients during the study based in National Research Center for Preventive Medicine. 44% of patients with hypercholesterolemia have high or very high risk of DM, 34.4% — moderately increased risk and 22% — low risk. Similar results were obtained for the patients with low level of HDL [63].

Patients with high level of TG had different results compared with other types of lipid disorders. Every second patient with high level of TG has a high or very high risk of DM, every third — moderately increased risk, and 13% — low risk.

We also analyzed biochemical RF of CVD. Table 5 shows that in general the average indicators of biochemical parameters (TC, LDL, TG, HDL, uric acid, HR CRP) do not differ between groups with different risk levels of DM. But patients with a high and very high risk of DM have tendency for higher average values of biochemical parameters compared with patients with low risk of DM.

The analysis of biochemical RF frequency demonstrates the difference between groups with different risk levels of DM (Table 12).

Generally, the risk of DM increases with the frequency of RF [35]. Thus, the number of patients with a high and very high risk of DM 2 times higher compared with low risk of DM among patients with hypercholesterolemia. We obtained similar results for the patients with elevated level of LDL and decreased level of HDL (Fig. 11).

Table 12. Average values of CVD RF in groups with different risk levels of DM

Biochemical parameters	Low risk of DM	Moderately increased risk of DM	High or very high risk of DM
TC, mmol/L	5.28±0.90	6.10±1.15	6.39±1.09
LDL, mmol/L	3.46±0.71	4.06±1.05	4.31±0.93
TG, mmol/L	1.80±0.69	2.30±0.88	2.46±0.83
HDL, mmol/L	1.00±0.15	0.95±0.14	0.90±0.13
Uric Acid, μmol/L	308.62±47.14	326.14±62.43	355.32±68.39
HR CRP, mg/L	2.97±1.52	4.39±2.18	5.58±1.95

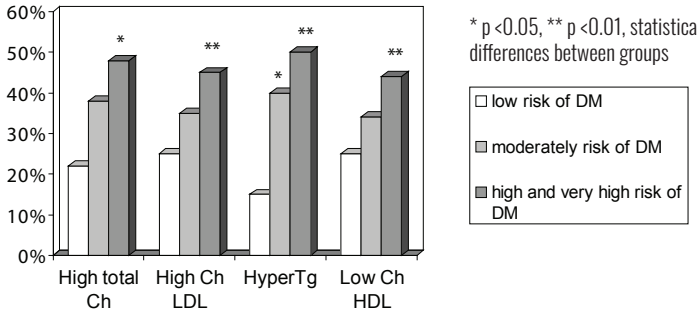


Fig. 11. Lipid metabolism disturbances and risk of DM according to the FINDRISC scale

Patients with high level of TG, have 3 times increase of moderately increased and 4 times increase of high or very high risk of DM compared with low risk. The difference between the groups is statistically significant.

The frequency of hyperuricemia and an increased concentration of HS CRP increased with the risk of DM. It is known that these two parameters are components of MS, that is the state of high risk of DM (Table 13) [37, 73, 102]. Every second patient with these disturbances had a high or very high risk of DM and every third — moderately increased risk.

We analyzed the correlation between cardiovascular RF and the risk of DM according to FINDRISC questionnaire, and found that the risk of DM mostly correlated with metabolic RF, including hyperglycemia after OGTT, high fasting glucose level, level of immunoreactive insulin, cardiovascular risk according to the SCORE scale, level of SBP, DBP, TC, LDL and TG (Table 14). We also found

significant correlation between the risk of DM and uric acid, HS CRP, HDL and LVH, and did not find it between the risk level of DM and smoking and tachycardia.

Table 13. The frequency of CVD RF in groups with different risk levels of DM

Biochemical parameters	Low risk of DM	Moderately increased risk of DM	High or very high risk of DM
High TC	22 %	34.4 %	43.6 %*
High LDL level	25.4 %	33.1 %	41.5 %**
High TG level	13.2 %	36.5 %*	50.3 %**
Low HDL level	22.1 %	34.9 %	43 %**
Uric Acid, μmol / L	15.5 %	31 %	53.4 %*
HR CRP, mg / l	17.9 %	33.8 %	48.3 %*

* p <0.05, ** p <0.01, statistically significant differences between groups.

Table 14. Correlation between DM RF and CVD RF

Risk factors	Coefficient of correlation, r	Statistical significance, p
Fasting glucose, mmol/L	0.723	0.0001
The glucose level during OGTT, mmol	0.712	0.0001
WC, cm	0.686	0.0001
Immunoreactive insulin, μU / ml	0.633	0.0001
BMI, kg/m^2	0.598	0.0001
Genetic determination of DM	0.514	0.0001
SCORE,%	0.478	0.0001
SBP, mm Hg	0.402	0.0001
TC, mmol/L	0.380	0.0001
DBP, mm Hg.	0.352	0.0001
LDL, mmol/L	0.347	0.0001
TG, mmol/L	0.305	0.0001
HR CRP, mg / l	0.297	0.0001
Uric Acid, μmol / L	0.203	0.001
HDL, mmol/L	0.125	0.03
LVH during ECG	0.123	0.03
Smoking	0.041	0.480
HR, b/min	0.085	0.140

Thus, the frequency of most cardiometabolic RFs increase with the risk of DM.

Chapter V
CONTRIBUTION OF PREDIABETES TO THE DEVELOPMENT OF CARDIOVASCULAR COMPLICATIONS

Nowadays, the epidemy of cardiovascular diseases is one of the important issues of medicine due to its high prevalence, complications and the highest mortality. CVDs became the most common cause of death among NCDs in 2014–17.5 million deaths (46 % of all NCDs deaths). 7.4 million of deaths were caused by myocardial infarction, coronary heart disease, and 6.7 million by stroke [36, 41]. All these facts create motivational basis for improvement of methods for prediction and prevention of CVDs.

A number of epidemiological studies showed that at the initial stage of type 2 diabetes, most patients already have macro- and microvascular complications [68, 81, 87].

International multicenter INTERHEART study demonstrated the correlation between DM and myocardial infarction [107]. 3250 patients with DM from 16 European countries took part in EURODIAB IDDM Complication Study that revealed CVD in 9 % among men and 10 % among women [100]. It increased from 6 % in the age group of 15–29 years to 25 % in the age group of 45–59 years, and also depended on the duration of DM. 20 years after the onset, CVD were diagnosed in 29 % of patients with DM and nephropathy and in 2–3 % of patients without nephropathy. A number of studies compared the risk of cardiovascular complications associated with type 2 diabetes and a history of CVD. 51735 men and women aged 25–74 years were observed for 17 years (on average) during

Finnish study (9201 of them died). The relative risk of coronary death adjusted for other RF [56] was 2.1, 4.0 and 6.4 in men with diabetes, myocardial infarction and both diseases, respectively, compared with men without diabetes or myocardial infarction. Women had 4.9, 2.5, and 9.4 relative risk, respectively. The relative risk of all-cause death was 1.8, 2.3, and 3.7 in men and 3.2, 1.7, and 4.4 in women, respectively. All-cause mortality was comparable for men and women with DM, but coronary mortality was significantly higher in men.

A recent British study revealed that DM had higher adverse effect on the amount of adipose tissue, homeostatic IR model (HOMA-IR), blood pressure, lipids, endothelial dysfunction and systemic inflammation in women compared with men, which may contribute to relative risk of coronary heart disease [95]. In addition, women are more likely to be overweight, which changes a set of RFs and increase the risk of DM.

