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**METABOLIC SYNDROME
IN RUSSIA:**

**PREVALENCE, CLINICAL PECULIARITIES
AND TREATMENT**

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Metabolic syndrome in Russia:
prevalence, clinical peculiarities and treatment

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**Both worlds can fit within me, but in this world I cannot fit
I am the placeless essence, but into existence I cannot fit.**

Nasimi

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List of abbreviations

ACE inhibitor	angiotensin-converting enzyme inhibitor
AH	arterial hypertension
ARB	angiotensin II receptor blockers (sartans)
ARIC	Atherosclerosis Risk in Communities Study
BMI	body mass index
BP	blood pressure
CCBs	calcium channels blockers
CHD	coronary heart disease
CVD	cardiovascular diseases
CT	computerized tomography
DBP	diastolic blood pressure
DEXA	dual-energy X-ray absorptiometry
ECG	electrocardiogram
ED	erectile dysfunction
EGIR	European Group for the Study of Insulin Resistance
FFA	free fatty acids
GLUT	glucose transporter
HbA1	glycated hemoglobin
HC	hypercholesterolemia
HDL-C	high-density lipoprotein cholesterol
HOMA	homeostasis model assessment

HR	heart rate
HTG	hypertriglyceridemia
IDF	International Diabetes Federation
IFG	impaired fasting glycemia
IGT	impaired glucose tolerance
IR	insulin resistance
ISA	intrinsic sympathomimetic activity
LDL-C	low-density lipoprotein cholesterol
MI	myocardial infarction
MRT	magnetic resonance tomography
MS	metabolic syndrome
NAFLD	nonalcoholic fatty liver disease
NCEP ATP III	National Cholesterol Education Program Adult Treatment Panel III
NO	nitrogen oxide
NYHA	New York Heart Association
OGTT	oral glucose tolerance test
PAI-1	plasminogen activator inhibitor-1
POS	polycystic ovarian syndrome
PPARs	peroxisome proliferator-activated receptors
RAAS	renin-angiotensin-aldosterone system
SBP	systolic blood pressure
SCORE	Systematic Coronary Risk Evaluation
T2DM	type 2 diabetes mellitus
TG	triglycerides
TNF α	tumor necrosis factor alpha
VLDL-C	very low-density lipoprotein cholesterol
WHO	World Health Organization

INTRODUCTION

In the last decades, chronic non-communicable diseases such as coronary heart disease (CHD), stroke, complications of peripheral atherosclerosis and Type 2 diabetes mellitus (T2DM) are dominant human diseases. Risk factors play a significant role in the development of these diseases. In the 1960s, the main risk factors were arterial hypertension (AH), smoking and hypercholesterolemia (HC), 30–40 years later the situation changed. Nowadays obesity and metabolic syndrome (MS) together with “classical” risk factors play an important role in the development of cardiovascular and associated diseases.

Theory of MS made progress in the 20th century. For the first time scientists mentioned correlation between risk factors in the early 20th century. In the 1960s, the role of hyperinsulinemia in the development of CHD (CHD) and other cardiovascular diseases (CVD) was proved. In the 1980s, scientists determined the important role of hyperinsulinemia and insulin resistance (IR) in pathogenesis of metabolic disorders. In 1988 G.Reaven, American scientist suggested a theory about IR, which is the baseline of current views on MS. Over the last 20 years international institutions suggested definitions and criteria of diagnosis of MS, where priority was given to various metabolic disorders. Multiple epidemiological studies on the exposure to MS in population were done. High prevalence of MS irrespectively of gender and socio-ethnic particular qualities was determined. In recent years, more and more attention is given to the significant role of AO in MS. Particularly, the International Diabetes Federation (IDF)

experts consider an AO with strict waist circumference cut-off points to be the main component of MS. This approach is highly debatable in the academic circles. Recently, key points of international consensus on MS were published. It was the first attempt to combine different points of view on this problem. Scientists consider that MS is a serious problem in modern medicine and it should be regarded as interdisciplinary problem. It is important to define and treat MS not only among adults, but also among adolescents and children.

My first encounter with the problem of MS was in 1995. When I was postgraduate student of the National Research Center for Preventive Medicine, my scientific advisers were academicians of the Russian Academy of Medical Sciences R. Oganov, Professor N. Perova and Professor V. Metelskaya. They suggested MS in patients with AH as a topic for my scientific work. Spur of the moment I agreed. While working as a doctor of intensive care unit of one of Moscow city hospitals I often encountered a problem of combination of myocardial infarction, obesity and T2DM. The information on this new topic could hardly be found in the Russian sources. It should be noted, that separate components of MS were studied by outstanding Russian scientists, as Professor L. Chazova, Professor I. Suntsov and Professor A. Britov.

In the 1990s, similar studies were conducted in a number of the big Russian cities: in Moscow (I. Sokolov, S. Butrova, Y. Zimin, V. Moiseev), in St. Petersburg (A. Almazov, E. Shlyakhto) and in Novosibirsk (Y. Nikitin, G. Simonova).

Later, a number of widespread clinical trials of metabolic effects of different groups of cardiological drugs were done under the supervision of Professor I. Chazova and V. Mychka.

In recent years, the interest in MS grew. A large number of clinical trials on different aspects of MS were done in Russia. In the last decade national conferences and symposia were held, numerous textbooks and articles were published. In 2008, the Society of cardiology of the Russian Federation established a department of MS. The leading experts participated in publication of the first national recommendations on MS.

For a long time there were no data on prevalence of MS in Russia. In the late 1990s, Academician Y. Nikitin and Professor G. Simonova fragmentarily concerned the problem. In 2006, the National Research

Center for Preventive Medicine and Ministry of Health and Social Development of Chuvashia, Russia, launched the first epidemiological study on MS among adults. The leading clinicians, epidemiologists and statisticians took part in the clinical trial. For statistical analysis a questionnaire was made both in hardcopy and electronic form. Practitioners participating in the clinical trials were instructed by specialists of National Research Center for Preventive Medicine. The laboratory tests were performed in central standardized laboratory of the town of Cheboksary. The results of epidemiological study helped to determine not only the prevalence of MS, but also its gender and age particularities, the role of social, demographic, behavioral factors and some ethnic differences. It is important that within the framework of the project the clinical features of MS were determined. This project was supported by the Russian office of Dr. Reddy's Laboratories Ltd.

This book presents the results of the 15-year research into the problem of MS done at the National Research Center for Preventive Medicine. This book accumulates the data of foreign and Russian researchers on diagnosis and treatment of MS and analyzes in details the international and Russian recommendations on MS. For the first time, the discussion focuses on the interdisciplinary aspects of MS as well as on MS in children and adolescents. The book also suggests the algorithms of drug-free correction and drug therapy of MS.

The monograph consists of 11 chapters, list of references, pictures and tables.

The book is intended for cardiologists, physicians, endocrinologists, neurologists, rheumatologists, gynecologists, urologists, scientists and residents.

The author is grateful to Alexander Tarasov, Boris Kas and Lubov Drosdova for their help in producing this book. Author welcomes recommendations and remarks on the monograph at mmamedov@mail.ru.

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Chapter 1

DEFINITION AND DIAGNOSTIC CRITERIA OF METABOLIC SYNDROME

According to the current views, MS is a cluster of disorders including AO (AO), IR, hyperglycemia, dyslipidemia, AH, hemostasis system disorders and chronic subclinical inflammation [1, 2]. These are the characteristics of the main disorders of MS:

- AO correlates with other components of MS. A large waist circumference is a clinical feature of AO.
 - Majority of patients with MS have IR and compensatory hyperinsulinemia that increases risk of CHD.
 - Patients with hyperglycemia have impaired glucose tolerance and/or high fasting glucose level. These two conditions can lead to T2DM in 40–50% of cases within 5 years.
 - In atherogenic dyslipidemia, the pattern of lipoprotein abnormalities includes elevation of triglycerides, VLDL-C, LDL-C levels and low HDL-C.
 - AH is connected with obesity, impaired glucose tolerance and IR.
 - C-reactive protein is a marker of chronic subclinical inflammation.
- In addition, inflammatory cytokines appear to be the major regulators of adipose tissue metabolism.
- Hemostasis system disorders are hypercoagulation (elevated concentrations of fibrinogen) and low fibrinolytic activity.

In the last decade, several groups of experts have developed the diagnostic criteria of MS. The most well known are: WHO criteria, European Group for the Study of Insulin Resistance (EGIR) criteria, the National Cholesterol Education Program Adult Treatment Panel

Table 1. Criteria of metabolic syndrome diagnosis

WHO 1998	EGIR 1999	NCEP ATP III (USA) 2001	IDF 2005
insulin resistance and/or hyperglycemia + ≥2	insulin resistance/hyperinsulinemia + ≥2	presence ≥3 out of 5: fasting hyperglycemia	abdominal obesity + ≥2
obesity/ abdominal obesity arterial hypertension	fasting hyperglycemia arterial hypertension	arterial hypertension abdominal obesity	fasting hyperglycemia arterial hypertension
↑ triglycerides ↓ high-density lipoproteins cholesterol microalbuminuria	abdominal obesity ↑ triglycerides ↓ high-density lipoproteins cholesterol	↑ triglycerides ↓ high-density lipoproteins cholesterol	↑ triglycerides ↓ high-density lipoproteins cholesterol

III (NCEP ATP III) criteria, and the IDF criteria. At first glance, there seems to be an agreement. The components of the MS are the same in all definitions [3–6]. Basic components are obesity, IR, dyslipidemia and AH (Table 1).

The main difference among these definitions is the question which component is considered to be the dominant one. In the WHO criteria, the main signs are IR and its glycemic markers. AO takes the first place in the IDF definition. Several definitions of MS are difficult to apply in clinical practice. Moreover, the use of different criteria makes it difficult to compare the data of various studies. This situation provoked into a big number of publications on the comparative analysis of different definitions of MS. For example, the data are published on synergism and contradiction between the two last definitions.

It is noteworthy that definition of NCEP ATP III (according to this definition, MS is a combination of three out of five components while none of the components is considered the principal one) gave an incentive for performance of widespread epidemiological and prospective studies. S. Grundy, President of International Atherosclerosis Society and one of the participants of International consensus on MS wrote on the importance of NCEP ATP III criteria, because from one hand,



Fig. 1. Basic document of International consensus on MS

their predictor role in development of CVD is proved and on the other hand, they are more justifiable from the economic point of view [7].

In 2009, the International consensus on the definition and diagnostic criteria of MS was established with the participation of IDF experts, American Heart Association, World Heart Federation, International Atherosclerosis Society, the National Heart Lung and Blood Institute and International Association for the Study of Obesity [1]. Key points of International consensus are published in «Circulation» (Fig. 1).

The experts discussed the importance of AO as a diagnostic criterion of MS. The expert opinions differ not only in regard of the role of AO, but also in the waist circumference cut-off points. Finally, experts concluded that AO is the main component of MS, but waist circumference measurement can be used as a provisional screening tool. Presence of three out of five disorders makes it possible to diagnose MS. The same cut-off points will be used for the diagnostics of all components of MS, with the exception of waist circumference. Provisionally the national or regional waist circumference cut-off points will be used for the definition of AO.

Later the IDF experts improved the previous criteria of MS. In October 2009, a new version of recommendations for the clinical management of MS was presented at XX World Diabetes Congress.

Criteria of diagnosis of metabolic syndrome (World Diabetes Congress, 2009)

AO is one of the two main pathogenetic mechanisms of MS. On the one hand, AO can be determined by the waist circumference measurement; on the other hand, it is associated with other components of MS, including IR [8]. In the new definition of MS AO is the main diagnostic criterion (Table 2).

Table 2. Definition of metabolic syndrome

Abdominal obesity (determined by the waist circumference measurement taking into account the ethnic differences) + ≥ 2:	
High level of triglycerides	≥ 150 mg/dL (1.7 mmol/L) or specific treatment of dyslipidemia
Low level of HDL-C	> 40 mg/dL (1.03 mmol/L) for males > 50 mg/dL (1.29 mmol/L) for females
High BP	SBP ≥ 130 or DBP pressure ≥ 85 mmHg or AH
High level of fasting blood glucose	≥ 100 mg/dl (5.6 mmol/L) or T2DM If the level of fasting blood glucose is more than 5.6 mmol/L or 100 mg/dL oral glucose tolerance test (OGTT) is recommended (not for MS diagnosis).

The main advantage of the IDF criteria is the possibility to reveal risk groups on early stages of the disease. Amid disagreements over this topic, the committee of experts published a statement that suggested considering MS as a combination of risk factors of CVD. The new consensus is a universal solution for clinical practice and research all over the world. Thus, AO is viewed as the main component for diagnostics as it plays an important role in the cascade of metabolic disorders. Experts suggest a differentiated approach for waist circumference measurement for different ethnic groups. This problem question is not solved, as the cut-off points for several ethnic groups are not yet determined. Today there are the criteria of AO for 4 ethnic groups (Table 3). The Russian Federation refers to the European group. USA experts suggest the previous cut-off points (waist circumference >102 cm for males and > 88 cm for females).

Table 3. **Ethnic values for waist circumference**

Country/ethnic group		Waist circumference
The Europeans (NCEP ATP III criteria -102 cm for males and 88 cm for females - are used in clinical practice in the USA)	Males	≥94 cm
	Females	≥80 cm
South Asian	Males	≥90 cm
	Females	≥80 cm
Chinese	Males	≥90 cm
	Females	≥80 cm
Japanese	Males	≥90cm
	Females	≥80cm
South and Central America ethnic groups	South Asia values are used until specific criteria are found	
African Sahara region	European values are used until specific criteria are found	
The eastern Mediterranean and Middle East (Arabic)	European values are used until specific criteria are found	

The change of fasting glycemia levels is another recommendation novelty. For a long time, fasting glycemia level ≥ 6.1 mmol/l in venous blood was understood as fasting hyperglycemia. In the present definition this level is ≥ 5.6 mmol/L. Moreover, an oral glucose tolerance test (OGTT) is recommended when fasting hyperglycemia is detected [1].

One should stress the importance of atherogenic dyslipidemia (a combination of high triglyceride level, low level of HDL-C and increase of apoB, small particles of LDL-C and HDL-C). Each separate component is an independent atherogenic factor [9-11]. Low level of HDL-C and high triglyceride level frequently occur in patients with IR and with or without T2DM. As a whole cut-off points of hypertriglyceridemia, low level of HDL-C and hypertension were not changed.

For the first time, additional diagnostic tests for MS were suggested.

«Platinum standard»-additional metabolic tests for verification

The IDF experts also suggest measuring a number of parameters related to MS (Table 4). In some cases, they can be used for the detection and differential diagnosis of MS, especially in some ethnic groups.

Table 4. Additional diagnostic methods

Fat maldistribution	The overall fat distribution in vivo (DEXA) Abdominal fat distribution (CT/MRT) Fat tissue biomarkers: leptin, adiponectin Fat content in liver
Atherogenic dyslipidemia	Apo B (or no HDL C), small fractions of LDL-C
Dysglycemia	Thyroid stimulating hormone
IR	Insulin / proinsulin fasting level HOMA-IR IR on Bergman minimal model Free fatty acids elevated level (fasting and after OGTT) Glucose clamp technique
Vascular changes	Endothelial dysfunction valuation Microalbuminuria
Proinflammatory status	High-sensitivity C-reactive protein increasing Inflammatory markers increasing (including tumor necrosis factor-alpha, IL-6) Adinopectin plasma level lowering
Prothrombotic status	Fibrinolytic factors (PAI-1 and others) Coagulation factors (fibrinogen and others)
Hormonal factors	Pituitary-adrenal axis

Thus, the universal definition of MS, which was suggested by the IDF experts, opens new prospects for:

- comparative analysis of different clinical trials
- MS etiology detection
- MS and its certain components contribution to the CVD development;

- development of new effective treatment methods for all MS components
- identification of high-risk MS patients in different populations.

A new stage comes in MS study – consolidation of the leading world scientific schools around the IDF consensus.

We think that large-scale prospective studies will allow evaluating the prognostic potential of the new MS definition.

Chapter 2

HISTORY OF METABOLIC SYNDROME THEORY

MS theory passed a complex evolution in the 20th century. However, the antique people knew that overnutrition and wine abuse often combined with obesity and gout resulting in a stroke. This phenomenon was most common among the nobility [12]. Ancient figurines and statuettes, discovered in archaeological excavations around the globe, indicate that wealth and sufficiency are often associated with obesity (Fig. 2).

In the early 20th century, Maranon for the first time specified several factors, which were the components of MS, and said that they have tendency for synergy. In 1923, a Swedish physician E. Kylin described

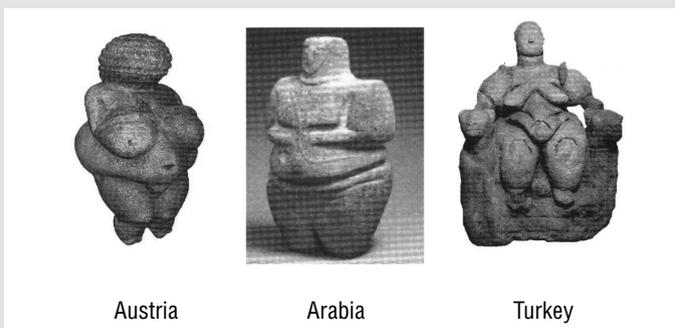


Fig. 2. In the ancient, times obesity was associated with well-being and “good” life

a syndrome, named hypertension–hyperglycemia–hyperuricemia syndrome [13]. At this time, a Soviet scientist G. Lang indicated the close link between AH, obesity, carbohydrate metabolism disorder and gout [14]. Similar descriptions in different variations were done until the 1970s. In the mid 20th century, the first assumptions were made about the interaction cause disorders that looked different at first glance. Thus, T. Smith suggested a theory about the role of insulin in atherogenesis and associated diseases [15].

MS prototype was described in 1966 by J. Camus. The combination of gout, hyperlipidemia and T2DM in the same patients was named metabolic trisynndrome (trisynndrome metabolique) [16]. In 1981, using the data of epidemiological and pathophysiological studies, east German scientists M. Hanefeld и W. Leonardt proposed a theory of MS (Das metabolische Syndrom). It included obesity, hypertension, hyperlipidemia, gout and T2DM. Hyperinsulinemia was indicated to be an important element/component in atherogenesis [17]. But East Germany scientists' ideas were not shared in the international medical circles.

In 1979, an American scientist R. De Fronzo discovered IR, for the first time using the glucose clamp method in vivo [18]. In 1988, in Banting lecture, G. Reaven suggested that IR is the underlying factor of MS and named the constellation of abnormalities as Syndrome X [19]. Three years later, R. De Fronzo and G. Haffner suggested the term «insulin resistance syndrome» indicating the leading pathogenic factor. At the end of the 20th century, N. Kaplan stopped the polemic about the multicomponent syndrome. He called it “The deadly quartet” (a combination of upper-body obesity, glucose intolerance, hypertr glyceridemia, and hypertension) [20]. Thus, in the literature, MS has 7 synonyms and 24 scientists are considered to be the pioneers of this theory. Analyzing the classical studies, we concluded that these scientists certainly influenced the present-day ideas about MS. However, almost all publications on MS admit G. Reaven was the founder of the MS theory. His article “Role of insulin resistance in human disease” is the most quoted research [19].

G. Reaven hypothesis consists of several points describing the syndrome X basics. According to G. Reaven, IR occurred not only in patients with impaired glucose tolerance and T2DM, but also in 25%

Banting lecture, 1988
Role of insulin resistance in human disease



Resistance to insulin-stimulated glucose uptake is present in the majority of patients with impaired glucose tolerance or non-insulin-dependent diabetes mellitus and in approximately 25% of nonobese individuals with normal oral glucose tolerance. In these conditions, deterioration of glucose tolerance can only be prevented if the beta-cell is able to increase its insulin secretory response and maintain a state of chronic hyperinsulinemia.

The relationship between insulin resistance, plasma insulin level, and glucose intolerance is mediated to a significant degree by changes in ambient plasma free-fatty acid concentration.

Patients with hypertension, treated or untreated, are insulin resistant, hyperglycemic, and hyperinsulinemic.

Diabetes. 1988 Dec;37(12):1595-607

Fig. 3. Central tenets of the G. Reaven's theory

of patients without obesity and carbohydrate metabolism disturbance. Hyperinsulinemia, IR and glucose intolerance lead to the increase of free fatty acids (FFA) concentration in blood serum, which are substrates of triglyceride synthesis.

According to this theory, the majority of patients with hypertension have hyperinsulinemia and IR regardless of their treatment status (Fig. 3). Syndrome X is the combination IR, hyperinsulinemia, glucose intolerance, hypertriglyceridemia, low level of HDL-C and hypertension. Hyperuricemia (high level of uric acid) and the increase of tissue plasminogen activator inhibitor (PAI-1) level (fibrinolysis factor) are also included in the syndrome, but they do not occur in all patients.

The term MS is frequently used all over the world. However, G. Reaven said in one of the last interview that this term is less preferable, because not all disorders with IR are metabolic disorders. For instance, the increase of PAI-1 level regulates fibrinolysis and it is not a metabolic disorder. It is worth mentioning, that the author does not agree with the term "The deadly quartet", since obesity could not be considered as the main component of the syndrome, as many people with overweight do not suffer from this syndrome. In G.Reaven's opinion, on the one hand, the term "syndrome X" characterizes the basic disorders, but on the other hand, it demonstrates the necessity of first cause research (www.cacr.ca/contact-us.htm).

In 1988, G. Reaven viewed syndrome X conception an open system and suspected new components emergence.

The present-day definition of MS has certain disagreement with its classical description. However, it is the subject for prospective and clinical studies.

Chapter 3

PREVALENCE, GENDER AND AGE-RELATED FEATURES OF METABOLIC SYNDROME: RUSSIAN DATA FROM A CROSS-SECTIONAL EPIDEMIOLOGIC STUDY

One of the important medical and social peculiarities of MS is its prevalence in population, and in particular among adult population.

Epidemiological studies are done to estimate prevalence one or another disease or disorder. They allow revealing a wide range of regularities, including age-related and gender-related features, social, economical and ethnic factors impact. These data are of outmost importance for the disease diagnostic and prevention [24].

In the 1990s, there were few data concerning MS prevalence, since IR was considered an integral part of MS and glucose clamp method was a laborious and costly diagnostic procedure. One of the first epidemiological studies is San Antonio Heart Study; its results provide the basis for syndrome X concept. According to the study, 25% of adult population sample has IR without clinical manifestations [25]. Another study done in two Finland regions demonstrated that all MS components occurred in 5% of males and in 8% of females. Furthermore, MS had clear correlation with age, insulin level and obesity extent. It is worth mentioning that cut-off points of triglycerides and BP were rather high in this study [26].