The review on association between gender and mortality from CHD showed that women to men ratio with DM is 1.46 (95 % CI 1.21–1.95) and 2.29 (95 % CI 2.05–2.55) without DM, in other words gender differences by CHD mortality decrease in the presence of DM. The meta-analysis of 37 prospective cohort studies (n = 447,064 patients with DM), which focused on coronary heart disease mortality, showed higher mortality rate in the presence of DM (5.4 compared to 1.6 %) [100]. The relative risk (RR), in the presence or absence of DM was significantly higher in women (RR 3.50; 95 % CI 2.70–4.53) compared with men (RR 2.06; 95 % CI 1.81–2.34). Thus, gender differences of the course of CVD are less among patients with DM, and the reason for this is not clear yet.

UKPDS study showed that only ½ of pancreatic β-cells by the time of clinical manifestation of DM continue to produce insulin, which significantly increase the risk of CVD and mortality in patients with type 2 diabetes [95].

It is known that T2DM has the period of prolonged euglycemic IR, which gradually cause β-cell deficiency and severe diabetes and leads to damage of target organs and increase the risk of cardiovascular complications. WHO and ADA experts disagree on the diagnosis of DM by the level of glucose during fasting or 2 hours after load. That is why it is important to know about the correlation between laboratory parameters, mortality and cardiovascular risk [3, 105].

Clinical and prospective studies data indicate that not only diabetes, but also early carbohydrate metabolism disorders are independent risk factors and predictors of CVD due to atherosclerosis (A level of evidence; I class) [8].

According to EuroHeart clinical study, 30 % of patients with CHD have prediabetes, which remains the same after discharge.

11-year Kuopio Ischemic Heart Disease Risk Factors Study found that people with MS have a 3–4-fold increase of CHD risk as well as all-cause mortality are 2 times higher compared with patients without MS. A Nurses Health Study showed a linear correlation between the stages of diabetes and the development of CVD]. Patients with DM have a 5 times higher risk of CVD compared with the control group, and patients with preclinical stage of DM have 2.40–3.64 % risk [100].

The Framingham study showed that IGT increases the risk of T2DM and significantly increases the risk of cardiovascular complications even compared with AH and hypercholesterolemia. The leading RF of complications during prediabetic period is PH [73].

We found lots of data on the prevalence of IGT prognostic significance compared with IFG as RF of CVD. A number of studies showed the association between IGT and twofold increase of CVD risk and death [7, 11, 91, 94].

The association between IGT with CVD risk was identified during 20 European studies, the results of which suggest that PH at the level of 7.8 mmol/L increase the risk of CVD by 1.58 [100].

Survival analysis of Japanese Funagata Diabetes Study concluded that rather IGT, than fasting hyperglycemia, is CVD RF. The Finnish study showed that IGT is an independent RF of CVD and premature all-cause and cardiovascular mortality [100].

About 12 thousand men without DM were included in the Chicago Heart Study. Men with asymptomatic hyperglycemia (glycemia 1 hour after glucose loading ≥11.1 mmol/L, or 200 mg%) had a higher risk of cardiovascular death compared with men with low PH (<8.9 mmol/L, or 160 mg%). Several studies estimated the association between CVD and fasting and 2 hours after eating plasma glucose levels. Long-term study conducted on Mauritius showed that the risk of cardiovascular death was 2 times higher in patients with isolated PH compared with patients without DM, while isolated fasting hyperglycemia did not show significant increase in mortality (fasting glycemia ≥7,0 mmol/L or 126 mg %, and glycemia 2 hours after glucose loading <11.1 mmol/L or 200 mg%) [100].

The results of the DECODE study, which combined data of 10 European cohort studies (over 22 thousand patients) also confirm the relationship between IGT and increased CVD risk [90]. Patients with diabetes diagnosed by hyperglycemia 2 hours after glucose loading had higher all-cause and CVD mortality compared with patients without PH. Patients with IGT also had significant increase in mortality compared with patients with impaired and normal fasting glucose levels. Multivariate analysis showed that high glycemia 2 hours after glucose load can serve as a predictor for all-cause and CVD mortality (adjusted to another major

CVD RFs), while fasting hyperglycemia can't. High PH was a RF regardless of fasting glycemia, while increased mortality in patients with fasting hyperglycemia was significantly associated with simultaneous increase of glycemia 2 hours after glucose load. The highest increase of CVD mortality was found in patients with IGT, especially with normal fasting glycemia. PH and mortality had linear correlation, while fasting glycemia hadn't. The DECODE study showed that patients with IGT have 1.32 increase of CVD mortality compared with patients with normoglycemia, and patients with IFG have only 1.14 time increase (Fig. 12).

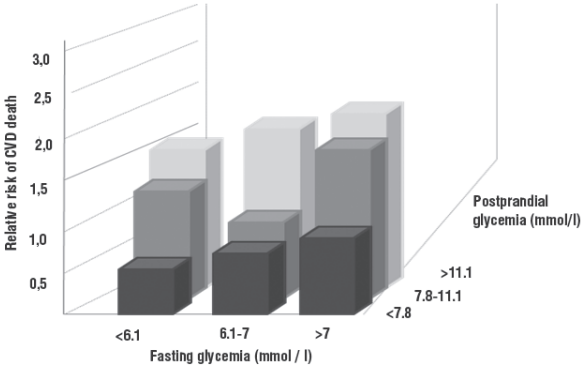


Fig. 12. DECODE study — postprandial glycemia level and CVD risk

The Norfolk Cohort of the Europe Prospective Investigation of Cancel and Nutrition study found the correlation between HbA1c and high cardiovascular male mortality in patients with type 2 diabetes. Men with 5–6% higher than normal level of HbA1c had higher cardiovascular mortality compared with patients with less than 5% level of HbA1c [20, 22]. 1% increase in the level if HbA1c increased the risk of death by 28%, regardless of age, blood pressure, TC, BM, and smoking. The STOP-NIDDM study suggests to reduce IR for effective prevention of type 2 diabetes [19]. A number of studies have shown that elevated HbA1c is associated with increased CVD risk [38, 73]. Studies that compared three parameters: fasting glycemic level, 2 hours after load glycemic level and HbA1c, found that 2 hours after load glycemic level significantly associated with mortality unlike fasting glycemia level and HbA1c.

The association between DM risk and cardiovascular mortality according to SCORE scale

Is there a correlation between the risk of DM and the risk of cardiovascular complications? Which level of cardiovascular risk can be considered as the threshold for a high risk of DM? The researches of National Research Center for Preventive Medicine conducted a series of simultaneous cohort clinical trials in order to answer these questions. We questioned and examined 300 men aged from 40 to 59 years who visited outpatient clinic for any reason. The study included 2 stages. During the first stage, we analyzed medical records of 500 men in order to assess the presence of RF and calculate total cardiovascular risk according to the SCORE scale. During the second stage, we divided 300 respondents into the group with low and moderate (<5 % SCORE), high (5–10 % SCORE) and very high (> 10 % SCORE) cardiovascular risk without clinical manifestations of CVD. The inclusion criteria were: more than one RF: 1–3 stage of AH with duration over 5 years, smoking, hypercholesterolemia (TC level > 5 mmol/L). We used Russian version of the standard Atherosclerosis Risk in Communities (ARIC) questionnaire. The questions revealed the following information: passport data, social status, family history, smoking status, alcohol consumption, nutritional assessment, concomitant diseases, medications taken.The groups with different levels of risk cardiovascular complications according to SCORE were comparable: 33.3 % had low or moderate SCORE risk, 33.7 % — high and 33 % — very high (Table 15).