Publication of the new WHO criteria in 1998 (as well its modified EGIR version) and the USA NCEP ATP III in 2001 stimulated to large-scale studies in many countries and ethnic groups. However, use of different criteria (NCEP ATP III criteria in general) makes difficult the

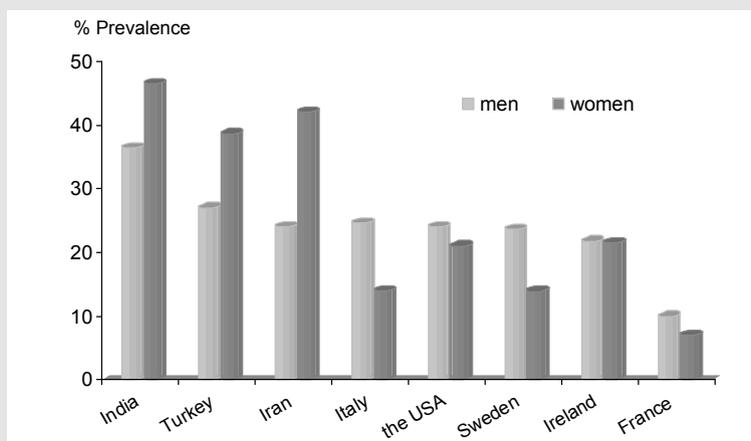


Fig. 4. Meta-analysis of epidemiological studies

standardization of obtained results. Currently, the data of more than 20 epidemiological studies on 5 continents are published. They allow to evaluate the global tendency of MS distribution worldwide [8, 21].

The lowest prevalence of MS was registered in China (Fig. 4). In Beijing study, MS was found in 10% of urban population and in 20% of people over 50. It is estimated that 90 million Chinese citizens suffer from MS [27].

In West European countries, MS without T2DM occurs in 10-15% of adult population and in 20% of elderly age groups [3, 22, 28]. In the Australian AusDiab study three types of criteria were applied (WHO, EGIR, NCEP ATP III). MS was found in 16-20% of patients over 35.

A collaborate epidemiological study was done in five Mediterranean countries, which detected the most common version of MS – combination of hypertension, low level of HDL-C and AO. Total 27% of patients in the 20 to 74 age brackets have its different variants. The similar tendency is registered in Turkey: 27% of males and 38.6% of females over 35 with low level of HDL-C and high level of LDL-C suffer from MS. It is of interest that in this sample CHD occurred in 50% of patients with MS [29].

The largest study was done in the USA. The average prevalence of MS was 24%. However in several groups (obese people, 60–69 age

group, postmenopausal females, Hispanics) this index increases to 43–56% [30]. It is estimated that about 47 million Americans have MS.

On the first International Congress on Prediabetes and the MS (April 2005, Berlin) Indian scientist A. Ramachandran reported results of an epidemiological study among Indian urban population. The highest (41%) prevalence of MS in India occurs in the 20–75 age brackets [31]. It is known that IR and T2DM are widely spread in South Asia population.

In the post-socialist countries, including Russia, almost no large-scale studies on MS was done. It is probably associated with funding constraints [32, 33].

In the literature, we found the results of the Poland study indicating that average 25–35% of urban population had the main components of MS [21].

The first Russian epidemiological study results of metabolic syndrome detection

In 2007-2009 National Research Center for Preventive Medicine and Ministry of Health of the Chuvash Republic (agreement №01/01 – 1027 from 22.11.2005) did a population study to detect MS in random sample of adults at the town of Cheboksary.

Sampling

The research team (30 primary care physicians and general practitioners) was formed with a random sampling technique. The study design was developed in National Research Center for Preventive Medicine in partnership with A. Deev, biostatistics laboratory director.

According to the protocol, 60 respondents from each of the 30 health care regions (1800 persons in total, 749 males and 1051 females at the age of 30-69) randomly selected. Research response accounted 88.7% in general.

At the first stage, 1718 persons filled in a questionnaire, which included social and demographic data, family history, smoking status, alcohol consumption, physical activity level, nutrition behavior, questionnaire for detection of stable angina, psychological and diabetic status, hypertension course and concomitant diseases survey, taking

medicines. For different reasons 148 respondents (8,7%) did not participate in the further instrumental and biochemical tests.

Clinical-instrumental tests

The anthropometric examination included waist circumference measurements, body mass and height measurement, BMI calculation.

The office BP measurement was performed twice in the resting sitting position with a 5-minute interval with accuracy of 2 mm Hg. The mean value of two measurements was taken for analysis. Heart rate data were also included in the questionnaire.

All respondents underwent 12-lead ECG at rest. ECG was interpreted according to the special scheme, which was developed for this study using the Minnesota code (the USA).

CHD was diagnosed on the basis of history analysis, physical and instrumental examination, including the standard WHO questionnaire on exertional angina detection and ECG-proved old myocardial infarction (Minnesota code).

Laboratory tests

The tests were done in the laboratory of the Republican cardiological clinic of Ministry of Public Health and Social Development of Chuvashia in Cheboksary.

Blood samples were taken in the morning from median cubital vein in vacutainers or test tubes after 12-hour fasting with minimal venous occlusion.

Total cholesterol, triglycerides, HDL-C (mmol/L) in serum was determined by enzyme sets "Human" on biochemical automatic auto-analyzer "ALCYON 160" (serial number 14161416) photolorimetric method by end point CHOD – PAP (HUMAN reagents). LDL-C were calculated by Friedwald W.T. (1982) formula:

$$\text{LDL-C (mmol/l)} = \text{cholesterol} - (\text{triglycerides} / 2,2 + \text{HDL-C}).$$

OGTT was done after 8–12 hour night fasting. After blood sampling, the respondents drank 75 g of glucose dissolved in 250–300 ml of water less than in 5 minutes. The blood sampling was performed twice with a 2-hour interval. Glucose concentration in venous serum was estimated by glucose oxidase test on photometer KFK-3.

Total cardiovascular risk was evaluated by European scale SCORE including the following parameters: age, sex, smoking status, SBP level and total cholesterol. Total risk < 1% was considered to be low risk, 1–4% – medium, 5–10% – high risk, > 10% – very high.

Two types of criteria were used to define MS: the NCEP ATP III (2001) and IDF (2005) definitions.

Metabolic syndrome prevalence in Russian population

MS, defined by NCEP ATP III criteria, was revealed in 314 patients (20.6%) among adults in a city of Volga Federal district (Fig. 5).

226 females (28,3% of the total number of females) and 88 males suffered from MS (14,2% of the total number of males), the difference is significant ($p < .0001$).

According to the IDF criteria, 28,5% of respondents ($n = 447$) have MS. It is more statistically significant ($p < .0001$) in comparison with MS diagnosed using NCEP ATP III.

MS 2 times more often occurs in females 35,5% ($n = 337$) than in males 17,8% ($n = 110$), ($p < .0001$).

Thereby, MS diagnosed using the IDF criteria demonstrates upward tendency in the Russian population. Dr. E.S. Ford's analysis, which was made in the Centre for Disease Control and Prevention in the USA

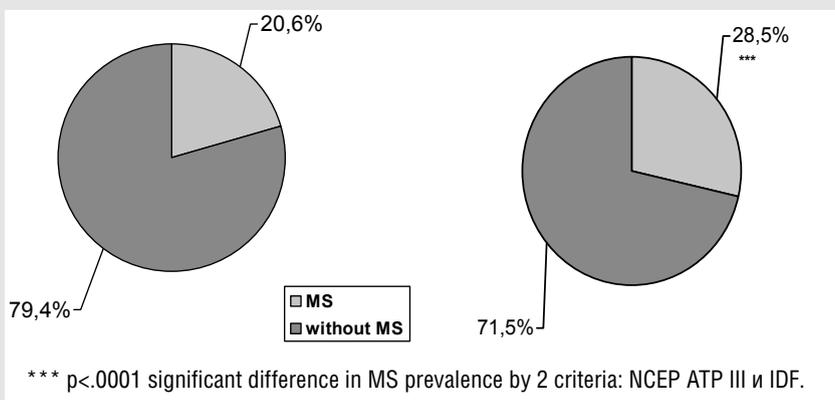


Fig. 5. MS prevalence in adult population by 2 criteria: NCEP ATP III and IDF

among people over 20 years using American Heart Association criteria, revealed MS in 35,2% of cases (34,8% among males and 35,5% among females). Whereas the little difference was found using the modified IDF criteria (presence of three of five components): total 40.1%, 41,9% in males and 38,3% in females.

In this study, the majority of patients with MS met criteria NCEP ATP III and IDF. However 39.4% (n = 176) of patients with MS diagnosed by the IDF criteria, did not meet the ATP III criteria. At the same time, 13.4% of patients with MS diagnosed by NCEP ATP III criteria were not included in the group of patients with MS, diagnosed by the IDF criteria.

Later in the study, we used criteria NCEP ATP III to evaluate MS associations with different social factors, and also to determine its clinical characteristics.

Age-dependent characteristics of metabolic syndrome prevalence

The analysis of MS prevalence in males as well as in females in different age groups shows that the MS prevalence grows with age. MS is diagnosed in 3.2% in males of 30–39, in the 40–49 and 50–59 age groups this rate triples to 12.2% ($p < .02$ compared with males of 40–49) and 14.6% ($p < .004$ compared with the 50–59 age group) respectively. In elderly age group (60–69 year old male) every fifth male had MS (22.6%), that is significantly more often in comparison with the 30–39 and 40–49 age groups ($p < .001$ and $p < .03$, respectively). The same pattern is typical for females. MS is diagnosed in 5% of females of 30–39; this rate grows up to 17% in the 40–49 age groups. In the 50–59 and 60–69 age groups, every third female has

Table 5. Prevalence of MS in different age groups

Age group	Males		Females	
	Total number, n	Patients with MS, n (%)	Total number, n	Patients with MS n (%)
30–39	94	3 (3.2%)	148	7 (4.7%)
40–49	197	24 (12.2%)	270	45 (16.7%)
50–59	206	33 (14.6%)	354	109 (30.8%)
60–69	124	28 (22.6%)	177	65 (36.7%)

MS – 30.8% and 36.7% respectively, which is statistically significant compared with the age groups of 30–39 and 40–49 (Table 5).

The analysis of gender characteristics of MS prevalence shows, that in general it is 40% more frequent in females, which is most evident in 2 age groups: 50-59 and 60-69 years old ($p < .002$ and $p < .05$ respectively), compared with males of the same age.

Social status, life style, educational background and the MS prevalence

This study analyzes the influence of wide range of social factors, life style and educational background on the MS prevalence.

Initially people of different nationalities and ethnical groups were included in the study. The majority (67.7%) of them were Chuvash, one third – Russian (29,5%) and representatives of other nationalities were less than 3%, among them Tatars, Ukrainian, Belarusians and others.

The analysis of MS prevalence in 2 main nationalities demonstrated that MS can be found in 18% of cases in Chuvash population and in 25% of Russian population ($p < .05$). MS is diagnosed in 12% of Chuvash males and in 19% of Russian males, which is significantly higher ($p < .03$). The prevalence of MS in Chuvash females is 2 times higher than in males: 22.6% and 11.7% respectively ($p < .0002$). The difference of MS prevalence in Russian males and females is not statistically significant (19% and 26.4% respectively).

Another potential risk factor of MS is marital status. In order to estimate prevalence of MS in people with different marital status participants were divided in 4 groups: married, single, divorced and widowers. The results of the study showed that among married people every fifth participant (20%) had MS, among single people – 14%, among divorced – 18%, and the highest prevalence of MS was registered in widowers – 28,3%. In general, the lowest frequency of MS is in the group of single participants. This can be explained by the fact, that single participants were all 30-39 years old, while every third widower had MS. Equal MS prevalence is registered for divorced and married people.

The prevalence of MS in males and females of different marital status is equal, only married females are an exception — 23.8% vs. 15% ($p < .002$).

There is enough data in the literature on the correlation of behavioral factors with MS. On the last World Diabetes and Prediabetes Congress (1–4 April, Nice) the results of several studies on the role of behavioral factors in the development of MS were demonstrated. The researchers of VIVIT University (Austria) demonstrated the possible association of eating disorders with MS in people with CHD [35, 36].

In this study, we studied the association of MS prevalence with life style alteration, so we analyzed data of physical activity and diet in a random sample of adults.

According to WHO questionnaire for life style, 50.9% of participants lead a sedentary life, the prevalence of MS among them was 21.8%, while among people with normal physical activity the MS prevalence was 18%. The differences between them were not statistically significant.

Every fourth participant (24%) didn't have eating disorders, while 41% of participants had light eating disorders, 27% — mild eating disorders, 8% — severe eating disorders. Among people with no eating disorders, MS was diagnosed in 14.6% of cases, in participants with mild eating disorders — in 19.2%. There is a statistically significant increase of MS prevalence in patients with mild eating disorders — 22% ($p < .02$ compared to people with no eating disorders). MS prevalence is the highest in group of patients with severe eating disorders and consists 32.2%, which is significantly higher compared with patients with no eating disorders or with mild eating disorders ($p < .0005$ and $p < .01$, respectively) (Table 6).

Table 7 shows the MS prevalence in correlation with smoking status. In general prevalence of MS is reliably lower in smokers (people, smoking at least 1 cigarette per day) and makes 11.3%, compared to no-smokers — 21.6% ($p < .0008$) and those who stopped smoking — 24.5%, ($p < .002$). This tendency is clear in males. In comparison to females, MS was diagnosed reliably often in smoking and non-smoking males.

To analyze the association of MS with alcohol intake patients were divided in 2 groups depending on their alcohol consumption status:

Table 6. Association between MS and eating disorders

Eating disorders	Males n (%)	Females n (%)
No eating disorders	12 (10.5%) out of 114	43 (16.4%) out of 262
Light eating disorders	30 (12.8%) out of 235	93 (23%) out of 404
Mild eating disorders	25 (12.7%) out of 197	70 (30.3%) out of 231***
Severe eating disorders	21 (28%) out of 75**	20 (38.5%) out of 52 ***

** $p < .01$, *** $p < .005$ difference reliability by differences in MS prevalence in patients with normal diet and various stages of eating disorders.

Table 7. Prevalence of MS among smokers

Smoking status	Males		Females	
	Total number, n	Patients with MS, n (%)	Total number, n	Patients with MS, n (%)
Smoking	267	27 (10%)	25	6 (24%)
Non smoking	209	27(12.9%)	914	216 (23.6%)
Quit smoking	144	34 (23.6%)	11	4 (36.4%)

people, who drink alcohol and those, who abstain from drinking. MS is significantly more frequent in people abstaining from drinking or consuming alcohol in small doses compared with people, consuming alcohol in higher doses — 21.1% and 8.8%, respectively ($p < .009$).

In a random sample of adults every second participant is suffering from a medium level of stress, every fourth suffered from high level of stress, while only 11% of participants experienced low stress.

Among people with low stress, about 28% have the main symptoms of MS, while in the groups with medium and high stress levels, MS is registered only in 20% and 17.5% of cases respectively (Table 8).

According R. Oganov, one of the factors, which may influence CVD in the Russian population, is the educational background [25]. In general, in a random sample of adults in Cheboksary the prevalence of MS in groups with different educational background is not significantly

Table 8. Prevalence of MS among people with different stress level by Reeder questionnaire

Stress level	Males	Females
Light	12 (19.3%) out of 62	36 (32.4%) out of 111
Medium	42 (13.9%) out of 303	116 (24.5%) out of 474 p ₂
High	32 (13.2%) out of 242	71 (20.5%) out of 347 p ₁ p ₃

p₁<.05, p₂<.03 reliability of difference in MS prevalence between males and females with different stress rate; p₃<.05 reliability of difference in MS prevalence between females with low and high stress rate.

different. It consists 17.4% in people with higher education, 19.9% – with professional education, and 21.8% – with secondary and incomplete education. MS is diagnosed significantly more often in females with secondary education as compared to females with higher education ($p < .05$). When compared to males, the MS prevalence in females with professional and secondary education is higher: 22.8% vs 14.2% ($p < .05$) and 28.3% vs 13.6% ($p < .0005$), respectively (Table 9).

Table 9. MS in people with different educational background

Educational background	Males		Females	
	n	Patients with MS, n (%)	n	Patients with MS, n (%)
Higher education	158	24 (15%)	226	43 (19%)
Professional education	204	29 (14.2%)	395	90 (22.8%) p ₂
Secondary and incomplete education	258	35 (13.6%)	329	93 (28.3%) p ₁ p ₃

p₁<.05 reliability of difference between females with different educational background;

p₂<.04, p₃<.0005 reliability of difference between males and females with different educational background.

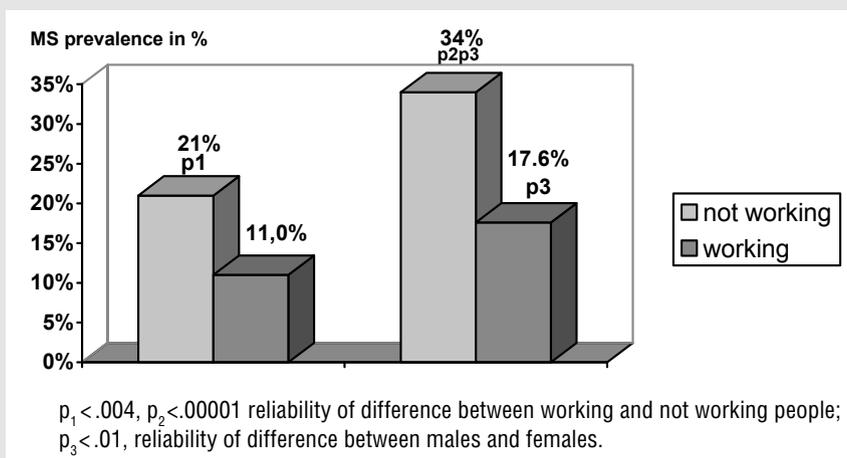


Fig. 6. MS prevalence in people with different employment status

Does working status influence the MS incidence? To get the answer to this question, we divided the participants of the study in 2 groups: working and not working.

Figure 6 shows MS prevalence in people with different working status (males as well as females). Generally MS is twice as frequent in not working people (housewives and senior citizens constitute the majority of them) as in working people and makes 29,4% and 14,9%, respectively ($p < .00001$). It is important to note, that in the group of not working people housewives and senior citizens were in majority.

As it can be seen from the above, in a random sample of people in a town in Volga Federal District there are up to 30% of cases of MS. In general, certain social and behavioral factors can directly affect MS prevalence, which should be considered in diagnostic algorithms of this highly atherogenic condition.

Chapter 4

NEW APPROACHES TO THE PATHOGENESIS OF METABOLIC SYNDROME

MS is a chronic disease of heterogenic etiology, in which behavioral factors and genetic alterations play a certain role [37–39].

In ancient times, people's survival and continuation of existence of human race required intensive physical exercises. People ate until there was something to eat. Overeating was rare and insignificant. In periods of rest, people tried to minimize the activity level in order to save the maximum of energy. This encouraged economical genotype, which used to help every human being to survive in conditions of constant food deficiency. In comparison with primitive society, nowadays food is available almost any time and there are no hard physical activities. Double increased intake of fat and partial replacement of amyloidal carbohydrates by refined carbohydrates (sugar) led to persistent unidirectional alteration of energy balance. Sedentary life or hypodynamia are associated with lipolysis and glucose disposal inhibition in muscular tissue, which also results in metabolic impairments. Australian scientist P. Zimmet once suggested in his speech that people with MS could hardly be found among the residents of blockaded Leningrad during the Second World War [40].

MS development undoubtedly is genetically determined process [41]. Some ethnic groups may serve as a model to demonstrate that fact. Traditional lifestyle alteration by people with widespread primary IR (Hindu and other peoples of Southern Asia, Pima people from Arizona and Nauru from Micronesia), led to sharp increase in prevalence of obesity, atherosclerosis, T2DM. Genetic predisposition

to MS and its complications was also shown in the study by National Research Center for Preventive Medicine. Thus, the family history analysis of people with MS (n=500) demonstrated that in majority of cases their parents had diagnosed CVD and/or diabetes mellitus: hypertension in 31%, T2DM in 33% and CHD in 51% [42].

Nowadays it is considered that MS is genetically heterogeneous (oligogenic or polygenic) disease [43]. Genetic abnormalities may influence the development of IR, impaired fat metabolism and other components of MS [44]. Among the possible reasons of genetically determined IR, the most important are the following mutations: of insulin receptor gene, of insulin receptor substrate-1 gene, of the protein responsible for glucose translocation into the cell (GLUT-4) of glycogen synthetase, the enzyme responsible for intercellular glucose metabolism etc [15]. Genetic modifications of other components of MS (beta-3 adrenoreceptors), main proteins of lipid-transport system, apo AI-CIII-IV (in combination), lipoprotein lipase, renin-angiotensin-aldosterone system (RAAS), transmembrane electrolyte system are also considered of great importance. Latest studies demonstrate that genetic variations of 2 isoforms (a and g) of nuclear peroxisome proliferator-activated receptors (PPAR), responsible for lipid catabolism, lipid storage processes and glucose metabolism regulation, may play a key role in MS development [23, 45].

Generalizing the results of genetic studies, we come to the conclusion, that the majority of genetic alterations are the cause of minimal metabolic disorders, however their combination may result in the synergism of these alterations development. In other words, several phenotypes of MS are the result of interaction of behavioral factors and various genetic disorders.

Polyvalent effects of insulin resistance in target organs

There is enough evidence demonstrating the key role of IR and compensatory hyperinsulinemia in MS pathogenesis [37, 46]. For a long time IR was understood as one of the three mechanisms of T2DM development [47]. In the late 1980-s the results of several big epidemiological studies were published devoted to the role of

hyperinsulinemia/IR in CVD development [48, 49]. It was shown in six prospective studies, which lasted 5-12 years, that chronic hyperinsulinemia is an independent CVD predictor. The results of 2 studies (prospective cohort study in Malmo, Sweden, and the VA-HIT study (VA-HIT) finally demonstrated that IR determined by Homeostasis Model Assessment (HOMA) method plays a key role in the development of cardiovascular complications (lethal and non-lethal myocardial infarction or stroke) in patients with or without T2DM.

The main results of these studies are in Table 10.

Table 10. CHD and insulin level correlation in different populations

City, country and date of study	Time of observation	Age and number of patients	Multivariational association of CHD with insulin level
Busselton, Australia, 1966	12 years	>21 1,634 people	CHD association with postprandial insulin level
Helsinki, Finland, 1971-72	5 years	35-64 1,042 people	CHD association with postprandial insulin level
Paris, France, 1968-73	5 years	43-54 7,246 people	CHD association with fasting insulin level
Caerphilly, South Wales, 1979-83	5 years	45-59 2,022 people	CHD association with fasting insulin level
San Antonio, USA, 1975	15 years	>25 589 people	There is no CHD association with insulin level
Moscow, USSR, 1983	Cross-sectional trial	20-69 1255 people	CHD association with fasting insulin level
MRFIT, USA 1973-76	7-10 years	35-57 622 people	There is no CHD association with insulin level

The studies were done on a big group of middle-aged people and lasted at least 5 years. In three studies (those undertaken in Paris, South Wales and Moscow), the significant association between fasting hyperinsulinemia and CHD development was found. While in the studies done in Finland and Australia, postprandial insulin level was considered the predictor of CHD development. Meanwhile, the data

are controversial. For instance, in Pima Indians aged 25 and elder significant association of basal and postprandial insulin levels with CHD development was not found, which may be explained by genetic and ethnic characteristics of this population [50].