Table 15. The distribution of patients by the level of cardiovascular risk according to SCORE

		Total	
		n	%
SCORE Cardiovascular Risk Grade	Low and moderate	100	33,3 %
	High	101	33,7 %
	Very high	99	33 %
Total		300	100 %

The risk of type 2 diabetes in the next 10 years was detected using FINDRISC questionnaire in all groups of patients with different cardiovascular risk according to the SCORE scale. Patients were suggested several answers, then total score was calculated. Gradations of type 2 diabetes risk include: low, slightly elevated, moderate, high, and very high.

40 % of patients with different levels of SCORE cardiovascular risk had high and very high risk of DM in the next 10 years according to FINDRISC questionnaire. 54.0 % of patients with low and moderate cardiovascular risk had low risk of DM, while patients with high and very cardiovascular risk had low risk of DM only in 20.8 % and 9.1 % of cases, respectively (Fig. 13).

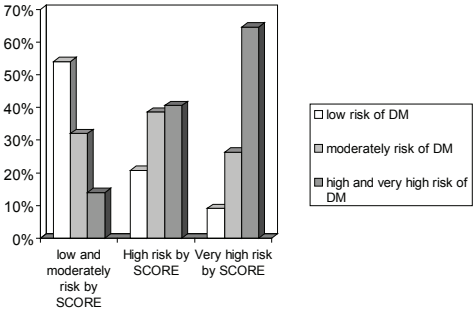


Fig. 13. DM risk according to FINDRISC questionnaire in patients with various cardiovascular risk

Every fourth patient with a high cardiovascular risk has moderate risk of DM. Every third patient with low and moderate cardiovascular risk has the same risk.

64.6 % of patients with high and very high cardiovascular risk have high and very high risk of DM, while in patients with low and moderate cardiovascular risk high risk of DM is 2–3 times less — 40, 6 % and 14.0 %, respectively.

We performed detailed analysis of different DM risk groups in patients with three levels of cardiovascular risk according to SCORE.

According to the data presented in Table 16, the largest number of patients with low risk of DM is detected in the group with low and moderate cardiovascular risk — 54 %. Every fifth patient with low risk of DM has a high cardiovascular risk, and 9.1 % of patients with low risk of DM has the same risk.

Table 16. SCORE cardiovascular risk distribution among patients with a low risk of DM according to the FINDRISC questionnaire

SCORE Cardiovascular Risk	n	%
Low or moderate	54	54.0 %
High	21	20.8 %**
Very high	9	9.1 %**
Total	84	28.0 %

** p <0.01, statistically significant differences compared with low and moderate cardiovascular risk group.

The groups with different cardiovascular risks are comparable by the frequency of a moderately increased DM risk (Table 17). Thus, among patients with moderately increased DM risk have low and moderate cardiovascular risk in 32.0 %, high cardiovascular risk — in 38.6 % and very high cardiovascular risk — in 26.3 % of cases. Therefore, there were no statistically significant difference between groups.

Table 17. SCORE cardiovascular risk distribution among patients with a moderately increased risk of DM according to the FINDRISC questionnaire

SCORE Cardiovascular Risk	N	%
Low or moderate	32	32,0 %
High	39	38,6 %**
Very high	26	26,3 %**
Total	84	32,3 %

** p <0.01, statistically significant differences compared with low and moderate cardiovascular risk group.

The analysis revealed that patients with a high and very high risk of DM have a very high cardiovascular risk in 64.6 % of cases. Patients with a high and very high risk of DM have a high cardiovascular risk in 40.6 %, and patients with low and moderate cardiovascular risk — in 14.0 % of cases. The differences between the frequency of high and very high risk of DM between groups with low, moderate, high and very high cardiovascular risk were statistically significant (Table 18).

Table 18. SCORE cardiovascular risk distribution among patients with high and very high risk of DM according to the FINDRISC questionnaire

SCORE Cardiovascular Risk	N	%
Low or moderate	14	14.0 %
High	41	40.6 %*
Very high	64	64.6 %**
Total	119	39.7 %

* p <0.02, statistically significant differences compared with low and moderate cardiovascular risk group;
** p <0.01 statistically significant differences compared with low and moderate cardiovascular risk group.

We also examined the association between age and DM risk. Patients were divided into 4 age groups according to the FINDRISC questionnaire: 40–44 years old, 45–49 years old, 50–54 years old, and 55–59 years old. Middle-aged men predominated among patients with a low risk of DM. Thus, there were 53.6 % of men aged 50–54 and 25 % of men aged 55–59. Patients of younger age had low risk only in 14.3 % (40–44 years old) and 7.1 % (45–49 years old) of cases. Therefore, 50–54-year aged men predominate in the group with low risk of DM.

One of the objectives of this study was to identify early carbohydrate metabolism disorders using OGTT in patients with different levels of cardiovascular risk according to SCORE.

We established prediabetes using IFG, IGT or its combination. 40.7 % of all patients with different levels of cardiovascular risk according to SCORE, had prediabetes. In other words, in 59.3 % of patients did not have carbohydrate metabolism disorders. In 28.3 % of patients had IFG, and 12.3 % — its combination with IGT, while IGT without IFG was not detected (Table 19).

Table 19. Carbohydrate metabolism disorders in men with different cardiovascular risk levels according to SCORE

Carbohydrate metabolism status	n	%
Normal	178	59,3 %
IFG	85	28,3 %**
IGT	0	0 %
IFG+IGT	37	12,3 %
Total	300	100 %

** p <0.01, statistically significant differences between IFT and IFT+ IGT groups

The analysis of average fasting and 2 hours after load glucose levels in three groups of patients with different cardiovascular risk levels did not show any no statistically significant differences (Table 20).

Table 20. Average fasting and 2 hours after load glucose level in patients with different cardiovascular SCORE risk

SCORE Total Cardiovascular Risk	Fasting glucose, mmol/L	After load (OGTT) glucose, mmol/L
Low and moderate	5,14±0,48	6,36±1,05
High	5,26±0,47	6,21±1,09
Very high	5,51±0,43	6,24±0,96

However, the analysis of carbohydrate metabolism in groups with different cardiovascular risk levels showed an increase of prediabetes in patients with high and very high cardiovascular risk. Prediabetes was detected in 21 % of cases in the group of men with low and moderate cardiovascular risk. 12 % of them had IFG revealed, and 9 % of patients had IFG and IGT (Fig. 14).

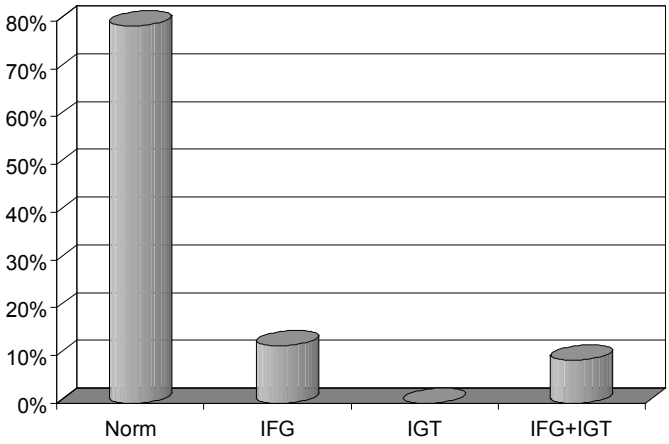


Fig. 14. Identification of prediabetes in patients with low and moderate cardiovascular risk

We detected prediabetes in 40 % of cases in patients with high cardiovascular SCORE risk. In the group of high cardiovascular risk, IFG occurs 50 % more often compared with IFG and IGT together — 26.7 % and 12.9 %, respectively (Fig. 15).

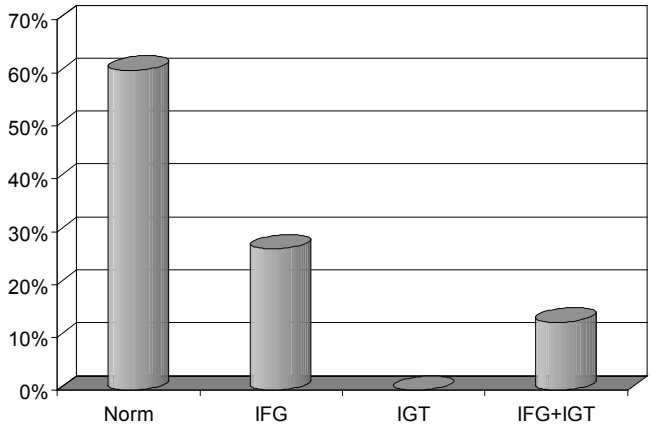
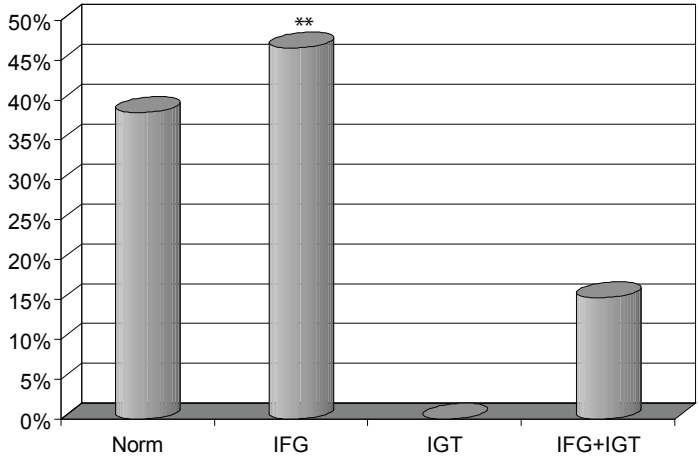


Fig. 15. Carbohydrate metabolism disturbances in patients with high cardiovascular risk.

38 % of patients with very high cardiovascular risk have normal glucose tolerance (Fig. 16). Almost every second patient with a high cardiovascular risk was diagnosed with IFG, 15.2 % — with the combination of IFG and IGT. Thus, two types of prediabetes had statistically significant differences (p <0.01).



** p <0.01, statistically significant differences between IFT and IFT+ IGT groups.

Fig. 16. The prevalence of prediabetes in very high cardiovascular risk group

The analysis of the results showed that 40 % of patients with different cardiovascular SCORE risk levels had high and very high risk of DM in the next 10 years according to the FINDRISC questionnaire. 54 % of patients with low and moderate cardiovascular risk have low DM risk, while only 20,8 % and 9.1 % of patients with high and very high cardiovascular risk, respectively, have low risk of DM in the next 10 years. Every fourth patient with a high cardiovascular risk had moderately increased risk of DM. Every third patient with low and moderate cardiovascular risk has the same risk. 64.6 % of patients with high and very high cardiovascular risk have high and very high risk of DM, while in patients with low and moderate cardiovascular risk high risk of DM is 2–3 times less — 40, 6 % and 14.0 %, respectively.

The frequency of early carbohydrate metabolism disorders increases with cardiovascular risk level. IFG is the most common carbohydrate metabolism disturbance in patients with high and very high cardiovascular risk. Combination of IFG and IGT is on the second place.

Thus, the results of simultaneous prospective studies demonstrate the association between high cardiovascular risk and early carbohydrate metabolism disorders that can be used as independent RFs of cardiovascular complications.

Chapter VI
DIAGNOSIS OF EARLY CARBOHYDRATE METABOLISM DISTURBANCES IN CARDIOLOGY PRACTICE

Diagnosis of early carbohydrate metabolism disorders include three main approaches:

1. Measurement of venous blood glucose level to estimate glucose homeostasis.
2. The use of demographic and clinical characteristics and laboratory parameters to assess the risk of type 2 diabetes.
3. The use of questionnaires to analyze etiological factors of type 2 diabetes [78].

Using of these strategies allows us to increase sensitivity regardless to specificity and vice versa. The first approach allows to identify undiagnosed diabetes but can lead to false diagnosis, and two other strategies involve risk assessment, and can serve as basis for lifestyle modification.

The last two approaches can be used at the outpatient level as cost-effectiveness analysis methods and can help to:

1. Identify patients with risk of metabolic disorders: obesity, hypertension, or a family history of type 2 diabetes
2. Identify patients with high risk of type 2 diabetes.
3. Identify patients with CVD.
4. Identify patients who need OGTT [21].

Screening of patients using FINDRISC questionnaire

Type 2 diabetes prediction scale (FINDRISC), based on the Finnish prospective study, can be used for the screening of patients with a high risk of DM [58]. This scale predicts a 10-year risk of type 2 diabetes with 85 % accuracy.

Finnish randomized controlled study on the prevention of DM, conducted in 2001, and the American program for the prevention of diabetes in 2002 showed that modification of lifestyle, including loss of body mass, increased physical activity and diet improvement, can reduce the risk of DM almost by 60 %. Finnish researchers used the results of researches on DM RF during over 25 years and created the FINDRISC 8 question-questionnaire, which was approved on 2 Finnish population cohorts, and confirmed in Italy and Germany. This method for the prediction of type 2 diabetes is not used in the cardiological practice of the Russian Federation. This can be explained by the lack of data on the effectiveness of questionnaire in practice, especially in patients with RF of CVD and DM.

Patients need to answer the questions on the anthropometric data, family history, antihypertensive therapy, diet and lifestyle habits in order to determine the degree of DM risk (Table 21).

Patients are divided into 5 risk groups of DM in the next 10 years depending on the total score:

— low risk (1 out of 100 or 1 %),
— slightly increased (1 in 25 or 4 %),
— moderate (1 in 6 or 17 %),
— high risk (1 in 3 or 33 %),
— very high risk (1 out of 2 or 50 %).

The advantage of the FINDRISC questionnaire is that it is based on the population data and can be used for large studies screening and in clinical practice for identifying patients with high risk of DM, especially in patients with early carbohydrate metabolism disorders without clinical manifestation.

Oral glucose tolerance test

WHO criteria for the diagnosis of carbohydrate metabolism disorders are based on fasting (GFL) and 2 hours after load plasma glucose level (2-hr PG). OGTT is recommended in case of the absence of significant hyperglycemia [106]. ADA criteria are, first of all, based on HbA1c level, fasting glucose and OGTT [2019]. Fasting glucose level and HbA1c are more preferable than 2 hours after

Table 21. Type 2 diabetes risk assessment in the next 10 years by Finnish Diabetes Risk Score (FINDRISC)

Finnish Diabetes Association

TYPE 2 DIABETES RISK ASSESSMENT FORM

Circle the right alternative and add up your points.

1. Age

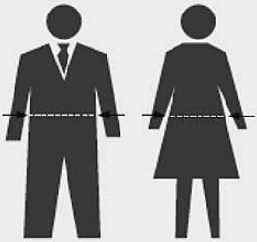
0 p. Under 45 years
2 p. 45–54 years
3 p. 55–64 years
4 p. Over 64 years

2. Body-mass index
(See reverse of form)

0 p. Lower than 25 kg/m²
1 p. 25–30 kg/m²
3 p. Higher than 30 kg/m²

3. Waist circumference measured below the ribs (usually at the level of the navel)

	MEN	WOMEN
0 p.	Less than 94 cm	Less than 80 cm
3 p.	94–102 cm	80–88 cm
4 p.	More than 102 cm	More than 88 cm



4. Do you usually have daily at least 30 minutes of physical activity at work and/or during leisure time (including normal daily activity)?