Later it was demonstrated in one clinical trial in National Research Center for Preventive Medicine that CHD correlates with hyperinsulinemia/IR as well as with other components of MS, including hypertriglyceridemia and AO [11].

In summary, meta-analysis of several prospective studies shows, that hyperinsulinemia, fasting or postprandial, correlates with CVD development and may be one of the most important predictors of CVD in people without T2DM.

What is insulin resistance?

IR is a condition when the tissues become less sensitive to the effects of insulin at physiological concentration. The pancreas synthesizes Insulin in within the β -cells from the proinsulin precursor molecule by means of modifications that remove the C-peptide. Physiological effects of insulin are numerous with the most essential being the regulation of glucose metabolism. Insulin binds to its receptors activating GLUT, which transfer glucose from the bloodstream into the tissues. Experiments show that insulin facilitates vasodilation via the increase in nitric oxide synthesis. It also amplifies renal reabsorption of sodium and potassium, stimulates vascular smooth muscle cell proliferation, exerts anabolic effects etc. Thus, the wide range of metabolic disorders seen in chronic hyperinsulinemia is due to multiple effects of insulin [51].

IR can be considered a physiologic condition in some cases (pregnancy, for instance). Partial IR is the fundamental feature of the “economic” genotype. At the dawn of civilization it helped to store excess nutrients and survive food shortage. Some endocrine diseases (hypothyroidism, Cushing’s syndrome, acromegaly, pheochromocytoma), systemic diseases (rheumatoid arthritis, cirrhosis, chronic renal failure and heart failure, burns and sepsis are associated with IR. Pathologic IR, however, is regarded as the starting point for the cascade of disorders comprising MS [19, 52].

The underlying mechanisms of the decrease in sensitivity to insulin are not yet known. Scientists identify three causes of insulin’s

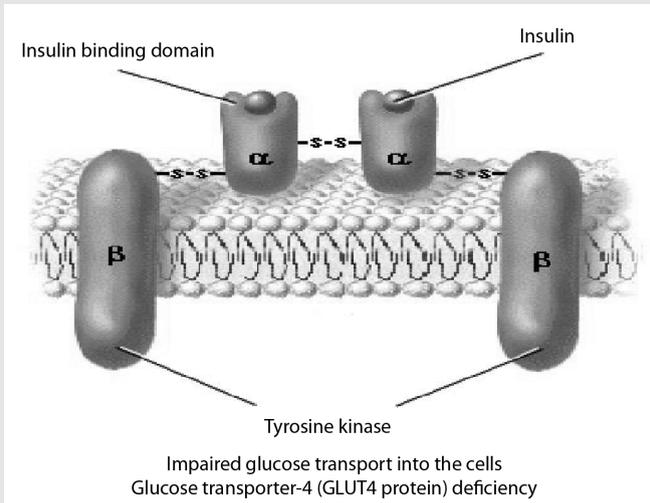


Fig. 7. The mechanism of IR on cellular level

failure to interact with target cells: prereceptor, receptor, or post-receptor abnormalities. The decline in the quantity of receptors or their affinity to insulin can be due to genetic predisposition as well as environmental factors (such as overeating, sedentary lifestyle, stress, smoking, alcohol abuse and hypoxia). Postreceptor abnormalities include impaired activity of transport proteins and enzymes (Fig. 7).

There are three insulin target tissues (skeletal muscle, adipose tissue and liver), each of them having a different type of IR development mechanism. Skeletal (striated) muscles are the main site for glucose utilization. Therefore insufficient insulin effect leads to impaired glucose intake and utilization. In the visceral adipose tissue apart from glucose utilization impairment, fat undergoes excess lypolysis due to the lack of the antilipolytic effect of insulin, which results in rapid release of free fatty acids.

In the liver insulin stimulates glycogen formation and decreases glucose production. Thus, IR leads to increased glucose synthesis, which is mostly due to gluconeogenesis rather than glycogen breakdown.

Unhealthy lifestyle (overeating, a diet high in animal fat and simple carbohydrates, sedentary lifestyle and frequent stress), i.e.

the prevalence of energy consumption over energy utilization in people with the “economic” genotype (in other words, with genetic predisposition), stimulates the deposition of fat around the abdominal region [53].

At this stage, IR is compensated by high enough insulin production, so there is no glucose utilization impairment seen. However, activation of the sympathetic-adrenal medullary system leads to a rise in cardiac output and heart rate, which cause vasoconstriction and increase in total peripheral resistance. Regular BP elevation also contributes to IR. Hyperinsulinemia stimulates reabsorption of sodium in the proximal and distal convoluted tubules, which results in fluid retention, elevated sodium and calcium levels in the blood vessels and their spasm [54].

Progression of IR/hyperinsulinemia contributes to impaired lipid metabolism. In addition to that, fats of the adipose tissue undergo lipolysis, which leads to the release of a high amount of free fatty acids into the blood flow and later to an increased production of very LDL-C that acts as an endogenous triglyceride transporter [55]. This process induces a line of changes in the lipid profile (elevation of LDL-C and drop in HDL-C).

MS may be present with no clear signs of carbohydrate metabolism impairment for at least 5 years. Hyperglycemia in MS develops because of IR progressing alongside decreasing insulin secretion, which leads to impaired glucose utilization. Additionally, constant high levels of free fatty acids result in increased glucose synthesis in the liver (gluconeogenesis) and compromise in glucose transporter function [56].

MS fully develops (with all its symptoms present) within at least 10 years. The development of MS leads to a rise in the levels of mediators of inflammation, increased thrombogenesis and endothelial dysfunction [57–60].

Obesity is the number one cause of metabolism disorders and diseases known as MS. The risk for the development of metabolism impairment and these disorders is highly dependent on the pattern of the fat deposition in the organism [61].

The deposition of fat in the abdominal region (AO) is particularly hazardous to health [62–63]. A frequent combination of visceral obesity, lipid and carbohydrate metabolism impairment, hypertension and a close pathogenetic connection between them led physicians to

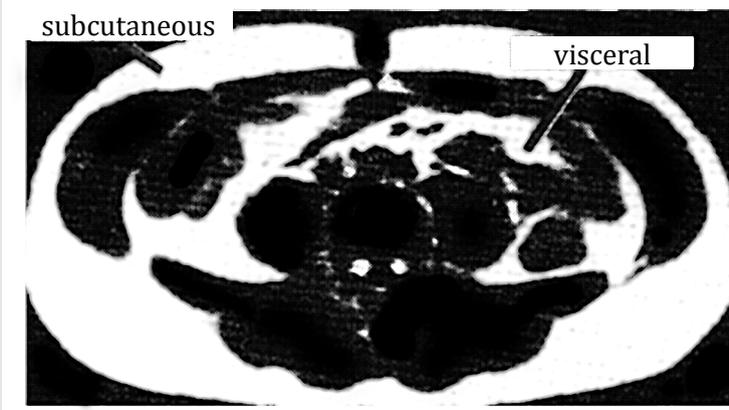


Fig. 8. MRI is an accurate method for evaluation of the contrast between visceral and subcutaneous fat deposition

regard them as a separate syndrome (Fig. 8). Abdominal (visceral) fat is composed of three components: omentum, mesentery and extraperitoneal fat.

In 1947, J. Vague was the first to see the link between the risk of obesity-associated diseases and the pattern of fat deposition. Author classified obesity into 2 types according to the localization of adipose tissue - android and gynoid obesity. J. Vague proved that people with android obesity are more likely to develop T2DM, hypertension and CVD.

Subsequent studies based on unified criteria for obesity pattern and risk for associated disorders assessment proved that AO is a stand-alone risk factor for dyslipidemia, carbohydrate metabolism impairment and hemostatic system dysfunction and that it is not dependent on the class of obesity [38,39,64].

The close link between AO and the risk of CVD development allows defining MS as a cluster of “metabolic” complications of obesity (Fig. 9).

Apart from being an energy depot, adipose tissue also functions as a stand-alone endocrine organ. Adipocytes synthesize hormones and other bioactive substances, including leptin, resistin, adiponectin, tumor necrosis factor-alpha, interleukins, PAI-1 and angiotensin.

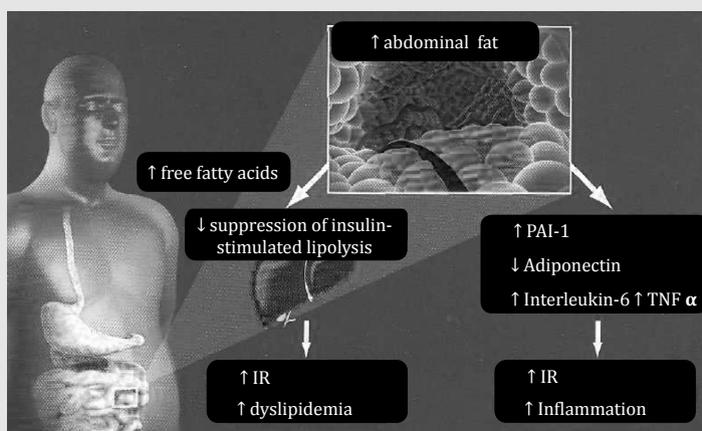


Fig. 9. The role of AO in the development of IR and cardiovascular risk

Leptin is a hormone that plays a key role in regulating appetite and satiation. Its function is to prevent obesity at times of excessive food intake by decreasing the effects of neuropeptide Y (a hormone that increases appetite and facilitates AO). However, in obese people with IR, leptin concentration rises and it loses the ability to regulate appetite. Resistin is secreted by adipocyte precursors; it stimulates IR development.

Tumor necrosis factor- α (TNF α) decreases the activity of insulin receptors and intracellular glucose transporters and in synergy with other cytokines (interleukins) aggravates IR.

Adiponectin has protective properties for it inhibits platelet adhesion and suppresses inflammatory cell proliferation and migration. There is also a distinct negative correlation between adiponectin levels and atherogenic lipid profile [65].

Thus, the combination of IR and chronic hyperinsulinemia triggers an array of disorders contributing to diabetes mellitus as well as clinical complications of atherosclerosis (Fig. 10).

The main stages of the cascade of metabolic syndrome continuum

Environmental and genetic factors incite a line of disorders that comprise the MS: lipid and carbohydrate metabolism impairment, hypertension etc. This raises a question of whether these disorders

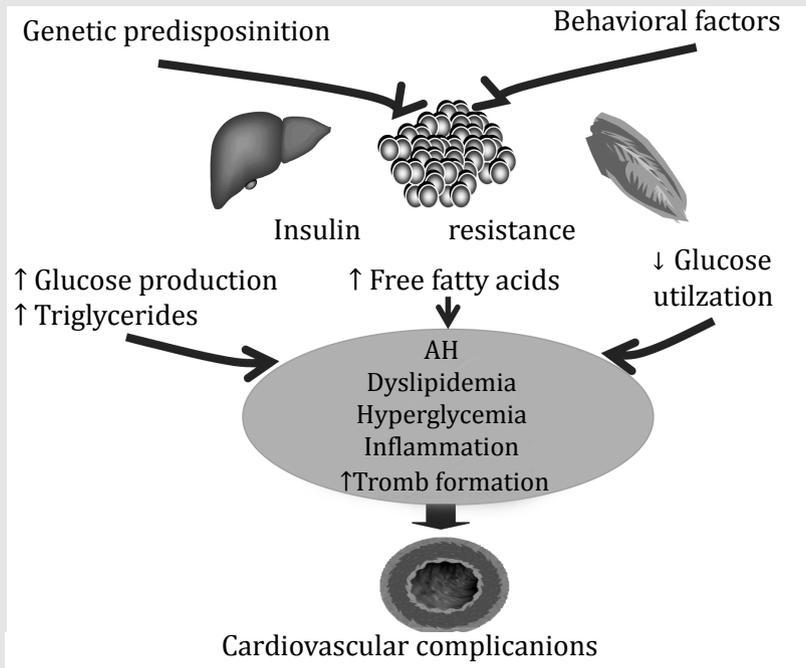


Fig. 10. The pathogenesis of MS

develop simultaneously. Or is there some kind of sequence? This is highly significant in early diagnostics and prompt prevention of MS complications.

In the 1990s, cardiologists coined a new term — “cardiovascular continuum” — that stood for a sequence of cardiovascular complications.

The results of several prospective studies including the one conducted within the National Research Center for Preventive Medicine, that monitored the sequence of metabolic disorders, allow us to work out the MS continuum. We certainly cannot claim that this sequence is true for all MS phenotypes; however, its classic type develops in this succession.

The first sign of MS — AO assessed by measuring waist circumference — becomes apparent at the age of 20–29. The patient may

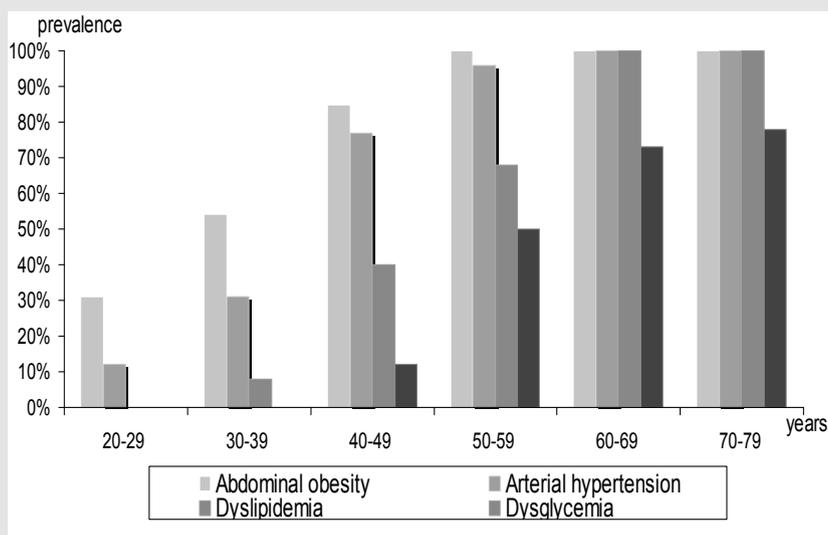


Fig. 11. The sequence of the metabolic disorders development

appear either overweight or obese. Some patients develop transient increase in BP. AO progresses through the later stages of life (30–39 years) along with BP elevation, which now becomes regular. At this age, mild lipid metabolism impairment may be seen which becomes more frequent at the age of 40–49. Progression of IR alongside decreasing insulin secretion, which leads to impaired glucose utilization, contributes to early carbohydrate metabolism disorders. Thus, 40–49 year-old patients with MS possess all of its main components that lead to subsequent complications. In other words, people over the age of 50 with MS are at increasing risk of CVD and T2DM. The sequence of the metabolic disorders development is shown in Fig. 11.

Chapter 5

CLINICAL MANIFESTATION OF METABOLIC SYNDROME

The difference in MS manifestation in various ethnic groups is an important element. These diversities are directly linked to traditions, lifestyle and genetic factors. This data may play a significant role in the discovery of the genetic defects that lead to the development of such a multicomponent syndrome with a high risk of atherogenesis [4, 21]. The review of literature offers the possibility of determining racial differences in the presentation of MS in the ethnic groups of Europe, America and Asia (Tab. 11).

The first studies represent a comparative analysis of two ethnic groups: the local peoples and citizens of European descent. In non-Hispanic Whites and European Canadians IR is closely connected to hypertriglyceridemia, hypertension and carbohydrate metabolism impairment with no signs of excessive body weight. In Canadian Indians and Mexican Americans, however, MS is linked to AO with no close correlation between IR and hypertension in Mexican Americans. It is note worthy that IR in Europeans is also associated with dyslipidemia, hypertension and T2DM without any link to AO. The French are different in that they develop AO and hyperlipidemia without hypertension. The Japanese study yielded quite intriguing results. Along with the usual MS components, IR is closely associated with coagulation factor VII activity and LDL-C levels. Similar results were obtained in Brazilians of Japanese descent. Moreover, researchers found a direct connection between the components mentioned above and visceral obesity [50].

Thus, the aforementioned data shows no universal pattern of MS manifestation in different populations. In some cases, metabolic

Table 11. Differences in the presentation of MS in different ethnic groups

Study	Ethnicity	Connection between IR and other components of MS
San Antonio Heart Study	Mexican Americans	AO, T2DM
	Non-Hispanic Whites	AH, normal weight, dyslipidemia
Canadian population-based MS study	Indians	AO, dyslipidemia, AH, hyperglycemia
	European Canadians	Dyslipidemia, AH, hyperglycemia
MS in the English and South Asians	Europeans (English)	Dyslipidemia, AH
	South Asians	Low levels of HDL-C, T2DM
MS in Finland	Finnish	T2DM, HTG, AH
The Paris Prospective Study	French	AO, HTG
The Jichi Medical School Cohort Study	Japanese	Excessive body weight, AH, hyperglycemia, coagulation factor VII and LDL-C

disorders “revolve around” obesity, in others the syndrome develops in people with normal body weight. There are groups without hypertension as the traditional component and there are groups with additional risk factors, such as elevated LDL-C levels. However, dyslipidemia (hypertriglyceridemia and low HDL-C) is a constant companion of IR in all populations. According to a Finnish researcher M. Laakso, dyslipidemia is a nucleus of MS [26].

A typical Russian patient with MS

Applied to a representative sample of the adult population, the NCEP ATP III criteria yielded 15 types of MS [34].

In general the majority of patients — 61.5% (n = 193), — have 3 MS components, 28.7% (n = 90) have 4 MS components and 9.8% (n = 31) have 5 MS components (Fig. 12).

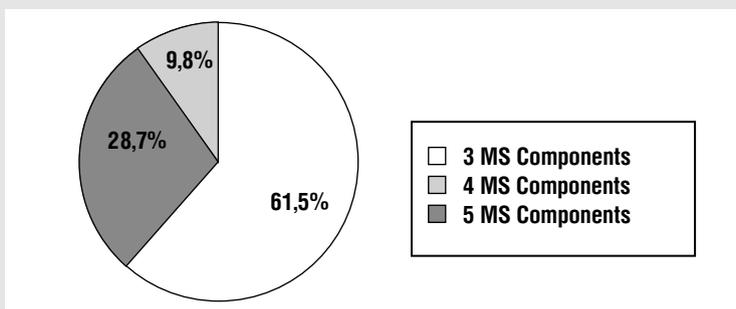


Fig. 12. Combinations of different MS components in a random sample of urban population

A 5-component MS is 3 times more likely to appear in females than in males. A combination of hypertension, AO and dyslipidemia is common in MS patients. However, 53% of males develop MS without AO (waist circumference < 102 cm), whereas in females (waist circumference < 88 cm) it is seen in 24.8% of cases.

In both males and females, hemodynamic and anthropometric measurements were taken in order to determine the distinctive features of MS presentation. These measurements included the body mass index (BMI), waist circumference, lipid profile and carbohydrate metabolism figures. Overall, the frequency of occurrence of MS components is as follows: 68.8% – low and HDL-C, 65.3% – HTG, 65% – AO according to NCEP ATP III criteria, 65% – AH and 45.2% – hyperglycemia.

Lipid metabolism disorders

About 80% of MS patients were shown to have one or another dyslipidemia types which is due to the high prevalence of low HDL-C levels, HTG and HC (Fig. 13).

The first parameters are among the main MS components while HC is considered an associated disorder.

Experts on MS define dyslipidemia as a lipid triad: elevated triglyceride level, increased quantity of small dense LDL-C particles and low HDL-C level [66].

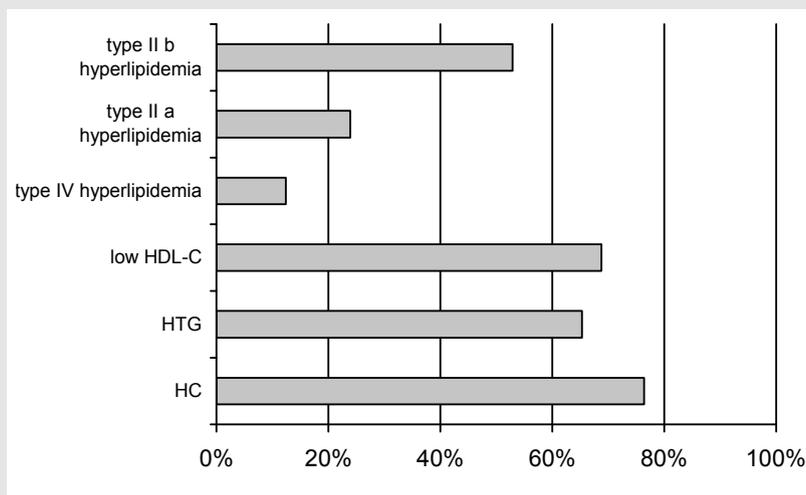


Fig. 13. Prevalence of different dyslipidemia types in MS patients

There is evidence that lipid metabolism impairment in patients with MS implies not only quantitative, but also qualitative changes [10]. Thus, according to W. T. Garwey et al., HDL and LDL-C particles are smaller and denser in patients with IR and T2DM than in those with intact carbohydrate metabolism. IR and T2DM are also associated with bigger very LDL-C particles (Fig. 14).

With our study being epidemiologic, we did not have an opportunity to do the qualitative evaluation of LDL-C particles.

It is note worthy that 77% of patients with MS were diagnosed with different types of HC with the majority having mild HC. Moderate and severe HC was found in 20% and 6% of patients respectively. This is true for both sexes. Only 33% of males and 18.6% of females have normal cholesterol levels. Thus, HC is the most common disorder among the main disorders of the lipid profile.

Hypertriglyceridemia was diagnosed in 65.3% of MS patients. It was present in 74% of males and 61.3% of females. Every third MS patient (33.7%) had mild HTG, 26.7% had moderate HTG and 4.8% had severe HTG. The comparative analysis showed no gender differences in HTG.

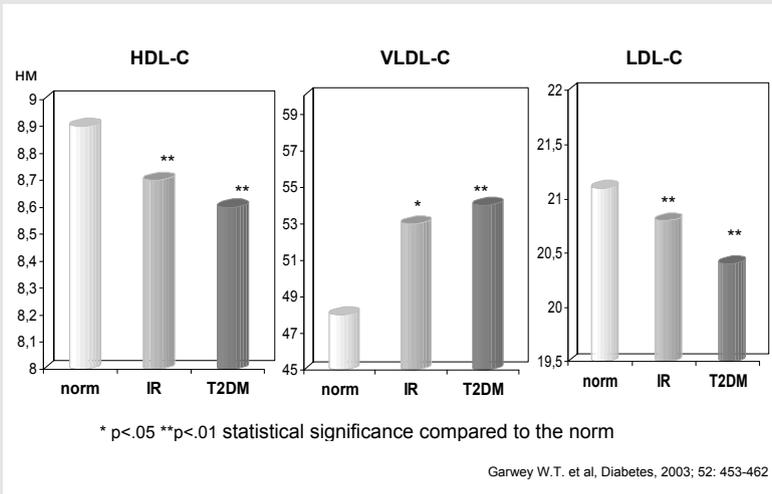


Fig. 14. IR and lipoprotein particle size

Low HDL-C level was diagnosed in 68.8% of MS patients. It was more common in males (81.8%) than in females (63.7%). Thus, normal HDL-C level is two times more common in females with MS than in males — 36.35% and 18.2% respectively ($p < .01$).

The frequency of hyperlipoproteinemia phenotype in MS patients was also studied. The majority of MS patients — 52.9% — had combined (type IIb) hyperlipoproteinemia (HC and HTG). Type IIa (HC and normal triglyceride level) came second and type IV (isolated HTG) was found in 12.4% of MS patients. Type IV hyperlipoproteinemia was two times more common in males (20.4%) than in females (9.3%), $p < .02$. However, type IIa hyperlipoproteinemia was more often diagnosed in females (28.8%) than in males (11.4%), $p < .008$.

The previous studies done by National Research Center for Preventive Medicine showed that the level of apolipoprotein B (the primary carrier of LDL-C and VLDL-C) is 50% higher in MS patients than in patients with hypertension without MS. Despite the fact that apolipoprotein A1 (the carrier of HDL-C) levels are equal in both groups, the atherogenic index (ApoB/ApoA1 ratio) was statistically higher in patients with MS.

Overweight and obesity in patients with metabolic syndrome

Taking into consideration controversial approach to the problem of obesity, we have analyzed several questions regarding prevalence and extent of obesity in people with MS.

Generally, in our sampling, 19.5% of males and 12.8% of females with MS have normal body weight. Among males with MS more than a half (57.9%) are overweight, I class obesity is diagnosed in 21.6%, II class obesity in only 1.1%, no patients with class III obesity. The picture is slightly different in females. Only every third female is overweight (31%), whereas obesity class I and class II is diagnosed in 39.4% and 14.6% of females respectively. Obesity class III is diagnosed in 2.2 % of females with MS.

Is manifestation of MS possible without AO?

Applying strict criteria of AO, we revealed that 13% of patients with from MS suffer from all its symptoms, having waist circumference less than 94 cm in males and 80 cm in females. In other words, these patients suffer from MS, manifesting a combination of lipid and carbohydrate metabolism impairment and hypertension, but without AO fulfilling either NCEP ATP III or IDF criteria.

Among people with normal body weight, 50% have normal waist measurements, 50% have AO meeting the IDF criteria (waist circumference ≥ 94 cm for males and ≥ 80 for females) and 26% have waist measurements meeting NCEP ATP III criteria (waist circumference ≥ 102 cm for males and ≥ 88 cm for females).

Among overweight patients suffering MS 14.9% have normal waist measurements, 84.1% have waist circumference meeting the IDF criteria of AO, and 47.9% are meeting NCEP ATP III criteria of AO.

Patients with MS and obesity class I have normal waist measurements in 2% of cases, 98% are diagnosed with AO meeting the IDF criteria and 88.9% of MS patients have AO meeting NCEP ATP III criteria. Practically all females with MS and obesity class 2 and class III have waist circumference > 88 cm.

It is interesting, that every second patient with MS and normal body weight according to the IDF criteria, has normal waist measurements. 15% among overweight people with MS and 2% of obese people don't meet the IDF criteria of AO.

In whole, body mass increase is associated with AO in both males and females with MS (Table 12). However, in some cases MS is not connected with AO.

Table 12. **Overweight and obesity in people with MS**

Anthropometric measurements	Males n = 88		Females n = 226	
	abs. number, %	Waist circumference	abs. number, %	Waist circumference
Normal body mass	17 (19,5%)	normal - 12 > 94 cm - 3 > 102 cm - 2	29 (12,8%)	normal - 11 > 80 cm - 8 > 88 cm - 10
Overweight	51 *** (57,9%)	normal - 14 > 94 cm - 22 > 102 cm - 15	70 *** (31%)	normal - 4 > 80 cm - 23 > 88 cm - 43
Obesity I class	19 ** (21,6%)	normal - 2 > 94 cm - 5 > 102 cm - 15	89 **** (39,4%)	> 80 cm - 8 > 88 cm - 81
Obesity II class	1 (1,1%)	> 94 cm - 1	33 (14,6%)	> 88 cm - 33
Obesity III class	-	-	5 (2,2%)	> 88 cm - 5

p < .001, *p < .0004 — reliability of differences in comparison with the first group.

We take a concept, that AO is a significant component of MS, yet, in some cases MS can be accompanied by normal waist measurements in both males and females.

Hypertension in MS patients

For primary care physician hypertension is considered a “bait” for diagnosing MS. [67, 68]. BP analysis among people with MS diagnosed using NCEP ATP III criteria, demonstrates that only 12% of patients have normal BP. Normal high BP was detected in 22.6% of patients

with MS. In 37.5% of MS patients stage I hypertension was revealed, In 22.6% — stage II hypertension, while stage III hypertension was revealed in 4.4% of patients.

Overall, such trend was noted in both males and females. Therefore, there are no gender differences in degree of hypertension among people with MS (Fig. 15). Moreover the majority of people with MS has stage I hypertension.

Previous clinical trials conducted by National and Research Centre for Preventive Medicine demonstrated two hemodynamic peculiarities within the framework of MS.

Firstly: patients with MS show impaired daily BP profile due to absence of night systolic and diastolic BP decrease (Fig. 16). In other words, patients with MS are non-dippers [69]. It is combined with high values of pulse pressure, which indicates increased rigidity of large arterial vessels.

Correlation analysis of IR and 24-hour BP monitoring parameters revealed statistically significant connection between IR and mean diurnal, daily and nocturnal systolic BP, as well as mean nocturnal diastolic BP. At the same time correlation with daily and nocturnal time index for systolic BP was detected.

Secondly, patients with MS were noted to have structural and functional changes in cardiac muscle [70–72]. It appears as concentric myocardial hypertrophy with left ventricular mass increase, with normal cardiac output and increase of total peripheral vascular resistance (Fig. 17). At the same time there is reliable correlation between hyperinsulinemia/IR and myocardial mass, left atrium size, end-systolic and diastolic dimension and volume, cardiac output and total peripheral vascular resistance.

Carbohydrates metabolism disorders and metabolic syndrome

One of the MS manifestations is early disorders of carbohydrate metabolism: impaired fasting glycemia (IFG) and impaired glucose tolerance (IGT).

According to the epidemiologic studies, number of patients with pre-diabetes is twice higher than with T2DM [73, 74]. According

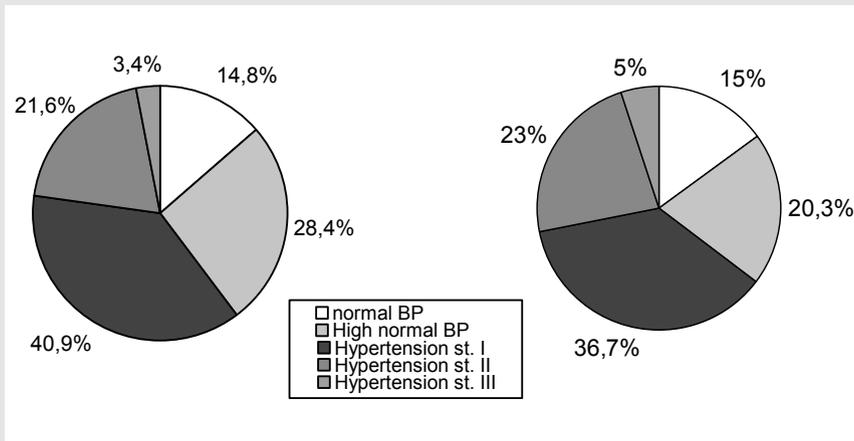


Fig. 15. Hypertension in males and females with MS

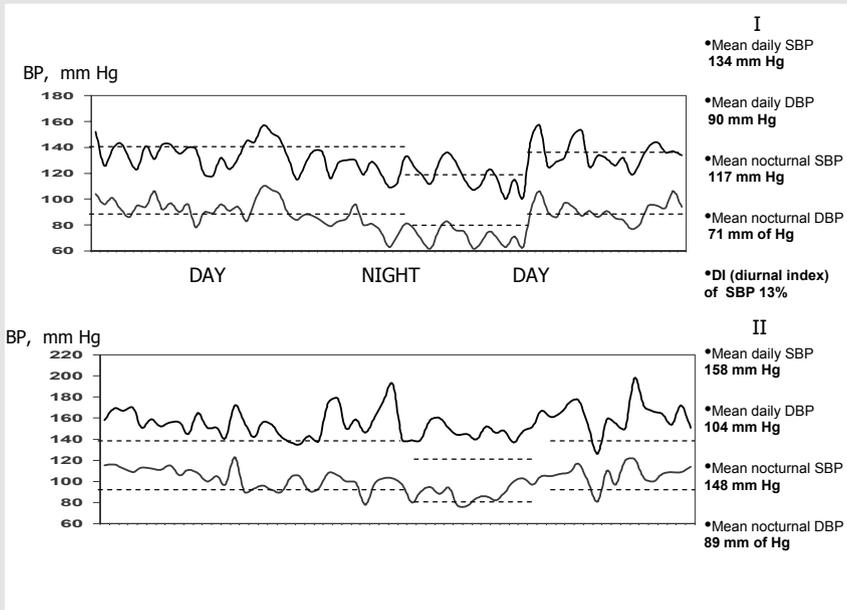


Fig. 16. 24-hour blood pressure monitoring data in patients without metabolic risk factors (I) and in MS patients (II)

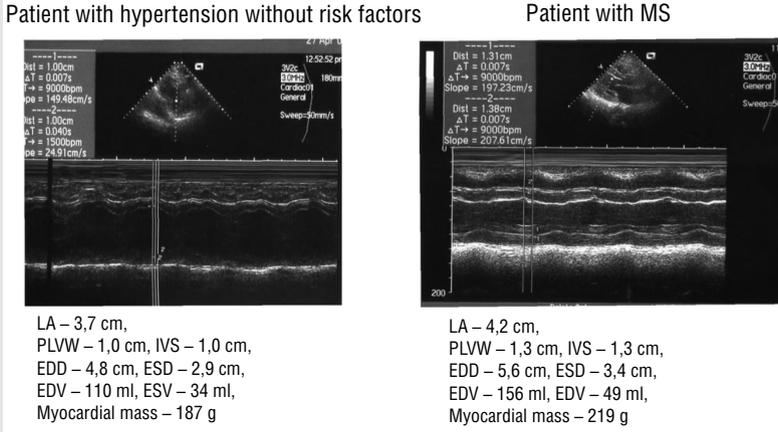


Fig. 17. Echocardiogram showing structural and functional changes in myocardium of a MS patient

to prospective studies annual conversion of pre-diabetes to T2DM reaches from 1.5% to 7.3% in different countries [75]. Conversion of pre-diabetes to T2DM depends on various factors: lifestyle, social status, other risk factors of CVD and T2DM [76]. On the other hand,

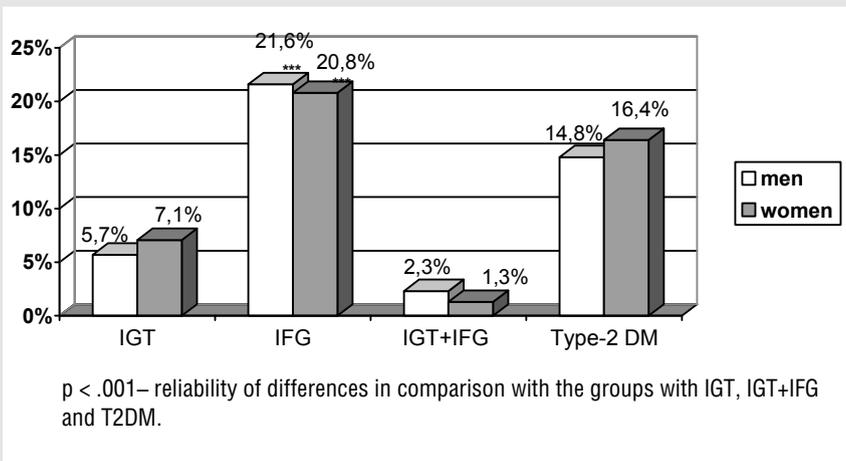


Fig. 18. Hyperglycemia in males and females with MS

it is well known, that patients with IGT have 1.32 times higher risk of cardiovascular complications over those, who have normal blood sugar level [77].

According to the study design, all respondents underwent OGTT to reveal various disorders of carbohydrate metabolism, including their early manifestations. It was shown, that among people with MS every third has pre-diabetes (29%), that is twice higher than T2DM cases — 15.9% ($p < .0001$). Among people with early carbohydrate metabolism disorder the majority had high fasting glycemia — 20.8%, while glucose tolerance impairment was diagnosed in 6.6% of patients and combination of glucose tolerance impairment and high fasting glycemia took place in 1.6% of cases (Fig. 18). It is true for both males and females; moreover, there are no statistically significant differences. In other words, early disorders of carbohydrate metabolism in MS occur with equal frequency in both males and females.

Chapter 6

ROLE OF METABOLIC SYNDROME IN DEVELOPMENT OF CARDIOVASCULAR DISEASES AND TYPE 2 DIABETES MELLITUS

Another one important aspect of MS is an opportunity to study its atherogenic potential, or more precisely, to estimate risk of atherosclerosis complications.

In theory, combination of just two or more risk factors increases risk of cardiovascular complications, in comparison with the impact of one factor. However, the crucial difference between combination of factors and MS lies in the fact that factor combination around IR forms vicious circle, where factors potentiate each other.

In the 1990s National Research Centre for Preventive Medicine did a comparative study of total risk of CHD complications in 8 years in patients with different risk factors (I group- isolated hypertension, II group-combination of hypertension and HC, III group- MS without T2DM, IV group- MS with T2DM). For this purpose one of the three risk assessment scales was used- computerized program PROCAM (Germany), which considers occurrence and intensity of 10 factors: 7 modifiable (BP, total cholesterol, TG, HDL-C – high density lipoproteins, T2DM, smoking, angina) and 3 non- modifiable risk factors (age, family history and history of myocardial infarction). Risk level graduation is assessed as follows: low coronary risk for value <20%, high or dangerous level for value > 20%. It occurred that patients with MS had 6 times higher risk of CHD complications development, then in group of hypertensive patients without other risk factors, and 2 times higher, then in group with hypertension and HC (Fig. 19) [79].

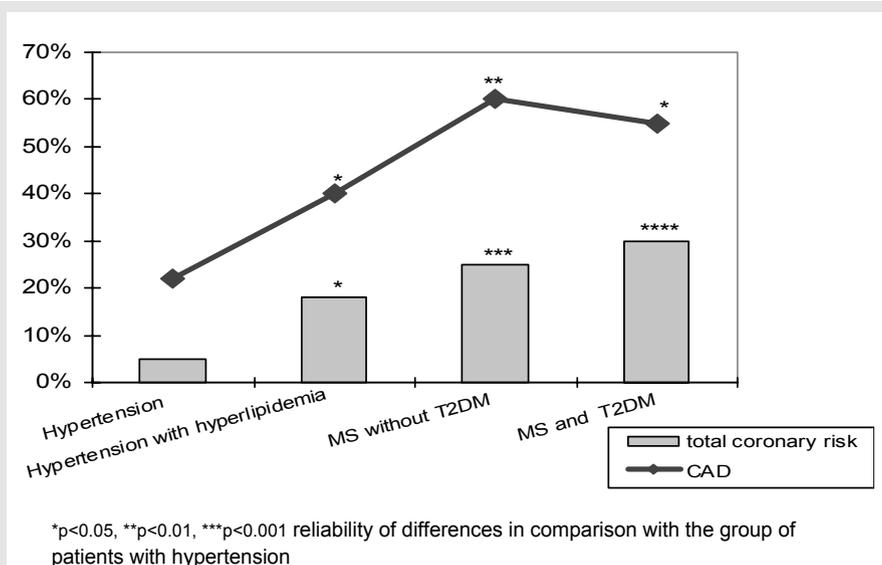


Fig. 19. Total coronary risk (PROCAM model) and CHD in patients with MS

The series of single-stage clinical trials show a correlation between MS and acute coronary syndrome.

For example, among patients with myocardial infarction MS was revealed in 39% of cases, where 10% were females [80]. Statistically significant correlation was discovered between MS and left ventricular ejection fraction, frequency of shock condition, arrhythmia, and heart failure ($p < .05$).

E. Rodrigues et al. did a study to reveal MS among patients with acute coronary syndrome [81]. It was shown, that according to NCEP ATP III criteria MS can be diagnosed in 49.5% of patients with acute coronary syndrome (60 % of females and 46.2% of males), while according to the IDF criteria MS was diagnosed in 50.1% of cases (67.1% of females and 45% of males).

In 2004, the results of international INTERHEART study (52 countries, 29972 participants) were published, where the relationship between 9 risk factors (and their combination) and development of myocardial infarction was estimated. It turned out, that MI developed

twenty times more often in patients with combination of dyslipidemia, hypertension, T2DM and obesity over patients with only one factor, and two times more often in patients, having combination of the first three risk factors [82].

One of the main tasks of Russian epidemiologic study, conducted in Cheboksary was to discover the association between MS and CVD disease of atherosclerosis origin and T2DM. With these purpose comparison study of association between MS, diagnosed through both criteria, and the prevalence of CVD disease, resulting from atherosclerosis and T2DM, was done [34].

Generally, every third respondent with MS has some or other clinical features of atherosclerosis (Table 13). In particular, among people with MS, diagnosed through NCEP ATP III criteria, CHD and exertional angina are diagnosed in 23%, cerebral atherosclerosis in 31%, atherosclerosis obliteration in 8%. According to available medical documents, history of myocardial infarction or stroke had 7.6% and 3.5% of patients with MS respectively. Mean prognosticated risk of cardiovascular complications according to SCORE scale makes around 5% among males that exceeds 1.5 times the same mark in females.

Similar analysis of relationship between CVD of atherosclerotic origin and MS diagnosed according to the IDF criteria, shows that CHD and exertional angina are diagnosed in 22% of MS cases, cerebral atherosclerosis in 29 %, atherosclerosis obliteration in 6% patients with MS. For males suffering from MS, total cardiovascular risk is reliably higher than in females.

Table 13. Association of MS with clinical features of atherosclerosis and T2DM

Clinical features of atherosclerosis and T2DM	MS diagnosed by NCEP ATP III criteria n (%)	MS diagnosed by IDF criteria n (%)
CHD, stable angina	72 (22,9%)	97 (21,7%)
Myocardial infarction	24 (7,6%)	26 (5,8%)
Peripheral atherosclerosis	25 (8%)	27 (6%)
Cerebral atherosclerosis	98 (31,2%)	130 (29%)
Stroke	11 (3,5%)	19 (4,2%)
T2DM	50 (15,9%)	50 (11,2%)

**Table 14. Metabolic syndrome – strong predictor of cardiovascular events
Botnia Study**

Independent variability	CHD (n = 2 401)		MI (n = 2 404)		Stroke (n = 2 395)	
	RR	P	RR	P	RR	P
MS	2,96	<0,001	2,63	<0,001	2,27	<0,001
Obesity	1,44	0,07	1,31	0,43	1,26	0,59
Dyslipidemia	1,73	<0,001	1,71	0,01	1,30	0,40
Hypertension	1,57	0,002	1,31	0,22	1,34	0,34
Microalbuminuria	0,94	0,77	0,76	0,37	0,85	0,73
IR	1,53	0,01	2,02	0,009	1,39	0,36

There are few literary data about cause-effect relations between MS and CHD. Thus in Kuopio Ischemic Heart Disease Risk Factors Study 14.3% among 1209 males aged 42–60 years were diagnosed with MS. During 11 years of follow up period, 109 lethal cases were registered, among them 46 due to CVD and 27 due to CHD. According to the results of this study it was concluded that CHD development risk is 2.9–4.2 times higher among patients with MS, CHD mortality rate – in 2.6–3.0 times and all death causes in 1.9–2.1 times higher than in patients without metabolic disorders [83].

According to B. Isomaa, cardiovascular complications risk in patients with MS is twice higher than in patients with dyslipidemia, hypertension and obesity (Table 14) [84].

In the prospective ARIC study, it was shown that in patients with MS (23% of population) incidence of MI was twice higher than in control group (1.92 in males and 1.52 in females) [85]. H. Lakka et al. demonstrated during a prospective study, that among people with MS mortality due to CVD is 3.5 times higher than in the group of people without MS (Fig. 20) [83].

T2DM, as well as CVD, is considered a MS complication. I. Saely et al. presented an interesting clinical study with prospective follow-up, which demonstrates advantage of NCEP ATP III criteria in T2DM prediction [86]. Among 503 patients who underwent coronarography and doesn't suffer T2DM, episodes of T2DM were monitored during

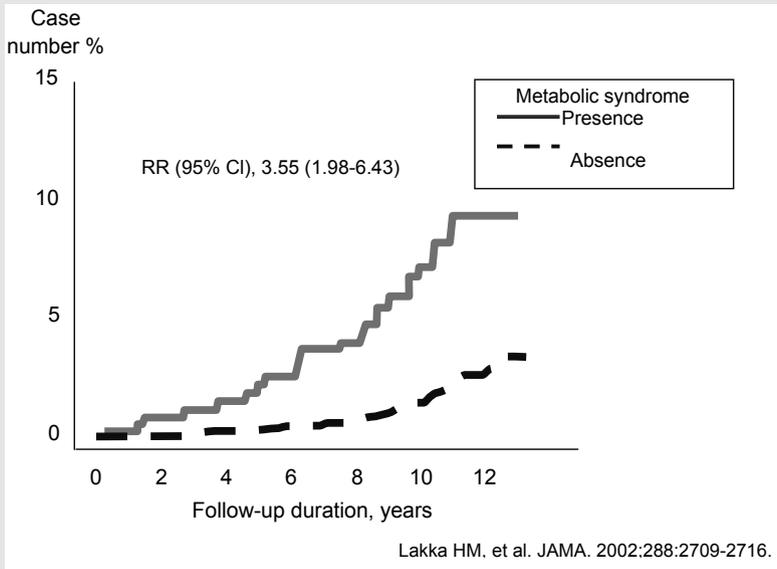


Fig. 20. Mortality resulting from cardiovascular disease

6 years. Initially 28.6% of patients had MS according to NCEP ATP III criteria, while using the IDF criteria? MS was diagnosed in 40.6% of cases. During the follow-up period T2DM was diagnosed in 17.1% of patients. NCEP ATP III criteria proved to be better T2DM predictor, than the IDF criteria (RR 3.55 against 2.13 $p = .002$)

In the Russian epidemiologic study, association between MS and T2DM was also estimated. Among patients with MS, diagnosed through ATP III criteria, T2DM was revealed in 16% of cases, while using the IDF criteria, T2DM was diagnosed in 11% of MS patients. The comparison study of association between MS (meeting both criteria) and T2DM didn't reveal statistically significant difference [34].