0 p. Yes
2 p. No

5. How often do you eat vegetables, fruit or berries?

0 p. Every day
1 p. Not every day

6. Have you ever taken medication for high blood pressure on regular basis?

0 p. No
2 p. Yes

7. Have you ever been found to have high blood glucose (eg in a health examination, during an illness, during pregnancy)?

0 p. No
5 p. Yes

8. Have any of the members of your immediate family or other relatives been diagnosed with diabetes (type 1 or type 2)?

0 p. No
3 p. Yes: grandparent, aunt, uncle or first cousin (but no own parent, brother, sister or child)
5 p. Yes: parent, brother, sister or own child

Total Risk Score

☐ The risk of developing type 2 diabetes within 10 years is

Lower than 7	Low: estimated 1 in 100 will develop disease
7–11	Slightly elevated: estimated 1 in 25 will develop disease
12–14	Moderate: estimated 1 in 6 will develop disease
15–20	High: estimated 1 in 3 will develop disease
Higher than 20	Very high: estimated 1 in 2 will develop disease

Please turn over

Test designed by Professor Jaakko Tuomilehto, Department of Public Health, University of Helsinki, and Jaana Lindström, MPS, National Public Health Institute.

load plasma glucose level mainly due to its convenience. WHO report (2011) included advantages and disadvantages of glucose tests and HbA1c, which are still under discussion. The WHO and ADA diagnostic criteria for average glycemia levels are the same for IGT, and different for GFL. The lower threshold of GFL for ADA is 5.6 mmol/L, while WHO recommend 6.1 mmol/L.

Venous blood glucose level is needed for the estimation standard glucose level. Venous whole blood parameters are usually 0.5 mmol/L lower. Capillary blood is often used for rapid testing, and it is remarkable that glucose level after load is less accurate compared with fasting level. Thus, recent comparative study suggests the following glycemic values as threshold (Table 22).

Table 22. Threshold for the diagnosis of DM, based on non-standard blood samples (venous plasma)

Diagnosis	Venous plasma mmol/L (mg / dl)	Venous blood mmol/L (mg / dl)	Capillary blood mmol/L (mg / dl)
Fasting glucose intolerance — fasting test	6,1 (110)	5,0 (90)	5,6 (101)
After load glucose level	7,8 (140)	6,5 (117)	7,2 (130)
Diabetes — fasting glucose level	7,0 (126)	5,8 (104)	6,5 (117)
Diabetes — after load glucose level	11,1 (200)	9,4 (169)	10,3 (185)

Hyperglycemia classification depends on whether only fasting glucose level was studied or its combination with 2 hours after load level. A patient with PH diagnosed with OGTT can suffer from IGT or DM. Normal fasting glucose level reflects the ability of organism to maintain insulin basal level, and in combination with liver insulin sensitivity — to control liver glucose release. After load glucose level also shows organism response to insulin and peripheral tissues insulin sensitivity. It is very important to pay attention for diagnostic method of glycemic data. This is essential for both glucose tests and HbA1c.

Oral glucose tolerance test method

The simplest method for diagnosis of carbohydrate metabolism disorders is capillary blood glucose level during fasting. At the same time, fasting glucose and HbA1c level, which is an integral indicator of glycemia over the last 2–3 months, do not allow us to assess glycemia fluctuations after eating or glucose load.

Individual glucose tolerance cannot be determined without 75 mg oral glucose tolerance test. For this reason, in general population the screening should begin with risk assessment and then OGTT in patients with high risk.

WHO recommend to take the following steps to perform OGTT [105]. After estimation of fasting glucose level, the patient takes orally 75 g of glucose dissolved in 100 ml of water. Reception lasts approximately for 5 minutes. Healthy individuals have an increase in blood glucose concentration 15–20 minutes after glucose intake, which reaches its maximum during the first hour (between 30 and 60 minutes). 2 hours after (120 min) glucose level decreases and reaches its initial (fasting) or decrease slightly below the initial level. Three hours after the level of blood glucose level reaches its initial level.

The first rise of glucose level after the load can be explained by irritation reflex of sympathetic nerves when glucose reaches the digestive tract. The following increase of glucose level is associated with the speed of carbohydrates absorption (determined mostly by the state of the intestinal wall) and liver function. Healthy individual has 50–75 % higher glucose concentration 1 hour after load compared with fasting glucose level (Fig. 17). The following decrease of glucose level reflects insulin production and depends on parasympathetic nervous system and pancreatic function. This is called the hypoglycemic phase. The last point on the glycemic curve, determined after 2.5–3 hours, and after 3.5–4 hours in case of IGT, is associated with glucose utilization system. Normally, the level of glucose should reach initial or 10–15 % less. Fig. 1 presents glycemia curve during OGTT in patients with various carbohydrate metabolism disorders.

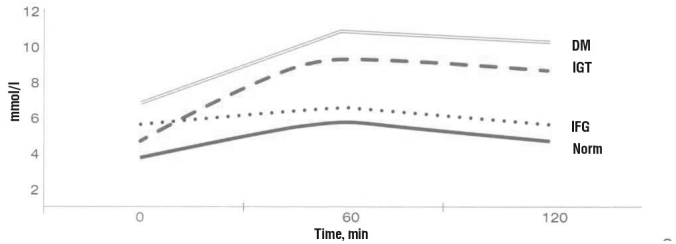


Figure 17. Hyperglycemia categories: dynamics of glucose blood level during glucose tolerance test

There are several diagnostic categories by the results of fasting and 2 hours after OGTT. The National Diabetes Data Group and WHO identified IGT as intermediate stage between normal glucose metabolism and DM. ADA and WHO experts slightly changed criteria for the diagnosis of DM and identified a

new category — fasting hyperglycemia. ADA recently proposed to decrease the diagnostic criteria for this condition from 6.1 to 5.6 mmol/L. However, WHO experts have not accepted them yet and recommend to use the criteria developed in 1999. New WHO expert group revised them in 2005 (Table 23).

Table 23. WHO (1999) and ADA (1997,2003) criteria for the diagnosis of glucose metabolism disturbances (venous blood glucose levels are given)

Categories	Organization	Criteria	Unit: mmol/L (mg%)
Normal glycemic metabolism	WHO,1999	Fasting glycemia	<6.1 (110) + 2-hour PG <7.8 (140)
	ADA, 1997	Fasting glycemia	<6,1 (110)
	ADA, 2003	Fasting glycemia	<5.6 (100)
Fasting blood glucose disorders	WHO,1999	Fasting glycemia	≥ 6.1 (110) and <7.0 (126) + 2-hour PG <7.0 (126)
	ADA, 1997	Fasting glycemia	≥ 6.1 (110) and <7.0 (126) + 2-hour PG <7.0 (126)
	ADA, 2003	Fasting glycemia	≥5.6 (100) and <7.0 (126) + 2-hour PG <7.0 (126)
Impaired glucose tolerance	WHO, 1999	Fasting glycemia	<7.0 (126) + 2-hour PG ≥7.8 (126) and <11.1 (200)
Impaired glucose homeostasis	WHO, 1999	Fasting Glycemia or	
Diabetes mellitus	WHO,1999	Fasting glycemia	≥7.0 (126) or 2-hour PG ≥11.1 (200)
	ADA, 1997	Fasting glycemia	≥7.0 (126)
	ADA, 2003	Fasting glycemia	≥7.0 (126)

IGT can be diagnosed only with an oral glucose load after an 8–14 hour fasting. Blood samples are taken before and 120 minutes after 75 g load of glucose dissolved in 250–300 ml of water for 5 minutes. It is recommended to measure glucose level in plasma in order to standardize the results of the analysis. However, many devices require the use whole, venous or capillary blood. Table 24 shows the translation formulas for the glucose values of various samples.

Table 24. Glucose translation formulas

Plasma glucose (mmol/L) = 0.558 + 1.119 x whole blood glucose (mmol/L)
Plasma glucose (mmol/L) = 0.102 + 1.066 x capillary blood glucose (mmol/L)
Plasma glucose (mmol/L) = — 0.137 + 1.047 x serum glucose (mmol/L)

WHO approved the use of HbA1c for the diagnosis of DM in 2011. Diagnostic criterion for DM is ≥6.5 % (48 mmol/mol) HbA1c. The study 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 of Diabetes Control and Complications Trial (DCCT) [100].

6.0 % (42 mmol/mol) level of HbA1c is considered normal.

Translation of HbA1c from % into mmol/mol: (HbA1c% × 10.93) — 23.5 = HbA1c mmol/mol.

Translation of HbA1c from mmol / mol into %: (0.0915 × HbA1c mmol / mol) + 2.15 = HbA1c%.

In the absence of acute metabolic decompensation symptoms, the diagnosis should be made based on twice determined HbA1c or a single determination of HbA1c + a single determination of glucose level.

Thus, both questionnaires and laboratory research can be used to identify early carbohydrate metabolism disorders. However, history taking, clinical examination and identification of other metabolic disorders allows to assess patient's condition.

Chapter VII
EVIDENCE-BASED NON-PHARNACOLOGICAL THERATMENT OF PREDIABETES

There are several methods for correction of early carbohydrate metabolism disorders, including lifestyle changes and antihyperglycemic therapy [4, 60, 74, 80].

Lifestyle changes are the main method for correction of early carbohydrate metabolism disorders for patients with low, moderate and high cardiovascular risk. There is even a scheme for health care workers.

Many prospective studies showed the effectiveness of lifestyle changes in patients with metabolic disorders and a high risk of DM [4, 13, 54, 74, 99].

Regular physical activity (PA) and diet in patients with prediabetes significantly reduce the risk of DM. Thus, the results of the Finnish prospective FDP study, which included 523 middle-aged patients with excessive BM and IGT, showed that 5 % MT decrease and total fat restriction (<30 % of daily calorie intake), saturated fat restriction (<10 % of daily calorie intake), increased fiber intake (15 g per day) and physical activity (at least 30 minutes per day) lead to 58 % reduction of type 2 diabetes risk. Chinese study included 577 IGT patients and also showed the effectiveness of lifestyle modification in primary prevention of type 2 diabetes. Initially, patients were randomized into 4 groups: only PA, only diet, diet + PA and control group. Cumulative frequency of type 2 diabetes during 6-year follow-up in first three groups was significantly lower compared with control group (41 %, 44 %, 46 % and 68 %, respectively).

Lower degree of risk reduction in Indian and Chinese protocols was associated with higher prevalence of type 2 diabetes in these populations, and the absolute risk reduction was the same — 15–20 cases per 100 person-years. It has been

established that lifestyle modification should be carried out for 6.4 high-risk individuals for 3 years to prevent 1 case of DM [54]. Clearly, this is very effective. Observation over 12 years of IGT patients during Malmö study [100] showed that all-cause mortality was lower in patients with lifestyle modification and was equal to patients with normal glucose tolerance (6.5 versus 14.0 per 1000 person-years; p = 0.009). Patients with IGT from Chinese study with 6-year lifestyle modification, had lower incidence of type 2 diabetes and a 17 % lower cardiovascular mortality compared with the control group even after 20 years the study. Moreover, the weighted mean incidence of severe retinopathy was 47 % lower compared with the control group, which can be explained by the lower incidence of type 2 diabetes. Finnish DPS study [57] with 7-year follow-up showed significant and sustained decrease in the frequency of type 2 diabetes in patients who participated in lifestyle modification programs (average duration — 4 years). During 10-year follow-up, all-cause mortality and CVD frequency did not differ between the control and intervention group, but patients with initial IGT had lower all-cause mortality and lower CVD frequency compared with a similar cohort of IGT patients from the Finnish study. The frequency of type 2 diabetes in the group with lifestyle changes remained lower compared with control group during the USA program for the prevention of diabetes outcomes with 10-year follow-up [100].

Table 25 presents the results of studies on the effectiveness of lifestyle changes in different cohorts and populations of individuals with a high risk of DM and metabolic disorders. Meta-analysis of the studies demonstrates that various modes of lifestyle changes reduce the risk of DM development from 29 % to 67 % on average.

According to international recommendations, patients with prediabetes are recommend to combine diet and physical activity.

Diet should be based on the following principles:

1. The correct distribution of food servings during the day.

2. An increase of protein intake, including plant-based protein.

3. Reduction of calories to 1500 kcal/day.

4. Reduction of carbohydrate intake (increased fiber intake to 30 g / day, decreased intake of liquid mono- and disaccharides).

5. Reduction of fat to 30–35 % of total calorie intake.

Malnutrition and a sedentary lifestyle play the enormous role in the development of type 2 diabetes. Evidence-based European guidelines for the prevention of type 2 diabetes [36] showed that lifestyle modification, including weight loss and increased physical activity, prevents or slows down the progression of glucose metabolism disorders in individuals with IGT. Therefore, physicians

Table 25. Evidence base for prevention of type 2 diabetes by lifestyle modification

Study (country)	Intervention	Sample (n)	Observation years	Relative risk reduction,%
Chine	Diet Exercises Diet + Exercise Control	130 141 126 133	6	31 46 42
Finland	Diet + Exercise Control	265 257	3,2	58
USA	Diet + Exercise Metformin Placebo	1079 1073 1082	2,8	58 31
India	Lifestyle Metformin Lifestyle+metformin Control	133 133 129 136	2,5	29 26 28
Japan	Diet + Exercise Control	102 356	4	67
Netherlands	Diet + Exercise Control	74 73	3	58
Great Britain	Diet + Exercise Control	51 51	3,1	55
Japan	Diet + Exercise Control	330 311	3	44

should explain to patients with high risk of type 2 diabetes and IGT the importance of lifestyle modification and help to perform it.

Physical activity can be assessed by simple questionnaires and pedometers. The «10,000 steps» program contributes to a decrease of key metabolic parameters, including glycemia up to 25%.

Patients without clinical manifestations of atherosclerosis, can choose any type of physical activity, including fitness; physical activity can also include stairs instead of elevator or any other everyday life activity. The most affordable aerobic exercise is vigorous walking. Patients with prediabetes should be prescribed 30–60 minutes exercise 5 days a week until they reach the heart rate, determined by 65–70% of the maximum pulse for their age. The maximum heart rate can be calculated by the formula: 220-age in years. PA is individually selected in patients with coronary heart disease according to the results of the exercise stress test [19].

Table 26 presents the main recommendations for lifestyle changes (diet and physical activity) in individuals with early carbohydrate metabolism disturbances.