American scientist S. Haffner conducted meta-analysis of three prospective studies (IRAS, MCDC and SAHS) of 5–7 years duration, where episodes of T2DM development in different groups with metabolic disorders and pre-diabetes were monitored (Fig. 21). The group I consisted of apparently healthy people, patients in the group II had MS with normal glucose tolerance, patients in the group III had IGT

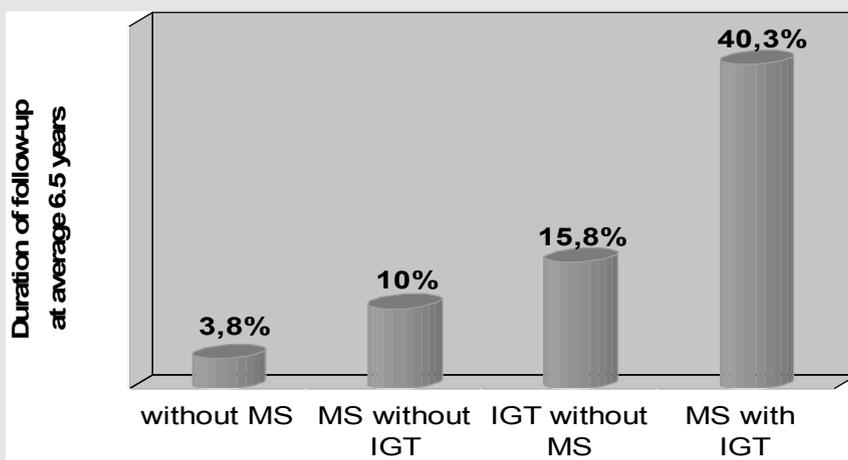


Fig. 21. T2DM development in patients with MS

without other metabolic disorders and group IV patients had IGT and MS [46].

It occurred that the highest risk of T2DM development in the nearest 5 years — 40% was in group with MS and pre-diabetes, that is 2.5 times higher, than in group of pre-diabetes without MS. Patients with normal glucose tolerance, but having other elements of MS had 3 times higher risk in comparison with apparently healthy people.

In meta-analysis represented by G. L'italien et al. was shown that in 256 prospective studies involving patients with MS, relative risk of T2DM development is RR 4.80 (4.17–5.52), CHD RR 1.60 (1.52–1.69), CVD RR 1.66 (1.57–1.75), all lethal cases RR 1.29 (1.24–1.34), stroke RR 1.63 (1.50–1.78). Authors conclude, that MS is an independent predictor of new cases of T2DM and CVD of atherosclerotic origin.

There by, MS patients, in comparison with people having separate risk factors (as well as combination of 2 factors), are at higher risk of CVD due to atherosclerosis (myocardial infarction and stroke), and T2DM, that finally lead to early disability (which means loss of life quality) and increase of lethal and non-lethal complications among adult population.

Chapter 7

METABOLIC SYNDROME

AS MULTI-DISCIPLINARY DISORDER

In the 90-s years of XX century MS was in the sphere of interest of cardiologists and endocrinologists. For today MS is studied like an interdisciplinary problem, which has its significance in rheumatology, gastroenterology, gynecology, urology and neurology [88, 89]. Literary sources has accumulated a lot of data on cause-effect relations between MS and non-alcoholic fatty liver disease (NAFLD), gout, polycystic ovarian syndrome in females, erectile dysfunction and hypogonadism in males.

Non-alcoholic fatty liver disease and metabolic syndrome

In 90-s years it was widely believed, that NAFLD liver disease is one of the clinical manifestations of MS [90]. NAFLD (also known as steatorrheic hepatitis or steatosis hepatitis) is characterized by intra- or extracellular deposition of fat droplets. This disease appears as metabolic disorder secondary to diverse intoxications, unbalanced diet or endogenous metabolic disorders that include T2DM and/or obesity [91].

According to L. Zvenigorodskaya et al. among 140 patients with NAFLD in 55.7% of cases was revealed impaired glucose tolerance and in 10% of cases, T2DM in combination with other metabolic disorders, while in 34,3% of patients there was no IR. It was shown that steatohepatitis activity and extent of liver fibroses increases with the increase of IR. Administration of antihyperglycemic drug-metformin decreases intensity of cytolytic and cholestatic syndromes and reduces liver structural changes.

Gout and metabolic syndrome

Gout is characterized by elevated levels of uric acid in the blood, retention of uric acid crystals in limb joints and kidneys damage. Prevalence of gout in population is low-0.4% and it occurs more often in middle-aged males. Hyperuricemia and gout are considered significant risk factors of CVD. Gout patients in 80% of cases suffer obesity, hypertriglyceridemia, hypertension and in some cases T2DM, that implies its association with MS.

At the beginning of the 20th century, the association between AH, T2DM and hyperuricemia was described by Swedish scientist E. Kylin [13]. E. Tareev, a Soviet scientist, wrote that AH is closely related to arthritic triad, which includes obesity, gout and T2DM, and to other manifestations of arthritic diathesis. Analyzing a group of investigations, Cannon et al. report that hyperuricemia may be diagnosed in 22–28% of patients with hypertension. According to M. Modan et al. hyperuricemia in patients with AH is associated with AO and IR [10]. Strong correlation between blood levels of cholesterol and thyroglobulin, body-weight index and uric acid level was discovered in the epidemiological study done in the National Research Center for Preventive Medicine [34].

According to our data, average uric acid levels in people with MS were higher than those in patients with AH but without MS. About 30% of patients with MS and high cardiovascular risk have elevated levels of uric acid in their blood. Manifestation of MS may be connected with purine metabolic disorder in the pentose phosphate pathway oxidation of glucose. In recent years, the Nephrology and Occupational Diseases Clinic obtained the data on probable impact of hyperuricemia on specific renal urate lesion, which additionally worsens the prognosis of AH, hyperlipidemia and T2DM.

Polycystic ovary syndrome and metabolic syndrome

Polycystic ovary syndrome is characterized by increased production of androgen in the thecal cells, which disrupts follicular growth and promotes follicular cyst atresia. Majority of scientists consider

polycystic ovary syndrome to be endocrine disease which is tightly connected with IR. Females with polycystic ovary syndrome are likely to have menstrual dysfunction, enlarged ovary and be infertile. Obesity, dyslipidemia and future impaired glucose tolerance may be detected as well. Females with polycystic ovary syndrome are 7 times more likely to have MS, T2DM and CHD than females of major population. It would be interesting to know that parents of patients with polycystic ovary syndrome have MS in 62% of cases. According to prospective study, polycystic ovary syndrome is a risk factor of metabolic imbalance and CVD. T. Sir-Petermann reports that females with polycystic ovary syndrome are 1.89 times more likely to have T2DM than healthy females, 60% of them had IR [92].

Erectile dysfunction and metabolic syndrome

The US National Institutes of Health gives following definition: erectile dysfunction (ED) is the inability to achieve or sustain an erection suitable for sexual intercourse. This term replaced old one – “impotence” [93]. This is a problem of medical and social value and it has influence on both life quality and fertility of males in reproductive age. In recent years it was called interdisciplinary problem, barometer of men’s health and iceberg of system vascular pathology [94]. There are 150 million males suffering from this disease in the world, 34 million of them are in the USA.

In practice CVD (such as atherosclerosis, AH, T2DM, hormonal disorders, chronic kidney disease, chronic obstructive pulmonary disease etc.) turn to be the main cause of erectile dysfunction (about 80%). Also contribute to ED such factors as smoking, alcohol abuse, hypodynamia and certain medication (antihypertension drugs, antidepressants, tranquilizers, narcotic drugs, H2-blockers, hormone drugs). Prevalence of ED in males with CVD (AH, CHD, T2DM) is high. As a whole, such risk factors as AH, HC, depression and T2DM are twice more likely to be found in males with ED than in males without ED [93].

In recent years the relationship between MS and ED is widely discussed. According to S. Gamidov, 51,2% of patients with MS have ED while 46,4% of patients with ED have major components of MS. MS is conducive to severe clinical course and early manifestation of

ED. The most important components of MS affecting erectile function are IR/ hyperinsulinemia, hypertriglyceridemia and T2DM [95]. Major pathogenetic mechanism of ED in patients with MS is lesion of arterial perfusion of cavernous body caused by endothelial dysfunction which is combined with neurogenic (42% of cases) and hormone (36% cases) disorders. Neurogenic ED in patients with MS is induced by lesions of somatic and vegetative innervation of penis [88]. Experts consider that treatment of ED in patients with MS should be complex and include (besides specific therapy) methods of correction of metabolic, neurological and hormone disorders [93–95].

Age-related androgen deficiency and metabolic syndrome

Hypogonadism is deficiency in gonadal production of testosterone in males followed by appropriate symptoms. It is a condition of depressed testosterone secretion that can be caused by disorders on different levels of hypothalamic-pituitary-gonadal system. Hypogonadism may be congenital or acquired. In 2005 the new term “age-related hypogonadism” which is characterized by gradual decrease of testosterone production was suggested by the International Society for the Study of the Aging Male. Certain pathologic conditions and chronic diseases may accelerate this process. It was revealed that probability of hypogonadism detection was significantly high in males with following somatic diseases or disorders: AH (1.84), hyperlipidemia (1.47), T2DM (2.09), obesity (2.38), prostate diseases (1.29) and obstructive lung disease (1.40) [88].

According to the data presented by U. Pagotto et al, patients with hypogonadism have significant expression of antigenically responsive insulin and markers of IR as compared with group of males with obesity and with normal weight. Positive correlation between testosterone levels and metabolic risk factors was discovered by San Antonio Heart Study in the studies on T2DM and CVD. High testosterone level was associated with low index of atherogenicity and insulin concentration [96].

In recent years, new studies showed that high level of testosterone improves insulin-stimulated glucose utilization and decreases risk of

MS appearance. Protective effect of testosterone does not depend on changes of obesity markers. Number of clinical studies proved that course of treatment with injective form of testosterone undecanoate promotes positive metabolic effects. Specifically normalization of total testosterone level was connected with significant reduction of IR risk in 24 males over 30-years-old with T2DM and testosterone levels under 12 nmol/L. Hormone replacement therapy decreases insulin requirement by 7 ± 1.9 units per day on average. Also reduction of waist circumference 6 cm and considerable 50% lessening of TG and 20% lessening of low density lipoprotein cholesterol blood concentration were registered [97].

Chapter 8

METABOLIC SYNDROME IN CHILDREN AND ADOLESCENTS

Nowadays MS more and more often manifests itself in children and adolescents because of growing epidemic of obesity in young population [98]. During the recent twenty years, strong growth of MS prevalence among adolescents and young people was registered [99]. In 1994–2000, the prevalence of MS in children and young people grew from 4,2 to 6,4% according to American data [100].

One of the major MS predisposing factors is fetal development events and factors of early childhood development. Maternal gestational diabetes, low birth mass and artificial feeding of infant also increases child's risk of metabolic disorders. The genetic and socio-economic factors and environment promote further weight gain. At the same time urbanization, unhealthy diet and sedentary life (impact of which is growing) result in further rise of predisposition to childhood obesity especially in developing countries [101].

WHO reports that in 2004, about 22 million of children under 5-yers-old were overweight or had obesity. According to report of International Obesity Task Force at least, 10% of schoolchildren (total 155 million children) between 5 and 17 are overweight. About 30–40 millions of them (2–3% of schoolchildren aged between 5–17 years all over the world) have obesity. In the USA, part of children between 6 and 18 with excess weight or obesity grew from 15% (1970) to 25% (1990) [120]. According to data of Professor E. Volkova et al., 21,5% of Chelyabinsk students between 18 and 22 (group of 543 students was analyzed) are overweight [103].

Early detection of obesity is critically important because of its influence on health and mental and social development of children.

On the other side obesity treatment is a hard work and much effort is needed to keep normal weight. Also in a number of studies it was shown that excess weight and obesity detected in children trends to persist in adults. Nearly quarter of overweight adolescents and more than a third of overweight children stay fat when they grow up [104, 105]. The Russian prospective study showed that excess weight in teenage boys is an independent predictor of AH and dyslipidemia in adult life. Serum levels of LDL-C and TG are in direct relation with atherogenic index while level of LDL-C is in reverse correlation with body mass and its lipid component in early teens, as well as with further changes in the parameters. In general, children's obesity also influences on the increase of morbidity and mortality [101, 104].

Experts forecast that present generation may become the first one to die before their parents if no measures are taken [106].

Preconditions for designing a universal diagnostics of metabolic syndrome

Until recently there were no diagnostic criteria for children and adolescents. The emergence of new criteria for MS detection promoted introduction of new diagnostics of MS in children and adolescents. Cut-off points of major components of MS in children, which were designed using similar indexes of adults, are presented in Table [102].

New methods of MS diagnostics can be easily introduced in clinical practice. AO in children and adolescents (as well as in adults) diagnosed by waist circumference measurement is the major component of MS being an independent predictor of IR, lipid metabolism disorders and AH.

Moreover, young people with excess weight and consequently increased BMI, with high level of calculated visceral adipose tissue and increased waist-hip ratio, have lower insulin sensitivity than people with normal indexes. However, universal correlation of MS diagnostics in adults and in children is problematic.

Present methods of diagnostic (including analysis of gender and ethnic peculiarities of adults) turned to be inappropriate in children and adolescents. Levels of AH and lipids, BMI, size and proportions change with age and development. On the other hand, puberty influences greatly on adipose tissue distribution, insulin sensitivity and

insulin secretion. The same cut-off points cannot be used for children and adolescents. Experts came to conclusion that in cut-off points design preference should be given to percentage but not absolute value of waist circumference. This makes it possible to decrease fluctuation inaccuracy owing to children development and ethnic differences.

In different studies values of 90th, 95th or 97th percentiles for age and sex were used. It was proved that the value of 90th percentile in waist circumference assessment is significantly more often associated with risk factors of cardio-vascular diseases than lower levels [101].

Diagnostic criteria of metabolic syndrome in children and adolescents

In new diagnostic methods suggested by IDF, cut-off points of MS components are divided into 3 age groups: 6–10, 10–16, 16 and older. Age group under 6 years was not taken into account because of data deficiency. AO is a key factor in each of the three age-group categories (Table 15).

The IDF experts recommend to diagnose MS in children over 10 years. But weight-loss measures are to be taken in case of obesity in a child under 10 years [99].

Thus MS can be diagnosed in children of 10 years and upwards basing on AO and if there is two or more components (HTG, low level of HDL-C, AH or serum glucose level growth).

If the necessary data are unavailable, criteria are taken into account according to absolute MS diagnostics parameters in adults recommended by IDF, with the exception of recommended waist circumference. HDL-C test is done instead (regardless of sex).

Recommendations for prevention and treatment of metabolic syndrome in children and adolescents

Early detection and treatment tactics is an effective method to slow down MS progression and to improve health status of children and adolescents in general [102].

Table 15. The IDF consensus on diagnostics of MS in children and adolescents

Age groups (years)	Obesity (waist circumference)	Triglycerides	HDL-C	BP	Glucose (mmol/L) or diagnosed T2DM
6–<10	≥90 th percentile	MS is not diagnosed. Need further measuring in case of hereditary load of T2DM, dyslipidemia, CVD, AH and/or obesity.			
10–<16	≥90 th percentile if lower than adult criteria should be used	≥1,7 mmol/L (≥150 mg/dL)	<1,03 mmol/L (<40 mg/dL)	SBP ≥130/ DBP ≥85 mmHg	≥5,6 mmol/L (If ≥5,6 mmol/L or T2DM OGTT is recommended)
16+	AO (waist circumference ≥94 cm in males and ≥80 cm in females) combined with two or more disorders: Triglycerides ≥ 150 mg/dL (1,7 mmol/L) or specific treatment of dyslipidemia; HDL-C > 40 mg/dL (1,03 mmol/L) in males and > 50 mg/dL (1,29 mmol/L) in females; SBP ≥ 130 mmHg and/or DBP ≥ 85 mmHg or treatment of AH; Fasting hyperglycemia ≥ 100 mg/dL (5,6 mmol/L) or diagnosed T2DM.				

The base for prevention and treatment of MS in children and adolescents is healthy life-style. It includes:

- moderate calorie restriction (until the first-year weight loss comes up to 5–10%);
- moderate increase of exercise;
- correction of diet qualitative composition.

Only drugs with their safety proved in clinical trials should be used in medication correction.

Suggestions for further research

Many studies were done on the role of MS in children and adolescents in development of T2DM and cardio-vascular diseases [105]. Experts think that in the future IDF criteria of MS in children and adolescents may be changed as new data are obtained. The key IDF recommendations on further studies are presented below:

More precise definition of adipose tissue percentage and its distribution in children's and adolescents' bodies. Search and analysis of more accurate methods to detect obesity (analysis of weight/height relationship, waist circumference etc.).

Design of normal ethnical, age-specific and sexual variations of waist circumference ideally based on normal values. Specific ethnic research on waist circumference compared with visceral obesity based on representation.

Search for a marker to predict development of obesity and other feature of MS. Does low body mass at birth appear to be a predictor of MS, T2DM and CVD in future?

Analysis of adiponectin, leptin and some other markers to find out prognostic value of MS development in adults.

Design of metabolic disorders classification including obesity, dyslipidemia, hypoadiponectinemia and hyperinsulinemia/IR.

Planning of prospective studies to track cohort of children of different ethnic groups till they grow up to determine natural course of MS development and to evaluate effectiveness of measures taken (including life-style correction).

Chapter 9

PRINCIPLES OF NON-DRUG TREATMENT OF METABOLIC SYNDROME

According to the IDF recommendations MS correction therapy should be aggressive as one of its main goals is to lower the risk of CVD and T2DM [1].

First course of MS treatment means changing lifestyle [107, 108, 109]. It includes:

- moderate calorie loss (decrease of body weight up to 5–10% during the first year);
- moderate increase of exercise;
- diet correction.

Lifestyle change is natural, economic and safe method to decrease MS manifestation and development of complications. Non-drug treatment has a great potential which is often underestimated by physicians and patients [110, 111].

American and Finnish study on preventive measurements shows that mass loss up to 7% combined with increased exercise (weekly physical training during 150 minutes) decrease risk of T2DM development by 58% among people with potential T2DM combined with overweight or obesity (Table 16) [112–114].

What is the best diet for metabolic syndrome?

Should we restrict calories or fats? American pilot programs showed that 6-month, 12-month, and 18-month restriction of carbohydrate and animal fat consumption resulted in weight loss of 6.5, 3.4,

Table 16. Results of non-drug prevention of T2DM in patients with potential T2DM

Study	Cohort size, n	Average BMI, kg/m ²	Time of observation, yrs	Decrease of relative risk, %	Decrease of absolute risk, %
Malmö	217	26,6	5	63	18
DPS	523	31	3	58	12
DPP	2161	34	3	58	12
Da Qing	500	25,8	6	46	27

2 kg and 5.1, 2.3, 0 kg, respectively. Conventional low fat diet for HC does decrease cholesterol levels but it requires more carbohydrates. Carbohydrate consumption along with IR leads to increase in TG levels and further decrease in HDL-C levels.

The best diet for MS is based on:

1. Proper distribution of food amount during the day.
2. Increase in protein consumption, including vegetable proteins.
3. Restriction of carbohydrate consumption (more fiber, complex carbohydrates and less easy-to-digest carbohydrates).
4. Increase in consumption of saturated fatty acids and restriction of consumption of monounsaturated fats, including fish oil.

The diet for MS should not only decrease **daily calorie consumption** by means of control of food consumption frequency and amount with 30% of fats, 55% of complex carbohydrates, and 15% of proteins. Changes in **food quality** are also important.

The diet should have several effects:

- hypolipidemic
- antihypertension
- antihyperglycemic.

Hypolipidemic diet aims to restrict foods containing cholesterol and saturated fats and to include foods containing fiber and antioxidants.

The cholesterol consumption is reduced by less than 300 mg/day at the first step and by less than 200 mg/day at the second step. Decrease in cholesterol levels is associated with restriction of consumption of high-fat cheese, milk (fat content of 2.5% and more),

sour cream (fat content more than 10%), butter, hard margarine, mayonnaise, lard, duck, goose, chicken skin, egg yolk, salami, meat with visible fat, animal liver, brain and kidneys.

Fiber moderately decreases C levels by means of stimulation of fecal neutral stearin excretion. Recommended amount of fiber consumption is 25 g/day. Graham bread, oats, and beans (pea, haricot, and lentil) contain fiber.

Antioxidants are substances capable of inhibiting the oxidation of atherogenic particles, such as LDL-C. However recent large-scale studies did not confirm the hypothesis. On the other hand, vitamins E, C, and A help improve metabolism.

Antihypertension diet. Small amount of table salt (up to 4 g/day) decreases BP in patients with AH. Furthermore, long-term restriction of salt intake results in improvement of left ventricular hypertrophy. Intake of potassium and magnesium is recommended. Tomatoes, prunes, oranges, dried apricots, and beans contain potassium and magnesium.

Antihyperglycemic diet. It is recommended to increase consumption of complex carbohydrates (fruits and vegetables) and decrease consumption of easy-to-digest carbohydrates (lump sugar, sponge cakes, chocolate candies, and drinks).

Alcohol consumption can worsen clinical manifestation of MS if marked HTG and AH are considered. Other patients are allowed for daily alcohol consumption (50 g of strong liquor or 150 g of dry red wine). Small amounts of alcohol are proved to increase HDL-C levels [110].

It should be pointed that efficacy of dietary measures depends on patient education on regular life with changes in dietary habits. Dietary diary helps patients to change dietary habits and quality by means of regulation of dietary intake. Furthermore, dietary diary helps the doctor to assess dietary habits and amount of food consumed and correct the diet. To achieve success the patient should trust the doctor and the doctor should not condemn the patient. Such kind of relations can help to avoid complex and shame aggravation due to overeating. Both the patient and the doctor should believe that positive outcomes can be achieved [109].

Efficacy of physical training for metabolic syndrome

According to the data of National Research Center for Preventive Medicine 22% of adult population have MS associated with sedentary life-style [34].