Table 26. Non-pharmacological therapy in patients with early carbohydrate metabolism disturbances

Diet (recommended by ADA)	Recommended by (servings, g / per day)	Not recommended
Bread, cereal and other starch products	6–11 servings	Fats, oils, sweets, including refined carbohydrates
Vegetables	3–5 servings	Sweet and spirit drinks
Fruits	2–4 servings	
Skimmed milk	2–3 servings	
Meat, meat substitutes and other protein products	100–170 g	
Physical activity	Exercise 30–60 minutes 5 days a week (start with 5–10 minutes per day) Physical activity may include: walking around the block, using stairs instead of an elevator, gardening, dancing, bowling, cycling, swimming.	The intensity of exercise without taking into account age, body weight, objective data of somatic state, without prior physical preparation. fatigue expressed, passing within 5–10 minutes or expressed for a long time remaining. Blood pressure and pulse exceeding the recommended limits with a recovery period in (5–10 min.)

One of the main problems in changing lifestyle is the patient's poor commitment.

The development of lifestyle change programs should be based on participant's understanding of their important role in accepting and participating in already implemented programs. The implementation of programs is still a difficult because the methodology is still on the early stage of development, is not fully understood and is rarely applied. In addition, we need to expand our theoretical knowledge using the data of our studies and analysis of researches in real life.

IDF recommend to establish schools for these patients. The support of family members is also very important. A team of specialists together with psychologists should develop various programs for lifestyle modification in the near future, as standard recommendations are not always successful.

Chapter VIII
PHARMACOLOGICAL TREATMENT OF PREDIABETES IN CLINICAL PRACTICE

Patients with prediabetes have poor commitment to non-pharmacological treatment and only 30% of them successfully change their lifestyle. That is why most patients with early carbohydrate metabolism disturbances require pharmacological treatment.

European Society of Cardiology recommend pharmacological treatment for patients with prediabetes and a high risk of cardiovascular complications in case of ineffective lifestyle changes. Such strategy can reduce the risk of CVD (I A level of evidence) [36]. Pharmacological therapy depend on metabolic status of patient and are aimed to achieve target levels of glycemia. In other words, the correction of carbohydrate metabolism disorders requires differentiated approach, and target glycemia levels should reduce all-cause and cardiovascular mortality.

According to data of prospective studies, control of glycemia is one of the most effective method to reduce the progression of the disease and its complications [2, 36, 106]. Portfolio of sugar-lowering medications has expanded significantly over the last years.

They can be divided into four groups:

1) stimulators of insulin secretion — secretagogues (sulfonylureas and meglitinides, GLP-1 analogues and DPP-4 inhibitors);

2) sensitizers (biguanides, thiazolidinediones) that increase insulin sensitivity;

3) intestinal glucose absorption inhibitors (alpha glucosidase inhibitors);

4) inhibitors of kidney glucose reabsorption — SGLT2 inhibitors.

Table 27 presents the main characteristics of carbohydrate metabolism disorders medications.

Table 27. Carbohydrate metabolism disorders medications

Class of medication	Effect	Body mass change	Hypoglycemia (on mono-therapy)	Side effects
Metformin	Insulin sensitivity	No/loss	Not	Side effects of the gastrointestinal tract, lactic acidosis, decreased GFR, hypoxia, dehydration
Sulfony-lureas	Increase insulin levels	Increase	Yes	Allergy, risk of weight loss, hypoglycemia
Meglitinides	Increase insulin levels	Increase	Yes	Frequent dosing, risk of hypoglycemia
Alpha glucosidase inhibitors	Absorption inhibitor glucose	Not	Not	Gastrointestinal side effects, frequent dosing
Pioglitazone	Insulin sensitivity	Increase	Not	HF, edema, fractures, bladder cancer (?)
Agonist GLP-1	Increased insulin level	Decrease	Not	Side effects of the gastrointestinal tract, pancreatitis, parenteral administration
Dipeptidyl Peptidase-4 Inhibitors (Gliptins) (DPP-4)	Increased insulin level	Not	Not	Pancreatitis
Insulin	Increased insulin level	Increase	Yes	Parenteral administration, risk of weight gain and hypoglycemia
SGLT2 Inhibitors	Glucose reabsorption unit in kidney proximal convoluted tubule	Decrease	Not	Urinary tract infections

GFR — glomerular filtration rate

Antihyperglycemic drugs are recommended in patients with early carbohydrate metabolism disorders and can be divided into three groups: biguanides, alpha-glucosidase inhibitors and thiazolidinediones. Antihyperglycemic drugs do not affect pancreatic beta cells and minimalize the risk of hypoglycemia.

Metformin is the only biguanide used in clinical practice [97]. The effect of metformin on carbohydrate metabolism include several mechanisms. Firstly, it increases insulin sensitivity of peripheral tissues. It potentiates insulin transfer into the cell on receptor and post-receptor level. Metformin normalizes insulin receptor tyrosine kinase activity and stimulates transporter proteins GLUT-1 synthesis, localized in the plasma membrane, and GLUT-4, localized mainly in intracellular membranes. Secondly, it increases glycogen synthesis and decreases glucose production due to gluconeogenesis inhibition and decreased oxidation of free fatty acids (FFA) and lipids. This is explained by increased hepatocytes sensitivity to insulin and the suppression of key gluconeogenesis enzymes (pyruvate carboxylase and phosphoenolpyruvate carboxykinase). The third mechanism includes decreased intestine glucose absorption and its increased utilization by intestinal cells that underline smoothing of hyperglycemic peaks after eating.

A number of large clinical trials demonstrated the effectiveness of metformin in patients with T2DM and its contribution to the reduction of macrovascular complications risk [86]. There is data on the role of metformin in primary prevention of diabetes in individuals with early carbohydrate metabolism disorders. DPP study showed that the use of metformin (1700 mg daily dose) in patients with IGT for three years reduced the risk of type 2 diabetes by 31 % [91]. In addition, there was no increase and even a decrease in body mass during metformin therapy. Metformin reduces the risk of type 2 diabetes most effectively in patients aged under 45 years and in patients with severe obesity (BMI ≥ 35 kg/m^2). The risk of T2DM decreased by 44–53 % in these groups. The results of three prospective studies (BIGPRO 1, BIGPRO 1.2 and DPS) confirmed the effectiveness of metformin in patients with IGT and in patients with AO, AH, hypertriglyceridemia [100]. Additional positive metabolic effects (weight loss, improvement of the lipid profile, lowering blood pressure, etc.), allows to use metformin in patients with MS [66].

Metformin is a first-line drug in patients T2DM, especially with obesity [26, 36, 48, 71]. The main adverse effect of metformin is the risk of lactic acidosis, especially in patients with impaired renal function or liver disease. A number of reviews based on the studies with particular groups of patients concluded that lactic acidosis is not that often. However, metformin is not recommended in patients GFR under 50 ml/

min. There is still no agreement on this value; some researches consider it excessively high. British National Institute of Clinical Efficiency recommend to use 30 ml / min GFR as a threshold and start dose reduction from 45 ml / min. Today metformin is the drug of choice for the primary prevention of diabetes in patients with prediabetes and high cardiovascular risk. A number of parameters should be taken into account when choosing a therapeutic dose: the duration of prediabetes, body weight, the presence of other risk factors and disorders, family history, etc.

Acarbose has fundamentally different mechanism of action and decrease the level of postprandial glycemia [4]. Acarbose is a local inhibitor of α-glucosidase — an intestinal enzyme — that is a pseudotetrasaccharide of bacterial origin with high affinity for α-glucosidase and is not absorbed in the intestine. When large amounts of carbohydrates arrive, acarbose prevents the breakdown of poly- and oligosaccharides in the duodenum and upper intestines and possible absorption of glucose at the very early stage and hyperglycemia and also reduces the toxic effect of glucose on pancreatic beta cells. This leads to postprandial glycemia decrease without increased secretion of insulin, which further contributes to a decrease of body mass and increases tissue sensitivity to insulin [17, 19].

According to a meta-analysis of 13 placebo-controlled studies, acarbose monotherapy reduced fasting plasma glucose level by 1.3±0.3 mmol/L, and 2 hours after OGTT glucose level by 2 times (2.9 ± 0.8 mmol/L) [69]. Multicenter randomized prospective study STOP-NIDDM was based on the predominant effect of acarbose on PH. The study objective was to find the possible effect of acarbose on the risk of DM and cardiovascular complications in patients with IGT. The incidence of DM was 25% less during acarbose treatment compared with placebo. Moreover, the use of acarbose contributed to restoration of normal carbohydrate tolerance in 35% of patients. Acarbose also reduced the risk of AH development by 34% and contributed to a decrease of cardiovascular events by 49% compared with placebo. According to the Russian APRIL study, 150 and 300 mg of acarbose positively affects the main cardiovascular risk factors — overweight, PH, dyslipidemia and AH [29].

Another class of antihyperglycemic drugs that affect IR are thiazolidinediones. They (rosiglitazone and pioglitazone) are selective agonists of the nuclear receptor PPARg (peroxisomal proliferator-activated receptor gamma) found in insulin-sensitive tissues such as adipose tissue, skeletal muscle and liver [89].

Rosiglitazone accelerate the differentiation of preadipocytes and increase in the production of small, insulin sensitive cells. Small adipocytes have more insulin receptors and glucose transporters, which increases glucose uptake from the bloodstream and decrease lipolysis. It also reduces tumor necrosis factor-α

(TNF-α) synthesis and activity, decreases lipolysis and, consequently, decreases FFA release into the bloodstream. Thus, insulin signal improves, gluconeogenesis in hepatocytes decreases as well as the level of FFA, and muscles uptake more glucose.

According to the DREAM study, 8 mg of rosiglitazone daily reduces the risk of IGT transition into type 2 diabetes by 62 % compared with placebo. Rosiglitazone also significantly decreases the level of inflammatory markers and improves lipid profile — decreases TC/HDL cholesterol ratio. It is contraindicated in patients with liver diseases; swelling of any genesis; any functional class of heart failure; coronary heart disease with nitrate treatment; ketoacidosis; during insulin treatment; during pregnancy and lactation [92].

The use of rosiglitazone was prohibited in Europe and limited in the United States. This is explained by high risk of cardiovascular complications including congestive heart failure, acute coronary syndrome and death.

Pioglitazone is a PPARg agonist that affects peroxisomal proliferator-activated alpha receptor (PPARa) and reduces glucose level by suppressing insulin resistance, while metformin is a biguanide that activates AMP kinase and have similar effect. Both medications decrease insulin consumption in patients with insulin-dependent type 2 diabetes and, as shown during PROactive pioglitazone study, are associated with a long-lasting decrease of insulin treatment.

Cardiovascular safety of hypoglycemic agents

There are a lot of data on the antihyperglycemic medications effectiveness and their effect on reducing the frequency T2DM. However, the effect of antihyperglycemic drugs on the risk of cardiovascular complications is still unclear. This issue has been discussed during the International and European congresses over the last years. Positive effect of some antihyperglycemic drugs on cardiovascular complications has been shown, as well as negative effect due to side effects and worsening of cardiovascular prognosis. This issue is relevant in most patients with prediabetes because they usually have high risk of cardiovascular complications. New data on the negative cardiological effects of some antihyperglycemic drugs limits their use in patients with cardiovascular comorbidities.

More questions appeared since it was unclear if lyrosiglitazone was safe, especially in combination with other medications, in patients with cardiovascular pathology [13].

The UKPDS study with 10-year follow-up revealed that during sulfonylurea derivatives and insulin treatment the risk of MI reduced by 0.85 (95 % CI 0.74–0.97; p = 0.01) and mortality by 0.87 (95 % CI 0.79–0.96; p <0.007) [14]. Recommended risk reduction for metformin in overweight patients was 0.67 (95 % CI 0.51–0.89; p = 0.005) and 0.73 (95 % CI 0.59–0.89; p = 0.002). Even though the UKPDS showed that metformin improves cardiovascular outcomes (which led to the recognition of this drug as a first-line treatment for obesity and type 2 diabetes), evidence base was insufficient for such conclusions. There is also an assumption that, in combination with sulfonylurea derivatives, morbidity and mortality may increase. However, the results of this meta-analysis also showed benefits of long-term treatment in younger patients [13].

Pioglitazone reduced the frequency of the secondary composite endpoint of all-cause mortality, fatal MI and stroke during the the PROActive study (RR 0.84; 95 % CI 0.72–0.98; p = 0.027) in patients with type 2 diabetes and a high risk of macrovascular complications [14]. The primary outcomes of the PROactive study were not statistically significant, therefore, interpretation of it results remains uncertain. Pioglitazone leads to fluid retention as kidneys secondary effect, to edema and deterioration of heart failure functional class. It is possible to use diuretics to reduce this effect.

Acarbose reduced the frequency of cardiovascular events, including cardiovascular mortality in patients with IGT during the STOP-NIDDM study.

Meglitinide was not studied in patients with type 2 diabetes, but it did not reduce fatal and non-fatal cardiovascular events in patients with high IGT risk [36]. There are also no RCT data on glucagon-like peptide 1 agonists, DPP-4 inhibitors, and SGLT-2 inhibitors outcomes, however, large-scale prospective studies on its on cardiovascular outcomes are currently performed [3, 36].

Antihyperglycemic drugs have contraindications in patients with comorbidities. Antihyperglycemic drugs side effects are presented in Table 28.

Table 28. Antihyperglycemic drugs contraindications

Somatic conditions	Acarbose	Metformin	Thiazolidinediones
Renal failure	Severe renal failure	Contraindicated	Not contraindicated
Liver failure	Not contraindicated	Contraindicated	Contraindicated
Coronary heart disease	Not contraindicated	Not contraindicated	Contraindicated in patients with heart failure

The supplement contains a scale on diabetes prediction and treatment algorithms for patients with prediabetes. It is important to monitor the state of carbohydrate metabolism and other RFs annually along with pharmacological and non-pharmacological treatment. Pharmacological treatment in patients with early carbohydrate metabolism disorders should be performed in accordance with their metabolic status.

Conclusion

Nowadays, the problem of DM prevention has national and international character as screening of high-risk groups is not enough anymore. We need to create population-based approach that includes screening and prevention programs at federal and regional levels. There are two main reasons why it is essential to identify and treat early carbohydrate metabolism disorders. First — high prevalence in population and clinical practice. Second — high risk of DM and cardiovascular complications in these patients.

To identify early carbohydrate metabolism disorders at primary health care level, we can use scales for DM prediction, OGTT, and HbA1C levels.

Early carbohydrate metabolism disorders, should be diagnosed primally in high risk patients. This group includes patients with risk factors: abdominal obesity, family history of DM (first-degree relatives suffer from DM), lipid metabolism disorders, including combination of hypercholesterolemia with high level of TG and low level of HDL, AH, fatty liver, hyperuricemia, erectile dysfunction, and various clinical manifestations of atherosclerosis.

Treatment of patients with prediabetes has two stages: non-pharmacological treatment and medications including antihyperglycemic (hypoglycemic) drugs.

Therapy effectiveness can be determined by the concentration of the fasting and after OGTT blood glucose, and other cardiometabolic parameters (waist circumference, BMI, blood pressure and lipid concentrations).

Thus, identification and treatment of early carbohydrate metabolism disorders is one of the important steps for the primary prevention of the DM and CVD.

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