Series of clinical trials showed that long-term exercise training resulted in weight loss (improvement in AO) and enhanced insulin-mediated glucose utilization in skeletal muscles. American scientists conducted a multi-center study that aimed to investigate if exercise training influenced insulin sensitivity as measured by an intravenous glucose tolerance test. The study involved a total of 1,467 males and females of African American, Latin American, and non-Hispanic white ethnicity, aged 40 to 69 years, with glucose tolerance ranging from normal to mild (including light degree of T2DM). After adjustment for confounders, levels of estimated energy expenditure were positively and independently associated with insulin sensitivity ($p < .01$). The association was attenuated after adjustment for the potential mediators, BMI and waist-to-hip ratio [115]. Similar data were obtained under the direction of Professor D. Aronov. Males with T2DM regularly exercised for 60 minutes 2 times a week as long as 6 months. Training program included bicycle ergometer exercises with 50%- and 75%-maximum tolerated load and special exercises for thoracic and cervicothoracic spine. The latter exercises influence visceral motor reflexes at the level of spinal cord segments that innervate pancreas. 6-month exercise training resulted in improvement of carbohydrate metabolism. HbA1c, glucose, and cortisol levels decreased. Decrease in TG levels, apo B levels, SBP and weight loss were also observed with no significant changes in insulin levels [116].

In whole, cardiovascular mortality among physically active people is 40% lower. High and moderate physical activity is associated with 33% and 17% decrease in cardiovascular mortality compared to sedentary life-style [108]. Therefore, decrease in cardiovascular risk associated with physical activity in patients with T2DM can be compared to pharmacotherapy effect.

To choose the level of physical activity age, sex, and concomitant diseases should be taken into account. The level of physical activity can be estimated with simple questionnaires and pedometers.

20–30-minute dynamic load is recommended 3–4 times a week. It includes slow and brisk walking, swimming, skiing, and cycling. As a rule, the level of physical activity is determined by HR. Maximum HR for adults not taking HR-lowering drugs is calculated as $220 - \text{age}$. For moderate and high physical activity HR should be 55–69% and 70–89% of maximum HR, respectively.

Life-style changes should be long-term because short-term measures for weight loss are not useful [109].

Chapter 10

PHARMACOTHERAPY OF METABOLIC SYNDROME

Diagnostic criteria for MS were developed and they are used in practical medicine. But pharmacotherapy of MS was not studied completely and no uniform regimen was developed.

Pharmacotherapy is indicated when life-style changes do not give desired results and patients are still at high risk for CVD [1, 42]. Pharmacotherapy of MS includes:

- Antihyperglycemic drugs
- Anti-obesity drugs
- Antihypertension drugs
- Lipid lowering drugs.

The International recommendations on treatment of MS components are listed below.

Lipid lowering drugs

The therapy aims to decrease TG, apo B, and LDL-C levels and increase HDL-C levels [1, 117–119].

Fibric acid derivatives, or fibrates, are drugs prescribed for simultaneous treatment of lipid disorders in MS.

Fibrates. Fibrates (clofibrate) were first introduced in clinical practice in 1970s. Gemfibrozil, bezafibrate, ciprofibrate, and fenofibrate were synthesized later. Fibrates split TG-rich particles, lower the production of free fatty acids, and increase HDL-C levels through gene upregulation and intensive catabolism of LDL-C particles. Depending

on the type of hyperlipidemia fibrates significantly decrease TG (20–50%) and LDL-C (10–20%) levels and increase HDL-C levels (up to 20%). Clinical trials showed that fibrates had a variety of effects. They significantly decrease uric acid (25%) and fibrinogen (14%) levels and improve insulin sensitivity (15–20%) [120].

Recent studies showed the link between fibrates and cardiovascular complications. The VA-HIT study demonstrated that fibrates increased HDL-C levels and decreased the risk of the main cardiovascular events in patients with CHD and low HDL-C and LDL-C [115]. The Canadian and European double-blinded placebo-controlled study demonstrated that micronized fenofibrate could control the progression of atherosclerosis in patients with T2DM. 418 patients with T2DM were included in 2–5-year DAIS study. Minimal luminal diameter decreased much less in micronized fibrate group compared to placebo group (difference 40%). Stenosis progression was 42% slower in active treatment group. Total number of acute coronary events (including death, myocardial infarction, transluminal angioplasty, and coronary artery bypass surgery) was significantly lower in micronized fibrate group (23%) compared to placebo group [121].

The FIELD study was a 5-year study of 9,795 patients from Australia, New Zealand, and Finland [23]. The study was completed at the end of 2005. The patients were randomized to receive either placebo or fenofibrate 200 mg. Inclusion criteria were as follows: T2DM (WHO criteria) in males and females aged 50–75 years, total C 3.0–6.5 mmol/L with total C/HDL-C ratio over 4.0, or triglycerides over 1.0 mmol/L. The median period from T2DM diagnosis to randomization was 5 years and average HbA1 level was 6.9%. The analysis of baseline clinical data revealed that 37% of included patients were females, 40% were aged over 65 years, and 78% had no signs of CHD. At inclusion about half of patients had no dyslipidemia and others had mild hyperlipidemia (low HDL-C in 59%, HTG in 52%, and combination in 38%). HDL-C increased by 5%, total C and LDL-C decreased by 12% and TG decreased by 28% 4 months later. Cardiovascular events insignificantly reduced by 11% and non-fatal myocardial infarctions significantly reduced by 24%. 36% of patients in placebo group and only 19% of patients in fenofibrate group were administered statins. Adjustment for statin intake revealed that cardiovascular events

significantly decreased by 19%. In some patients with T2DM (females under 65 years of age without CHD and with low baseline HDL-C and LDL-C) fenofibrate was more effective. In patients with HTG, MS, AH, and obesity cardiovascular events reduced similar to general group. Secondary end-points significantly reduced: coronary revascularization by 21% and stroke by 11%. FIELD study was the first large-scale study that aimed to investigate if lipid lowering therapy influenced diabetic microvascular complications. The results of the study showed that necessity for laser therapy for diabetic retinopathy was reduced by 30% ($p < .01$), non-traumatic amputation was reduced by 38% ($p = .011$), and progression of albuminuria and nephropathy was significantly delayed by 14% ($p < .002$) [122].

In whole, long-term fenofibrate therapy resulted in a 24% reduction of cardiovascular mortality, a 22% reduction of risk of cardiovascular events, and a 23% reduction of total mortality.

Side effects of fibrates such as increased gallstone formation due to inspissation of the bile and myopathy should not be missed. Fenofibrate should be taken once a day in the evening before going to bed. Lipid profile, hepatic enzymes, bilirubin, urea and creatinine levels should be checked every 3–6 months [120].

Therefore, fibrates (agonists of PPAR alpha) improve all the components of atherogenic dyslipidemia and reduce the risk of CVD in patients with MS.

Statins. At present statins are considered as gold standard in lowering cholesterol level and reduction in frequency of CVD complications and mortality [123, 124]. The standard is also useful for patients with MS because more than half of them have HC [42, 119]. Statins decrease intracellular cholesterol synthesis by inhibiting the enzyme HMG-CoA reductase. It results in increase in the number of LDL-C receptors and rate of C elimination from bloodstream. Furthermore, statins have pleiotropic effects (anti-inflammatory effect, improvement in endothelial local function, and plaque stabilization) [125]. The large-scale Russian FARVATER study showed that in patients with hyperlipidemia 24-week therapy of atorvastatin 10–20 mg reduced C-reactive protein by 20%, improved endothelium-dependent vasodilation by 52%, increased vessel wall compliance by 45%, and reduced vessel wall rigidity by 25% [126]. It is noteworthy that pleiotropic

effect appears when LDL-C levels decreases by more than 25%. In addition to reduction of LDL-C levels (27–54%), modern statins significantly lower TG levels (6–30%) and increase HDL-C levels (6–12%) depending on baseline levels and drug dose. In the other words, the higher baseline C and TG levels, the more marked lipid lowering effect of statins is. However, lipid lowering effect has a limit: double dose leads to a 6% reduction of cholesterol level (“rules of six”). Statins not only lower lipid levels but also reduce cardiovascular complications and total mortality.

Several large-scale studies of primary and secondary prevention of CVD aimed to investigate effects of statins in patients with T2DM. The data on statin efficacy in patients with MS are accumulated elsewhere [115].

Prospective HPS study showed that simvastatin 40 mg/day reduced risk of cardiovascular events by 22% in patients with moderate T2DM, other risk factors, and microvascular complications [127]. People with high risk of CHD ($n = 20536$) and mild HC, including about 6000 patients with T2DM ($\frac{1}{3}$ with CHD and $\frac{2}{3}$ without CHD) were included in the study. The study aimed to assess how 5-year therapy of simvastatin 40 mg/day influenced coronary (non-fatal MI or CHD-related death) and primary vascular complications (serious coronary complications, any type of stroke, coronary or non-coronary revascularization procedures). High-dose simvastatin resulted in target levels in 90% of patients in simvastatin group and 45% of patients in placebo group. The trend was preserved up to the end of continuous follow-up. At the end of the study serious vascular complications, stroke, and necessity for revascularization (coronary angioplasty and coronary artery bypass surgery) in patients with T2DM reduced by 22%, 24%, and 17%, respectively, compared to control group. In spite of the results were obtained with high-dose simvastatin (in clinical practice average dose is 10–20 mg/day), HPS helped develop strategy of primary and secondary prevention of cardiovascular complications in patients with T2DM.

Results the CARDS study were presented at the 64th Scientific Sessions of the American Diabetes Association by H. Colhoun et al. several months after publication of the HPS study results. The CARDS results seem to be breakthrough in strategy of primary prevention of

cardiovascular complications in patients with T2DM [122]. The CARDS was a multi-center study conducted at 132 centers in the United Kingdom and Ireland. The study included 2,838 patients with T2DM who had no clinical signs of atherosclerosis (no CHD, cerebrovascular disease, or peripheral vascular disease) but had one or several risk factors, including hypertension (84%, mainly AH stage 1), obesity (74%), smoking (44%), retinopathy (30%), or microalbuminuria (15%). LDL-C level should not exceed 14.4 mmol/l, i.e. the level corresponds to criteria of mild HC. Main group was administered atorvastatin 10mg/day for 4 years. Cardiovascular events, including sudden coronary death, non-lethal myocardial infarction, unstable angina, or stroke, were the end-points. More than 80% of patients reached LDL-C target level after 3 months of treatment and the trend was preserved for 48 months. Only 25% of patients in placebo group reached the LDL-C target level. In whole, the difference in total C and LDL-C levels between groups was 26% and 40%, respectively. Atorvastatin was associated with a 37% reduction in main cardiovascular complications, a 48% reduction in stroke, and a 27% reduction in total mortality. The changes were observed in all subgroups of patients with T2DM regardless of age, sex, and lipid levels.

In March 2007, the results of CARDS new analysis were presented in the USA. In 2,200 patients with MS and T2DM atorvastatin 10 mg/day was associated with a 41% reduction in risk of major cardiovascular events (CVD-related death, heart attack, stroke, or CVD surgery) compared to placebo. Atorvastatin also significantly reduced the risk of stroke by 61%.

In 5-year JUPITER study, rosuvastatin 20 mg/day was associated with a 44% reduction of major cardiovascular events compared to placebo ($p < .00001$) in males and females with high C-reactive protein and low or normal C. According to the protocol of the study MS was identified in 41% of included patients [128]. Rosuvastatin was also associated with:

- nearly double reduction of complex risk of myocardial infarction, stroke, or cardiovascular death (47%, $p < .00001$).
- more than double reduction of risk of myocardial infarction (54%, $p = .0002$).
- nearly double reduction of risk of stroke (48%, $p = .002$)

- significant reduction of total mortality (20%, $p = .02$).

LDL-C levels also significantly decreased (50%, $p < .001$) with average LDL-C level of 1.4 mmol/L (55 mg/dL).

The tolerability of rosuvastatin 20 mg was well with no significant differences between treatment groups in relation to muscle weakness, malignant neoplasms, or disorders of blood system, gastrointestinal system, liver, and kidneys. In rosuvastatin group doctors reported on T2DM more frequently (270 patients in rosuvastatin group and 216 patients in placebo group, $p = .01$). Assessment committee did not confirm those events. However there were no differences between groups in relation to fasting glucose levels (98 and 98 mg/dL; $p = .12$) and firstly appeared glycosuria (36 and 32, $p = .64$). Minimal difference was observed in relation to HbA1c (5.9 and 5.8%, $p < .001$) but it was hardly of clinical relevance. Effect on glucose level and T2DM in the study corresponds to data of other large-scale prospective placebo-controlled studies of statins [129].

In whole, analysis of large-scale prospective studies reveals that long-term statin treatment (5 years) lead to 22–30% reduction in total mortality, 32–42% reduction in cardiovascular mortality, and 31–33% reduction in cardiovascular events [130].

As for statin side effects, the attention should be paid to rhabdomyolysis which is very rare (0.15% per 1 million patients). Lipid profile, hepatic enzymes (ALT, AST), and blood CPK should be controlled every month when choosing effective dose of statins and every 3–6 months afterwards. Initial dose is usually taken in the evening before going to bed and maximum dose should be divided and taken in the morning and in the evening.

Therefore, statins decrease the level of all apoB-containing lipoproteins and help achieve LDL-C target level and reduce the risk of cardiovascular events.

Combined lipid lowering therapy. To achieve target lipid levels high dose statins or their combination with other lipid lowering drugs are increasingly used [131]. The researches have been investigating the efficacy of statin-fibrate combination. Recently the results of the ACCORD study have been published. The study aimed to investigate if fenofibrate in combination with statins reduced macrovascular events and microvascular complications. 5,518 patients with T2DM were

included in the study. The patients were divided into two groups: the first group (n = 2,765) was administered simvastatin 20–40 mg in combination with fenofibrate 160 mg and the second group (n = 2,753) was administered simvastatin 20–40 mg in combination with placebo. It should be pointed that inclusion criteria included not only T2DM but also CVD and/or ≥ 2 of cardiovascular risk factors (dyslipidemia, AH, smoking, or obesity). The therapy lasted for 4.7 years. In combination therapy group TG and HDL-C levels significantly improved. After the therapy average HDL-C and TG levels were 1.05 and 1.66 mmol/L in fenofibrate+simvastatin group and 1.04 and 1.92 mmol/L in control group, respectively. In whole, combined lipid lowering therapy was associated with a 31% reduction of microvascular complications in patients with atherogenic dyslipidemia (TG ≥ 2.3 mmol/L and HDL-C ≤ 0.87 mmol/L). Furthermore, 5-year follow-up of fenofibrate and simvastatin combination revealed no increase in side effects, including myopathy and rhabdomyolysis. The ACCORD study showed that reduction of cardiovascular events could be achieved only with correction of LDL-C, TG, and HDL-C levels. Therefore, the ACCORD study confirms international recommendations on fibrates addition to statin therapy if TG level is 2.3 mmol/L [122].

Efficacy of C absorption inhibitor ezetimibe and statins combination is also discussed in literature. The benefits of the combination are:

- Inhibition of bile and food C and liver C = double action
- Statin 10 mg + ezetimibe 10 mg = statin 80 mg
- Statin + ezetimibe = additional 25% reduction of LDL-C
- LDL-C target levels are achieved in 72% of patients

The safety of combination is similar to placebo and statin monotherapy.

In patients with MS simvastatin and ezetimibe combination decreases LDL-C by 52%, TG by 30%, C-reactive protein by 36% and increases HDL-C by 10.5%. Combination therapy is 30% more effective than simvastatin monotherapy [122].

Notice that ezetimibe should not be administered with fibrates and should be used with caution in patients who take cyclosporine.

Correction of insulin resistance and hyperglycemia

IR correction is nosotropic method of MS treatment [132]. It also should be pointed that one of the important components of MS is disorder of carbohydrate metabolism in the form of pre-diabetes (high fasting glycemia and impaired glucose tolerance) [133–135]. Can we administer antihyperglycemic drugs to patients with pre-diabetes? When should we use antihyperglycemic drugs?

Life-style changes seem to be difficult in clinical practice due to low compliance. They can be successful only in 30% patients with pre-diabetes [114, 133]. According to European recommendations on T2DM, pre-diabetes, and CVD patients with pre-diabetes need drug therapy to correct initial disorders of carbohydrate metabolism. Such strategy can reduce risk of both CVD and T2DM (level of evidence I A). Drug therapy that aims to achieve target glucose levels is chosen in accordance with metabolic status [136]. In the other words, correction of disorders of carbohydrate metabolism requires differentiated approach. Total mortality and cardiovascular mortality are definitely reduced if target glucose levels are achieved.

At present the following strategies of drug correction of pre-diabetes are widely accepted: IR, fasting and postprandial hyperglycemia correction. Three groups of antihyperglycemic drugs are used for these purposes: biguanides, alpha-glucosidase inhibitors, and thiazolidinediones. antihyperglycemic drugs do not influence pancreatic beta-cell function, so the risk of hypoglycemia is minimal [137, 138].

Biguanides. Metformin is the only biguanide that is used in clinical practice [139, 140]. First experiments in metformin administration in 20s of 20th century had no clinical effect because of hepatotoxicity and lactate-acidosis (caused by its cumulation in muscles). In the 1990s, metformin was a sensation due to growing interest in MS [141].

Metformin influences glucose metabolism in several ways. The first one is the increase of tissue insulin sensitivity due to the effect on the receptor and postreceptor chains of insulin transaction into the cell. Metformin normalizes tyrosine kinase activity of insulin receptor and stimulates synthesis of transporting protein GLUT-1, localized on plasma membrane and GLUT-4, localized generally on intracellular

membranes. The second one is the increase of glycogen synthesis and reducing of increased glucose production by the way of gluconeogenesis inhibition, reduction of free fatty acids and lipid oxidation. These effects result from the increase of hepatocyte insulin sensitivity and suppression of main gluconeogenesis enzymes (pyruvate carboxylase and phosphoenolpyruvate carboxykinase). The third one is slowing down glucose absorption in intestines which increases its utilization in intestinal cells and smoothes down the postprandial picks.

Metformin demonstrated effectiveness in T2DM in a number of major clinical trials that confirmed decrease of the risk of macrovascular complications. So in the UK Prospective Diabetes Study, metformin was used in the group of patients with newly diagnosed T2DM and excessive weight or obesity ($n = 1704$ patients with 120% excess of standard weight). Average therapeutic dose was 2550 mg per day. Long-term intake contributed to 36% decrease in overall mortality, 42% decrease of T2DM-associated mortality, 32% decrease in complication rate, 39% decrease in myocardial infarction frequency. Cardioprotective effects were similar in the groups of patients taking metformin in doses < 1000 mg, 1000–1699 mg and 1700 mg. It was also demonstrated that metformin more effectively in decreases micro- and macro vascular complications (-32% versus 7% , $p = .0034$), stroke (-41% versus $+14\%$, $p = .032$) and overall mortality (-36% versus -8% , $p = .021$) in comparison with sulfonylurea and insulin. Considering that, European prescribing information included metformin in the list of medications for cardiovascular protection. On the international consensus on T2DM, 2006, metformin was placed at the start of the algorithms of drug correction of hyperglycemia. Besides modifying lifestyle, metformin is the agent of choice for the patients with newly diagnosed T2DM [141].

Published works confirm the role of metformin in primary prevention of T2DM in patients with impaired carbohydrate metabolism. In particular, the DPP study showed decreased risk of T2DM development by 31% in 3 years of metformin administration (1700 mg per day). Besides there was no putting on weight during metformin intake and there was a reducing tendency was detected. Metformin was most effective in decreasing risk of T2DM development in patients before 45 years of age and also in ones with significant obesity ($BMI \geq 35$ kg/m²).

In these groups the risk of T2DM was lower by 44-53%. In published results of three diabetes mellitus prospective studies (BIGPRO 1, BIGPRO 1.2 and DPS) metformin effectiveness was confirmed in the group of patients with impaired glucose tolerance and other metabolic disorders. The Chinese study revealed high effectiveness of metformin (250 mg 3 times a day for 3 years) in T2DM prevention. Three years later, T2DM risk was decreased by 77% in the group of patients using metformin [115].

Decreasing glucose level is not the only effect of metformin. Affecting IR it also has positive systemic effects on lipid specter, AO, BP, endothelial function, microcirculation and hemostasis. Metformin effectiveness and tolerance were studied in cardiology. Twenty patients with MS and impaired glucose tolerance were included in a 3-month study. At the beginning of the course, the dose of metformin was 850 mg per day, later in 15% of the cases, the dose was increased to 1700 mg to achieve normal glucose level. At the end of the study, fasting glucose level decreased by 6.2%. The change in glucose levels was more significant in 2 hour interval after the load — by 19.5% (aim glucose level was achieved at average of 80% patients). IR by the index HOMA-IR was decreased significantly by 38% during treatment. AO rate was changed slightly but significantly. Body mass was decreased by 2.3%, waist circumference — by 1.9%, waist-to-hip ratio — by 1.3%. The influence of antihyperglycemic therapy on BP and lipid profile was studied along with other factors. Systolic BP decreased by 4.7%, diastolic BP — by 4.4%. In 10% cases aimed BP level was achieved. Notably, metformin induces significant decrease in triglyceride level by 25%, raise of high density lipoprotein cholesterol by 12.8%, but whole cholesterol and LDL-cholesterol decreased insignificantly (3.3% and 2.9% respectively). Metformin intake for 3 months had no effect on lactate and creatinine levels in patients with MS and impaired glucose tolerance [138].

Similar results were obtained by Professor I. Chazrova. Metformin monotherapy in the dose of 1000 mg per day for 12 weeks in patients with moderate AH, AO and IGT resulted in body mass decrease (at an average of 6 kg), atherogenic LDL-cholesterol decrease by 11% and had a moderate antihypertension effect (target level of BP was achieved in all 15 patients) [142].

So additional positive metabolic effects (body mass decrease, lipid specter modifications, BP decrease etc.) give ground to metformin usage in patients with MS.

Clinicians still debate about the daily dose of metformin. Results of number of clinical trials had demonstrated that metformin dose-related effects appear at the dose of 1000 mg per day. However, it was demonstrated that optimal curative dose in endocrinology is 1700–2000 mg. In practice, doctors in European countries prescribe lower doses of the drug.

In accordance with international recommendations metformin dose titration is done this way:

1. Low doses (500 mg) one time or twice at mealtime (breakfast or dinner)
2. 5–7 days later if there are no side effects (including glucose level) the dose is increased to 850 mg or 1000 mg before breakfast or dinner.
3. If side effects occur, the dose should be lowered or the drug could be discontinued
4. Maximal effective dose is 850 mg two times. The dose can be raised to 3 gr. per day.
5. Metformin generics can also be used as drugs of choice to decrease treatment costs. In some countries prolonged metformin is also used.

Metformin is well tolerated if it is taken in the mealtime or after the main meals and the dose is increased gradually. 5–20% patients develop gastrointestinal side-effects (metallic taste in the mouth, loss of appetite, diarrhea, sometimes nausea, and vomiting, abdominal pain). That could be explained by the inhibition of gastric and intestinal motor activity, duodenogastric reflux, increased gastric acidity, vasoactive intestinal peptide and glucocagon-like peptide levels. The observed gastrointestinal symptoms can be from light to moderate and elapse after dose reduction [139].

One of the main mechanisms of metformin action is inhibition of glucogenesis out of alanine, purine bases and lactate, so in some occasions lactate-acidosis can develop. In many clinical studies metformin-induced lactate-acidosis prevalence is 8.4 per 100,000 patients. When other drugs are used (glybenclamide) its prevalence reaches 9 per

100,000. The data shows that lactate-acidosis risk is not connected with duration of treatment and metformin doses. Contraindications for metformin are acute and chronic hypoglycemic conditions (myocardial infarction, cardiac failure, severe respiratory illnesses with respiratory failure, compromised renal and/or liver function, operations/traumas, and chronic alcoholism), Type 1 diabetes mellitus, ketoacidosis, lactate-acidosis, pregnancy, lactation and infancy [138].

Tiazolidinediones. Tiazolidinediones are the group of antihyperglycemic medications, affecting insuline resistance. These drugs (rosiglitazone and pioglitazone) are selective antagonists of nuclear receptor PPAR γ (peroxisomal proliferator-activated receptor gamma), found in the insulin-sensitive tissues like adipose tissue, skeletal muscles and liver [137, 143].

Tiazolidinediones promote preadipocytes differentiation and induce production of smaller, more insulin-sensitive cells. Small adipocytes have more insulin receptors and glucose transporters, which results in glucose pickup increase and decrease of lipolysis activity. Tiazolidinediones decrease tumor necrosis factor- α (TNF- α) activity which results in decrease of lipolysis and reduces free fatty acids release. Decreased free fatty acids level in plasma stimulates glucose pick-up in muscles by the way of insulin signal enhancement and reduces gluconeogenesis in hepatocytes [144].

The DREAM study analyzed the effectiveness of rosiglitazone in T2DM prevention on the group of patients with impaired glucose tolerance and/or increased fasting glucose level. The primary end points were new cases of T2DM or death. Average duration of a study was 3 years. Rosiglitazone significantly decreased end point frequency in comparison with placebo (11.6% and 26.0%, respectively; odds ratio 0.40; confidence interval 0.35–0.46; $p < .0001$). In other words rosiglitazone in daily dose of 8 mg decreased the risk of conversion of impaired glucose tolerance into T2DM by 62%. The frequency of cardiovascular events was similar in rosiglitazone and placebo groups. In rosiglitazone group increase in body mass and frequency of cardiac failure was detected (0.5% and 0.1%; $p < .01$). The study design did not include cardiac events analysis because of prolonged observing time required. Long-term follow-up is necessary to conclude if prophylactic effect of rosiglitazone remains when the drug administration is ceased. So rosiglitazone could not be considered as an

adequate drug for prevention of cardiovascular complications in patients with impaired glucose metabolism [122].

National Research Center for Preventive Medicine did a pilot study to determine rosiglitazone effectiveness and safety in patients with MS and impaired glucose tolerance without CHD and its complications. In the case group (n = 20) patients received 4 mg of rosiglitazone and later the dose was raised to 8 mg (in 2 patients only). In the control group (n = 20) there were no change in therapy. During rosiglitazone intake fasting glucose level decreased by 14% and in 2 hours after the load — by 17.9% (p < .01 in comparison with control group). These changes were associated with decrease in IR HOMA-IR by 44.2%. At the end of the treatment, a slight weight gain by 1.1% and BMI increase by 1.2% was revealed but the waist circumference decreased by 3% and waist-to-hip ratio — by 6%. We traced lipid profile parameters: whole cholesterol decreased by 2.6%, LDL-C — by 4.1%, triglyceride level — by 11% and HDL-C increased by 9.6%. Triglyceride and HDL-C changes were significant in comparison with control group. BP decreased at the average of 4% in comparison with basic level. Antihyperglycemic therapy with rosiglitazone resulted in reduction of high-sensitive C-reactive protein level. Several parameters were used to monitor the safety of therapy: AST and serum glutamic pyruvic transaminase activity, haemoglobin, creatinine and lactate levels. Antihyperglycemic therapy with rosiglitazone resulted in no change in these parameters. The safety was comparable to the control group [143].

It was pointed out earlier in publications that thiazolidinediones have several side-effects like edema and weight gain. These side effects limited drug usage in patients with cardiac failure. Patients with cardiac failure FC II (NYHA) should begin with minimal doses: 2 mg of rosiglitazone, 5 mg of pioglitazone. Dose titration should pass under the control of body mass and signs of cardiac failure. Thiazolidinediones should not be prescribed to patients with cardiac failure FC III-IV (NYHA) and those receiving nitrates and insulin [136]. The glitazone safety is a debatable question. International organizations recommend further clinical trials.

The α -glucosidase inhibitors. Acarbose is one of the local inhibitors of intestinal enzyme α -glucosidase. Acarbose is a bacteriogenous pseudotetrasaccharide with high α -glucosidase affinity that is not absorbed in intestines. As opposed to other drugs used for T2DM

management, acarbose has no systemic effects. It acts by preventing the breakdown of large quantities of oligo- and poliaccharides in duodenum and upper part of intestines. That prevents glucose absorption on the earliest stage of digestion [144]. Carbohydrates continue to pass into the lower parts of intestines and monaccharide adsorption is prolonged from 1–2 to 3–4 hours. As a result, it prevents early hyperglycemia that reduces glucose toxic effect on pancreatic beta cells.

At first acarbose was designed to use as a monotherapy in endocrinology or in combination with other drugs (metformin, sulfonylurea, insulin e.t.c.). Meta-analysis of 13 placebo-controlled studies demonstrated decrease in fasting glucose level by 1.3 ± 0.3 mmol/l and two-fold decrease after two hours after the load during acarbose monotherapy. Systemic acarbose monotherapy helps to maintain normal glucose level for 24 hours [138].

In 2001 the results of the acarbose effectiveness study in monotherapy ($\frac{1}{3}$ patients) and in combination with other drugs including insulin ($\frac{2}{3}$ patients) were published. 1954 patients with T2DM were observed for 5 years, HbA1c level and body mass were measured. So acarbose usage combined with diet resulted in decrease of HbA1c by 1.8%, combination with sulfonylurea or insulin resulted in decrease by 2 and 2.1% respectively. It is of interest that acarbose helps to prevent putting on weight by the other drugs. Combination of acarbose and metformin resulted in maximal body mass reduction.

The main effect of acarbose on postprandial hyperglycemia was the reason to conduct the multicentre prospective study that included 40 centers in 9 countries (Canada, Germany, Austria, Norway, Denmark, Sweden, Finland, Israel and Spain). The aim of 3.3 year STOP-NIDDM study was to detect possible effects of acarbose on diabetes mellitus development and cardiovascular complications in patients with impaired glucose tolerance. 1429 males and females (average age of 55 years) were randomly divided on two groups: one group received acarbose 300 mg per day by the increasing scheme, the other one received placebo. At the end of the study T2DM incidence was 25% lower in comparison with placebo. In absolute values in the placebo group 41% were diagnosed with T2DM. In the studied group this level was significantly lower — 32%. Besides, acarbose usage helped to restore normal glucose tolerance in 35% cases [145].

Experts demonstrated that positive cardiovascular effects of acarbose are connected not only with postprandial hyperglycemia normalization but also with other positive metabolic changes. Receiving 300 mg of acarbose resulted in BP reduction by 3 mm Hg. In 250 days of treatment, the risk of AH development was significantly lower: only 78 from 682 patients demonstrated BP rise. In placebo group AH incidence was significantly higher (115 from 686 patients, $p = .006$). In the whole, acarbose decreased the risk of AH development by 34% for 3 years.

Under the supervision of German Professor M. Hanefeld, intima-media thickness was studied in 132 patients, participated in the STOP-NIDDM study. In patients who took acarbose for 3.9 years intima-media thickness was shown to increase by 0.02 mm (0.05 mm in placebo group, $p = .027$), that corresponded to 50% reduction of the marker. Drawdown of intima-media thickness is one of the main markers of risk reduction associated with impaired cerebrovascular blood flow.

The APREL study was initiated by Russian cardiologists (the head of the study — Professor I. Chazova) and held in Russia. The aim of the study was to determine the effectiveness of acarbose used in two different doses (150 and 300 mg) and compare it with 24-weeks — hypocaloric diet (500–600 kkal deficit) in patients with MS. In this case MS was associated with impaired glucose tolerance (IGT) [146]. 383 patients participated in the study and 17 research centers all over Russia were involved in the study. Initially, the patients suffered from AO, IGT, AH (mainly I stage according to WHO, 1999) and combined hyperlipidemia (increased C and triglyceride).

The results showed that two doses of acarbose had identical metabolic effects. Acarbose monotherapy during 6 months brought about 9 kg average weight reduction with the significant difference compared with diet (4 kg, $p < .05$).

In the end of the study evident decrease of postprandial glycemia rate was seen in 70% of patients that was also combined with insignificant decrease of fasted glucose rate. Most patients with MS and impaired glucose tolerance achieved target glucose level during 24-weeks treatment with acarbose used in different doses. In group of patients who took 150 mg of acarbose target fasted glucose level was achieved in 49.7% of patient and 2 hours after OGTT this marker

made up 73.5%. In group of patients who took 300 mg of acarbose target fasted glucose level was seen in 54.2% of patient and 2 hours after OGTT — in 65.5%. These levels are several times more than those in case of diet. Acarbose treatment as well as diet brought about significant decrease of triglycerides and increased level of cholesterol and HDL-C. It is interesting that in groups with acarbose treatment BP decreased by 14 mm Hg, while only 7.3 mm Hg decrease was detected in control group. Generally, target BP level was achieved in most patients(83–89%).

According to data of clinical trials, side effects of acarbose treatment decreased significantly (dyspepsia: flatulence , diarrhea and abdominal pains) after 2 weeks [145, 146]. It is essential to keep to a diet with limited intake of highly digestible carbohydrates and the medication is to take with the first portion of the food to avoid side effects.

Taking into account the fact that acarbose starts working and develops its effects slowly it is assigned in the following regimen: I week — 1 tablet during dinner; II week — 1 tablet twice a day (breakfast and dinner), III week — 1 tablet 3 times a day. Most patients with impaired glucose tolerance take acarbose at dose of 150 mg (maintenance dose). This dose helps to achieve and maintain the target level of postprandial glycemia in 75% of patients. Maximal dose is 300 mg per day.

Acarbose has several use restrictions associated with local mechanism of action. Such conditions include bowel diseases with impaired absorption, diverticulosis, ulcers, cracks, stenosis and gastrocardiac syndrome. Pregnancy, lactation and age under 18 are contraindications for acarbose treatment as well.

Prospects for antihyperglycemic therapy in correction of hyperglycemia and metabolic disorders

Scientists look forward to the results of glitazone and fibrate clinical trials and new data on effectiveness of Peroxisome proliferator-activated receptors (PPARs) agonists of the new generation. Alpha and gamma peroxisome proliferator-activated receptors have effect

on both lipid and carbohydrate metabolism. Incretin mimetics and dipeptid-peptidase IV inhibitors are very promising [137].

Antihypertension therapy in patients with metabolic syndrome

The IDF experts place large emphases on hypertension management and target BP level in patients with MS [1]. Fundamental positions of international recommendations are following:

- AH ($\geq 140/90$ mm Hg) should be treated in accordance with clinical guidelines (JNC 7, USA).
- In patients with T2DM antihypertension drugs are used when $BP \geq 130/80$ mm Hg.
- ACE inhibitor or ARB (sartans) are widely used in patients with MS and T2DM. Some studies showed their advantages in patients with T2DM.
- Risk of complication decreases with BP reduction independent of therapy type. In Russia, there is great experience of mono- and combined therapy of hypertension management in patients with MS. This experience was used to develop the national recommendations on AH and MS [2].

Taking into account hemodynamic characteristics of MS antihypertension drugs should answer the following criteria:

- have prolonged action (improve daily BP profile, decrease BP during the day and at night),
- stimulate damage regression of target organs (reduce left ventricular hypertrophy),
- have positive or neutral metabolic effect [147–149].

Taking into account metabolic effects of antihypertension drugs, medication can be divided into three groups: with positive effect – ACE inhibitors, sartans, imidazoline receptor agonists and selective alpha 1-blockers; with indifferent or neutral effect – calcium channels blockers (CCBs), thiazides-like diuretics, high-selective beta-blockers; with negative effect – nonselective beta-blockers, thiazides and loop diuretic [42,150].

Mechanism of action and metabolic effects of different antihypertension drugs and their role in CVD prevention will be discussed below.

Angiotensin-converting enzyme inhibitors

ACE inhibitors are the optimum treatment of hypertension in patient with MS. Their mechanism of action is based on interaction with renin-angiotensin and kallikrein-kinin systems [151, 152]. This results in systemic arterial and venous vasodilatation, left ventricular hypertrophy and fibrous changes suppression, improvement in tissue insulin sensitivity, it brings about reduction of inflammation through inhibition of monocyte/macrophage migration and normalization of endothelial function [153, 154].

Meta-analysis of three big clinical trials (CAPPP – captopril study, ABCD – enalapril study and HOPE – ramipril study) showed that ACE inhibitors in patient with AH and MS decrease the risk of lethal cardiovascular outcomes by 41%, myocardial infarction by 66% and other cardiovascular outcomes by 33% compared to other antihypertension medications [155–157].

The results of numerous clinical trials allow viewing ACE inhibitors at drugs with positive or neutral metabolic effect [158]. T. Pollare et al showed improvement of insulin-dependent glucose absorption (from 5.7 to 6.3 mg/kg/min) when treated with ACE inhibitors (12 weeks). In the other study enalapril was shown to decrease the glucose basal level and glibenclamide dose (approximately 2 times less) in 40 patients with T2DM. A number of studies showed either positive or neutral effects of ACE inhibitors on the lipid profile. The ACE inhibitors have been proved to correct erectile dysfunction. The ACE inhibitors are known to increase the level of tissue bradykinin, that stimulates the release of endothelium depended relaxation factor (NO, endothelium depended hyperpolarization factor). On the other hand ACE inhibitors block angiotensin formation, which is NO antagonist. ACE inhibitors can restore the balance between two vasoactive systems [159, 160]. In the TREND study, 6 month quinapril therapy in 129 patients with ischemic heart disease showed 10–20% decrease of vasoconstrictive effects.

Angiotensin II receptor blockers (sartans)

ARB or sartans, block selectively type I angiotensin receptors. This impact on RAAS allows to achieve most specific blockade of this system. Compared with ACE inhibitors, ARB do not influence bradykinin system and, consequently, side effects associated with increase of bradykinin level (non-productive cough and angioneurotic edema) are not typical for them [142].

A number of large studies have analyzed sartans' effects on end points, including fatal and nonfatal cardiovascular outcomes and T2DM progression [150]. In the ONTARGET study, telmisartan was shown to have comparable effectiveness with ACE inhibitors in cardiovascular risk reduction. Telmisartan decrease cumulative rate of cardiovascular outcomes, including myocardial infarction, compared with placebo (384 cases — 13% to 440 — 14.8%, $p < 0.047$). Telmisartan has better drug tolerance and less side effects compared with ACE inhibitors. Meta-analysis of PROFESS/TRANSCEND studies showed that telmisartan has significant antidiabetic effect, compared with placebo. The risk of T2DM decreases on average by 16% (3–28%) [122].

The LIVE study showed that the rate of new T2DM cases was 25% lower in group treated with losartan compared with atenolol (beta-blocker). The same results were obtained in the VALUE study. The risk of T2DM was 23% lower in patients, taking valsartan, compared with patients, taking amlodipine [122].

A number of studies showed that ARB decrease IR index in patient with MS and hypertension and cause hypolipidemic effect [161]. Particularly, in Professor I. Chazova study, telmisartan caused significant decrease of hyperglycemia, hyperinsulinemia, HbA1c level and IR index. This drug also significantly lowered C and LDL-C level and caused HDL-C increase [142].

Calcium channels blockers

Prolonged CCBs cause significant arterial vasodilatation as a result of potential depended calcium channels activation in smooth muscle cells of the blood vessels and decrease total peripheral vascular resistance. Along with antihypertension effect CCBs increase myocardial

and renal blood flow so they can be used in patients with concurrent angina and peripheral vessel diseases [162].

The results of the INSIGHT study indicate that nifedipine effectiveness GITS can be compared with diuretics effectiveness in their ability to lower BP and prevent cardiocerebrovascular complications.

Moreover, it has better drug tolerance compared with diuretics. Nifedipine GITS long-term therapy decreased T2DM and gout risk. It is also known to have positive (or neutral, depended on the initial condition) lipid lowering effect and to improve rheological properties of the blood. The FISH study has showed that isradipin monotherapy has neutral effect on lipid level. The large-scale HOT study was to show felodipine decreases death risk by 51% as well as BP in patients with T2DM and hypertension and does not deteriorate carbohydrate metabolism [122]. In another study nifedipine and verapamil were proved to decrease insulin level during OGTT in patients with hypertension, compared with diuretics and beta-blockers. Last generation CCBs (lacidipine) was proved to have significant antiatherosclerotic effect, blocking LDL-C and intima hyperplasia [109].

Meta-analysis of the large clinical trials indicated that ACE inhibitors, sartans and prolonged CCBs drugs of choice in patients with concurrent subclinical target organ lesions [11].

Alpha-blockers

In recent years alpha-blockers as antihypertension treatment are used seldom and usually administered in patient with hypertension and prostate adenoma. Positive metabolic effect of this group is shown in the studies: it decreases total cholesterol level, LDL-C, triglycerides level and increases HDL-C level [150]. Double blind randomized clinical trial, comparing doxazosin and hypothiazide, indicated that doxazosin decreases total cholesterol level by 5.2%, LDL-C by 4%, triglycerides by 4.4% and improves HDL-C and triglycerides ratio by 4.95%. The HALT study showed that proved reduction of HDL-C and triglycerides went with doxazosin neutral effect on HDL-C. The mechanism of positive effect on lipid profile is associated with decrease in HMG-CoA reductase activity (cholesterol biosynthesis enzyme in the liver), enhanced lipoprotein lipase activity, activation of cholesterol

low-density-lipoproteins receptors, what improves binding by 40% [122]. Long-term alpha-blockers use increases tissue insulin sensitivity. The mechanism of this action is still not fully understood.

IR of muscle tissue is considered to be decreased by alpha-blockers as a result of increased muscle blood flow and insulin utilization in the muscles. In 20 patients with T2DM alpha-blockers were shown to improve the control of blood glucose levels and more effectively lower blood lipid level compared to ACE inhibitors. Nevertheless, these group medications are seldom used in clinical practice. In particular, according to the ALLHAT study doxazosin treatment was discontinued because of higher rate of cardiovascular insufficiency compared to ACE inhibitors, diuretics and CCBs [160]. In new European and Russian recommendations alpha-blockers as well as selective II- imidazoline receptor agonists are not included in the main group of antihypertension drugs [136].

Imidazoline receptor agonists

Relatively recently , selective imidazoline receptor agonists were introduced into clinical cardiology [109]. According to the TOPIC study data moxonidine showed good antihypertension effect and drug tolerance. A. Sanjuliani et al demonstrated that moxonidine effectively decreases BP, suppress sympathetic nervous system activity (plasma adrenaline and noradrenaline level was decreased), lower IR (HOMA index decreases by 18%), while lipid metabolism markers remained the same. In E. Kaan study the same drug decreased the fasten blood glucose level. However, long-term outcome of treatment is still not fully discovered [163].

Beta-blockers

Developed in the 1960s beta-blockers were initially used as anti-anginal drugs, however, in 1964 antihypertension effect of these drugs was discovered. In many clinical trials (MAPHY, MRC, GMT) beta-blockers were shown to effectively prevent cerebral stroke and cardiovascular complications (decrease by 29% and 42% respectively) [122].

The UKPDS study proved the effectiveness and safety of beta-blockers in patients with AH and T2DM (atenolol had the same effectiveness as captopril in prevention of vascular complications) [164]. According to the SAFE and TOMHS studies antihypertension effect of beta-blockers is as good as antihypertension effect of other classes of antihypertension drugs. However, the results of longstanding studies indicated adverse effects of these drugs on lipid and glucose metabolism.

Beta-blockers impair glucose tolerance because of impaired tissue sensitivity to insulin and its pancreas secretion. A 6 month treatment with nonselective beta-blockers (with and without intrinsic sympathomimetic activity) as well as with cardioselective beta-blockers without intrinsic sympathomimetic activity significantly decreased tissue insulin sensitivity in patients with hypertension. Propranolol as a nonselective beta-blocker influence mostly the insulin sensitivity compared with selective beta-blockers such as atenolol and metoprolol.

At the same time the 8 year-study of selective beta-blocker showed negative effect of beta-blockers on insulin sensitivity remained during the whole period of treatment.

Risk of T2DM was assessed in the ARIC study, involving more than 12000 patients, when ACE inhibitors, CCB, beta-blockers and diuretics were used.

6 years later risk of T2DM was 28% higher only in the group treated with beta-blockers. In the LIVE study, selective beta-blocker treatment during 4 years (atenolol) resulted in T2DM development de novo in 8% of patients.

More significant negative influence of nonselective beta-blockers on glucose tolerance is connected with the blockage of beta-2 receptors. However, selective beta-blockers without intrinsic sympathomimetic activity can also have negative influence on carbohydrate metabolism especially in high doses, because selectiveness of beta-blockers is dose-dependent. In contrast, selective and nonselective beta-blockers with intrinsic sympathomimetic activity can have no negative influence on glucose tolerance. According to S. Jacob metanalysis summarizing several studies of patients with hypertension some beta-blockers were found to increase tissue insulin sensitivity. Selective as well as nonselective beta-blockers with A1

or A2 blocking effects were found among drugs that improve tissue insulin sensitivity.

Thus, the GEMINI study, which compared two beta-blockers (metoprolol and carvedilol) in patients with hypertension and T2DM, showed that carvedilol increases insulin sensitivity better than metoprolol and does not worsen glucose blood levels. Several studies have also found that beta-blockers, particularly nonselective and without intrinsic sympathomimetic activity, may have an adverse effect on the lipid profile, increasing levels of TG and reduced levels of HDL-C due to decreased activity of lipoprotein lipase that splits the TG into FFA [165].

In recent years, highly selective beta-blockers such as bisoprolol, nebivolol, and metoprolol appeared and are now widely used in clinical practice. For example, nebivolol has an additional vasodilation effect by activation of beta 3 adrenergic receptors and mediated release of endothelial NO. This leads to a decrease in total peripheral vascular resistance and an improvement in the peripheral insulin sensitivity. Russian and international studies involving more than 10000 patients showed improvement in carbohydrate and lipid metabolism. During the placebo-controlled study, the number of new cases of T2DM in patients receiving nebivolol was lower compared with the placebo group. According to I.Chazova et al. nebivolol therapy led to a mild antihypertension effect accompanied by improvement of the daily profile of BP and decreased heart rate in patients with MS. In addition, the researchers note the reduction in triglycerides by 12%, postprandial glucose levels by 14% and increased insulin sensitivity trend.

Bisoprolol is another highly selective beta-blocker whose b2 to b1 activity ratio is 1:75 that makes it an attractive drug for the treatment in patients with hypertension and T2DM. Bisoprolol is a lipophilic and hydrophilic agent, which is soluble both in fat and in water. The drug has a prolonged and dose-dependent effect. Tolerance is good in more than 90% of cases. Bisoprolol has no adverse effects on carbohydrate metabolism. Another study involving healthy volunteers showed that the glycemic response to insulin was similar in patients treated with 10 mg bisoprolol and patients receiving placebo. In addition, a neutral effect of bisoprolol on lipid metabolism was found. In general, bisoprolol is safe for the treatment of hypertension in patients T2DM of any age.

As mentioned above, beta-blockers are fairly heterogeneous group, including both non-selective and highly selective drugs. In this regard, their influence on the metabolic profile is not the same. Therefore, in patients with metabolic disorders highly selective drugs can be prescribed as antihypertension therapy in the mid-therapeutic doses [166].

Diuretics

In three subgroups of diuretics (loop, potassium-sparing and thiazides) only thiazide and thiazide-like drugs are used as a long-term antihypertension medication [42]. Diuretics and beta-blockers were the first among all antihypertension drugs to demonstrate their efficacy in decreasing BP and cardiovascular complications [166]. However, in recent years, considerable attention is paid to the adverse metabolic changes that occur during long-term thiazide diuretic therapy. Several large international studies have found the adverse effects on lipid profile, glycemic status, and uric acid level. So that, in the INSIGHT study negative metabolic changes in patients receiving 25 mg hydrochlorothiazide in combination with 2,5 mg amiloride were revealed compared to nifedipine. The ALLHAT study also found that the frequency of HC and new cases of T2DM was significantly higher in the chlorthalidone group than in the amlodipine and lisinopril groups [160]. Also a meta-analysis by B. Kasiske et al., concerning the impact of different classes of antihypertension drugs on BP and lipids is of the interest. A meta-analysis that covered 65 000 patients from 474 studies showed that the biggest number of adverse effects on lipid profile were caused by thiazide diuretics. On the other hand, the ARIC study, comprising 12,000 persons without T2DM showed no increased in risk of T2DM development in patients using thiazide diuretics (12,5–25 mg for 6 years) [85]. According to different authors, the conflicting data on the diuretics effect of the risk of T2DM may be linked with the drug dose, the duration of therapy, and the age of the patient. For instance, in young people impaired glucose tolerance develops in an average of 5 years of continuous thiazides treatment, whereas in patients older than 65 years in 1–2 years. In patients with T2DM, glucose metabolism aggravates within a few days but in hypertensive

patients without T2DM tolerance to carbohydrates impairs after 2–6 years of continuous treatment. Their dose-dependent potassium eliminating effect [165] may explain the mechanism of diabetogenic effect of thiazides. The effects of different doses of hydrochlorothiazide on the number of parameters of homeostasis are listed in Table 17. The lack of extracellular and intracellular potassium in the beta cells of the pancreas results in impaired insulin secretion and, consequently, in hyperglycemia. Uric acid levels can also increase after the long-term use of thiazides. One of the mechanisms is the competitive binding of tubular excretion site for uric acid by diuretics. Moreover, there is increased urate reabsorption due to reduced circulating blood volume.

Table 17. The dose depending effects of hydrochlorothiazide on metabolism

Parameter, mmol/l	Placebo	Hydrochlorothiazide		
		3 mg	6 mg	12,5 mg
Sodium	-1.10	-1.60	0	-0.60
Potassium	-0.12	-0.09	-0.02	-0.19
Magnesium	0	-0.10	0.02	0.02
Uric acid	-1.20	9.20	10.3	3.80
Glucose	-0.03	0.04	-0.21	0.12

Loop diuretics also have adverse effects on metabolism, though to a lesser extent. Potassium-sparing diuretics, even at high doses, do not adversely impact on carbohydrate metabolism. There is a certain thiazide-like diuretic indapamide, which is metabolically neutral. It does not cause hypopotassiumemia, changes in carbohydrate metabolism and lipid profile. According to a meta-analysis, including three studies, no effect on carbohydrate, lipid profile and uric acid levels of indapamide retard has been found within 9–12 months of treatment. The Russian MINOTAVR study involving 619 patients with AH and MS indapamide-retard has demonstrated not only a good antihypertension effect (target levels were achieved in 61.8% of patients), but also positive effects on carbohydrate (normalization of glucose tolerance in 47% of patients) and lipid metabolism. In addition, indapamide reduces microalbuminuria and left ventricular hypertrophy [126].

Thus, indapamide may be safely used in patients with AH and metabolic disorders.

Table 18 summarizes the metabolic effects of different antihypertension drugs.

Table 18. Effects of antihypertension drugs on metabolism

	Total-C	TG	Glucose	HDL-C	IR
ACE inhibitors	0	0	0	0	0/↓
Diuretics	↑	↑	↑	↓	↑
Beta-blockers	↑	↑	↑	↓	↑
Alpha-blockers	0/↓	↓	↓	↑	↓
CCBs	0	0	0	0	0
Sartans	0	0	0	0	0/↓
Imidazoline receptor agonists	0	0	0/↓	0	↓

↓ – decrease, 0 – neutral, ↑ – increase.

Combined antihypertension therapy

According to the results of large clinical studies, in most cases achievement of target BP levels is only possible with two or more drugs. In the SHEP study, the number of such patients was 45%, in the ALLHAT – 62%, in the INVEST – 80%, in the LIVE – 92%. Two clinical studies (UKPDS and HOT) showed that in patients with hypertension and impaired carbohydrate metabolism effective antihypertension therapy resulted in decrease of incidence of stroke by 44%, microvascular complications by 37% and macrovascular complications by 39% [122].

According to the European and Russian national guidelines for AH, the combined antihypertension therapy in patients with metabolic disorders should include inhibitors of the RAAS (class I recommendations and evidence level A) [167].

Nowadays, rational combinations of antihypertension drugs for patients with MS are well known. They are as follows:

ACE inhibitors and CCBs,

ACE inhibitors and imidazoline receptor agonists,

ACE inhibitors and diuretics,

ARB and CCBs,
ARB and a diuretic,
CCBs and beta-blocker,
Beta-blocker and a diuretic.

However, for some combinations mentioned above the definition of “rationality” is given with some reservations. So according to the AH guidelines by the Society of Cardiology of the Russian Federation, the combination of beta blocker and a diuretic is possible only with nebivolol, bisoprolol or carvedilol, and this combination should not be used in patients with metabolic disorders and a high risk of T2DM. This “reservation” is based on the data of many large studies.

Results of recent studies raise a question about the reasonability of using diuretics as part of combined therapy in hypertensive patients with a high risk of cardiovascular complications. The combination of a beta-blocker and a diuretic has a negative metabolic effect. For example, the ALPINE study compared two therapy types: beta-blocker (atenolol) + diuretic (hydrochlorothiazide) and ARB (candesartan) + CCBs (felodipine). Both combinations showed a good antihypertension effect. However, in patients receiving beta-blocker and a diuretic, adverse metabolic changes were observed: increased insulin, cholesterol, LDL-C, TG, reduced HDL-C. In the group of hydrochlorothiazide and atenolol, T2DM was frequently detected [165].

In the ASCOT study, comparison of two antihypertension therapy approaches was demonstrated: the “old” (beta blocker + diuretic) and the “new” (CCBs + ACE inhibitor). The effect of two treatment regimens on the primary endpoint was studied. That included the total incidence of nonfatal myocardial infarction (including so-called silent myocardial infarction) and fatal CHD. Secondary endpoints were total mortality, cardiovascular mortality, incidence of stroke, all coronary and cardiovascular events, indications for surgical revascularization, and development of T2DM. The study included 19,527 hypertensive patients aged from 40 to 79 years with 3 or more risk factors and without a history of coronary events. The study found no significant differences in the frequency of the primary endpoint between the groups. However, in the amlodipine + perindopril therapy resulted in a decrease in number of secondary endpoints, that is a 30% decline in the number of new cases T2DM, the overall mortality has decreased

by 11%, the number of all cardiovascular events and myocardial revascularizations performed decreased by 16% [122].

The National Research Center for Preventive Medicine did a study of 5 mg CCBs amlodipine and 10 mg ACE inhibitor lisinopril administered during 6 months in 21 males with high cardiovascular risk and metabolic abnormalities. The study revealed a good antihypertension and neutral metabolic effects. Thus, the target BP levels were achieved in 85% of patients with I-II degree AH. A combination of two metabolically safe antihypertension drugs did not have any impact on lipid (total cholesterol, LDL-C, TG and HDL-C) and glucose (fasting and 2 hours after load level) metabolism. Moreover, combined therapy does not worsen erectile function in males of working age [168].

Currently, one of the most frequently prescribed antihypertension drug combinations is ACE inhibitor and diuretic. There is a fairly wide range of medications with fixed-dose ACE inhibitor and a diuretic. High efficiency and safety of this combination was noted in the Society of Cardiology of the Russian Federation guidelines [167]. When combined with diuretics, ACE inhibitor can reduce their negative metabolic effect, resulting in a cumulative effect to become neutral or weakly positive in patients without hypertension or in combination with T2DM [109, 165].

The Institute of Cardiology (Russian Cardiology Research and Production Complex) studied for 16 weeks the influence of a fixed combination of 20 mg enalapril and 12.5 mg hydrochlorothiazide on circadian BP, carbohydrate, lipid and purine metabolism in patients with mild to moderate hypertension and T2DM. Target BP levels were achieved in 70% of patients. The maximum, minimum and average SBP and DBP decreased significantly, as well as the pressure load and variability of BP during the daytime and at night. There was a statistically significant reduction in the initially high levels of fasting and postprandial glucose plasma level. On the average both lipid metabolism and uric acid level did not change significantly in a group. The concentration of potassium and sodium in the blood did not change as well [109].

The National Research Center for Preventive Medicine did a similar study of combined drug lisinopril and hydrochlorothiazide in patients with high cardiovascular risk and metabolic disorders. In a 6 months

study, patients initially received 20 mg lisinopril and 12.5 mg hydrochlorothiazide. In 1 month if target levels of BP not achieved patients were shifted to another mode of therapy: 20 mg lisinopril and 25 mg hydrochlorothiazide. 85% of patients achieved target levels 35% of which received 20 mg lisinopril and 12.5 mg hydrochlorothiazide. Overall, SBP decreased by 16.5% and DBP by 12,6%. In this case, heart rate remained virtually unchanged. In the group of patients receiving lisinopril, a significant decrease in the concentration of TG in 15.6% was observed, while the levels of total cholesterol, LDL-C and HDL-C did not change. The combination of fixed-dose diuretic with ACE inhibitor had no negative effect on carbohydrate metabolism, including fasting glucose, 2 hours after loading, immunoreactive insulin and HOMA-IR index. In addition, the blood concentration of uric acid and potassium remained unchanged. We also found no adverse effect of the ACE inhibitors and hydrochlorothiazide combination on erectile function in males with hypertension and metabolic disorders [169].

Thus, these data suggest that combined therapy with fixed doses of ACE inhibitors and thiazide diuretics can be used in patients with metabolic disorders as they have positive antihypertension and neutral metabolic effects.

Another promising combination is a fixed-dose drug with perindopril and indapamide. The ADVANCE study demonstrated that adding perindopril/indapamide to the conventional therapy in patients with T2DM reduces the risk of coronary events by 14% and cardiovascular mortality by 18%. This study is one of the first showing the reduction in mortality when using a fixed combination of antihypertension drugs [122].

Anti-obesity drugs

Correction of obesity in MS patients is important, since, according to the prospective studies, obesity is often an early clinical manifestation and is the catalyst for a number of metabolic disorders [63, 171].

According to FDA recommendations (Monitoring Committee in Food and Drug Administration), drug correction of obesity is indicated, if non-drug measures failed to produce a steady reduction of body weight by more than 5%. The literature indicates that the body weight

loss by 5% enhances the control of risk factor profile and potentiates the effect of antihypertension and lipid lowering drugs. The improvement of the control of risk factor profile such as BP, parameters of lipid and carbohydrate metabolism by body weight loss by 10% is clinically significant [142]. According to WHO recommendations, the indications for pharmacological correction of obesity are:

- BMI ≥ 30 kg/m² or
- BMI ≥ 27 kg/m² in combination with AO, hereditary predisposition to T2DM and risk factors for cardiovascular complications.

Current anti-obesity pharmacotherapy has a limited number of drugs used in clinical and outpatient settings. From a practical point of view, anti-obesity drugs are divided in 2 groups:

- 1) central action anorexics, mainly the adrenergic and serotonergic system;
- 2) local gastrointestinal agents: orlistat [170].

The history of central action begins in the 1940s. The fate of several anorexic generations was sad because of serious side effects such as pulmonary hypertension, vascular endothelial and heart valves damage. Currently in clinical practice, anorexic of a new generation (sibutramine) is used. Sibutramine activates serotonin and adrenergic pathways in the central nervous system, whereas it affects dopamine and cholinergic processes to lesser extent. Sibutramine affects both components of the energy balance — energy intake and utilization. On the one hand, this results in a rapid onset of satiety, the extension of a satiety and, thus, in decreased appetite. On the other hand, the drug increases utilization of energy on generating heat, that is, a person spends more energy to warm oneself, which also helps to reduce body weight. Sibutramine has dose-dependent effect. Studies showed that the selective decrease in consumption of carbohydrates and fats leads to a significant reduction in body weight, including the amount of abdominal fat (by 25%), which is associated with an improvement in lipid and carbohydrate metabolism. However, there is an increase of BP and heart rate (HR) at 5%, which should be considered when treating patients with MS. In general, because of large projects, sibutramine has been proved safe for continuous intake during two years [172].

Drugs with non-systemic (local) effect are prospective for obesity correction in MS patients. For example Orlistat is an inhibitor of

stomachic and pancreatic lipases. About 30% of triglycerides are not absorbed creating calories deficiency. In the duodenum lumen, small fat drops are amalgamated and released with the feces resulting in minimal systemic adverse effects. Orlistat does not inhibit other intestinal ferments (for example pancreatic alpha-amylase, tripsin, chymotrypsin). Besides main effect (body mass decrease and stabilization, prevention of recurrent weight gain, Orlistat positively affects blood lipids, AH, glucose level and IR. The 24 to 52 week studies show that administration of 120 mg of Orlistat 3 times a day decreases body mass by 6–10% and waist circumference by 5,8 % in MS and obesity patients. It is noteworthy that 6 month Orlistat treatment results in decrease of total cholesterol by 7% and systolic and diastolic BP (by 7% и 9% respectively) and fasting insulin level by 18%. Orlistat intake decreases fasting glucose level by 20% making it possible to decrease glucose lowering drugs dosage by 40% in T2DM patients. The prospective studies showed that long-term administration of Orlistat reduces T2DM risk. Systemic metabolic effects of Orlistat reduce total coronary risk by 5%. As for side effects, one should pay attention at adverse reaction of the gastro-intestinal tract at the early stage of the therapy, which are, however, temporary and occur only in 20% of patients. They are meteorism, oily discharge, liquid and soft stool in the first days of the drug administration [109, 173].

Combined antihypertension and lipid lowering therapy in MS patients

The screening and diagnostics reveal high and very high total CVD risk in more than 50% MS patients that necessitates immediate multifactor intervention. It calls for combined administration of several drugs correcting main MS components. Meta-analysis of clinical data showed that antihypertension, lipid- and glucose lowering drugs can reduce cardiovascular risk by 40–45% only if administered separately (Fig. 22).

The published data of several large-scale studies showed the advantages of multifactor drug therapy. According to the STENO 2 study treatment of hyperglycemia, AH, dyslipidemia combined with Aspirin administration in patients with high risk of microalbuminuria

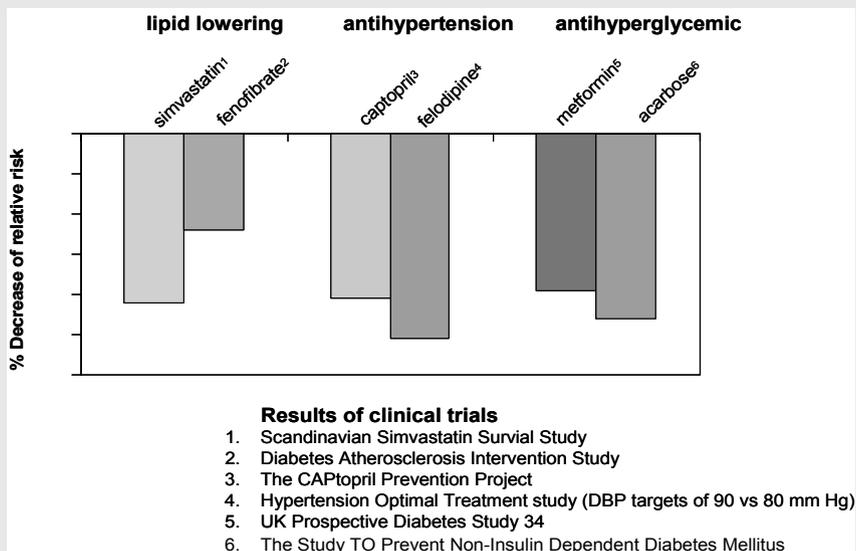


Fig. 22. Influence of various drugs on cardiovascular risk

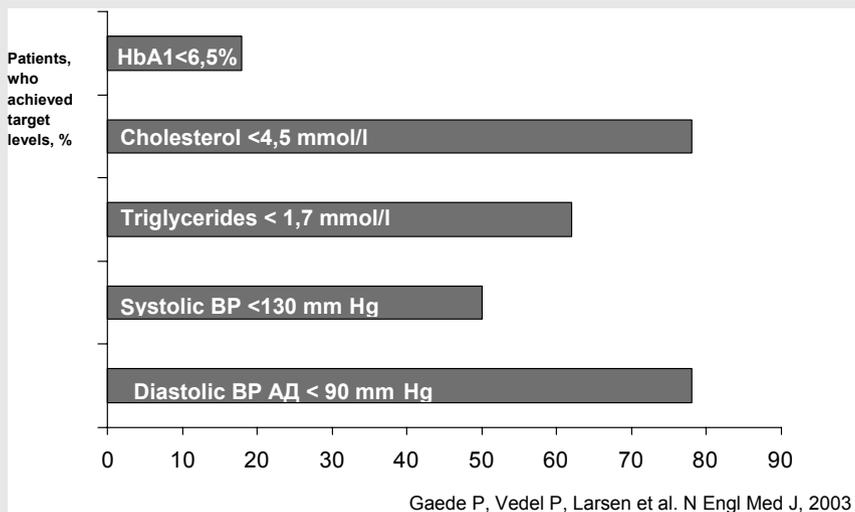


Fig. 23. The STENO 2 study. Patients, who achieved target levels of main risk factors

reduced the risk of major cardiovascular outcomes by more than 50% [174]. It was not always possible to achieve target levels of risk factors. The most difficult was to achieve necessary glycemia levels (Fig. 23).

In the ALLHAT study, 10 000 out of 42 000 AH patients took daily 40mg of pravastatin in addition to antihypertension therapy. The therapy resulted in questionable decrease of fatal outcomes of CHD, non-fatal myocardial infarction and stroke by 9% [160].

In the ASCOT study, the effect of additional lipid lowering therapy was higher. The study was terminated before term as good cardiovascular outcomes were achieved. Total cardiovascular events rate, including myocardial infarction, and risk of lethal and non-lethal strokes decreased by 36% and 27% respectively. The combined therapy, which included amlodipin antihypertension therapy + atorvastatin, decreased lethal cardiovascular events and non-lethal myocardial infarction by 53% in comparison to the placebo group. In the group of patients, who were treated with atenolol and atorvastatin, number of cumulative incidents decreased only by 16% in comparison to the placebo group [122].

In 1998–2000, the department of metabolic disorders of National Research Center for Preventive Medicine studied efficiency of combined antihypertension and lipid lowering therapy in MS patients. 148 patients were divided into 8 groups. The first 4 groups were treated with statins in combination of one antihypertension drugs: a beta-blocker, an ACE inhibitor, a CCBs of prolonged action and thiazide-type diuretic. The other groups were treated with a fibrate combined with one of the 4 above-mentioned antihypertension drugs [175].

The 8-week therapy with the combination of statins or fibrates with one of the various antihypertension drugs resulted in similar significant decrease of SBP and DBP in the MS patients. The BP decreased both at night and in the daytime, which was determined by 24-hour monitoring.

The 8-week therapy with the combination of fibrates with antihypertension drugs resulted in significant decrease of fibrinogen concentration, VII factor activity, uric acid as well as decrease of IR in average 58% of MS patients. The changes in lipid spectrum after therapy with fibrates and antihypertension drugs were manifested by lipid lowering effect characteristic to fibrates.

The 8-week therapy with the combination of statins with one of the various antihypertension drugs did not affect parameters of IR, hemostatic system and blood level of uric acid. The combination of statins with antihypertension drugs resulted in lipid lowering effect characteristic to statins.

Antihypertension and lipid lowering effects of combined therapy were accompanied by significant (threefold) decrease of total coronary risk, which was especially evident after therapy with statins and antihypertension drugs of various classes and fenofibrates with a selective beta-blocker.

Thus the combined antihypertension and lipid lowering therapy decreases total coronary risk and breaks single chain of metabolic disorders, that eventually decreases atherogenic potential of MS.

In recent years, much attention is focused to **“polypill”** drugs technology. Three types of polypill drugs are discussed:

- A drug for primary CVD prevention containing a lipid lowering drug, antihypertension drug and Aspirin.
- Drugs for secondary prevention of CVD containing a statin, a beta-blocker, Aspirin, ACE inhibitor, and possibly fish oil.
- Drugs for T2DM treatment, including two oral glucose-lowering drugs, a statin, Aspirin, and two antihypertension drugs.

We hope a polypill drug for MS patients will appear soon.

Chapter 11

THE RUSSIAN NATIONAL RECOMMENDATIONS ON METABOLIC SYNDROME: ANALYSIS OF MAJOR POINTS

Since 2008, the MS section the Society of Cardiology of the Russian Federation, which unites leading national experts in various fields, makes the national recommendations on MS [2]. The national recommendations are based on the data of international and Russian studies.

It is noteworthy that for the first time, the Society of Cardiology of the Russian Federation suggested criteria and algorithms of MS diagnostics in various settings: from primary health care facilities (outpatient clinic) to specialized highly equipped clinics and centers.

The national MS diagnostic criteria are based on IDF criteria [1]. In other words, the main MS component is AO with cut-off points of more than 94 cm and 80 cm for males and females respectively. Additional criteria are AH, HTG, low HDL-C and fasting hyperglycemia. A distinguishing feature of the Russian criteria is the inclusion of high level of LDL-C and IGT. In the IDF criteria, the fasting glycemia cut-off point is more strict 5.6 mmol/L (while the Russian recommendations have the fasting glycemia cut-off point at > 6.1 mmol/L). Unlike the Russian recommendations, IDF federation criteria do not distinguish glucose tolerance disorders separately: fasting hyperglycemia is an indication for OGTT due to higher probability of detection.

The International Classification of Diseases (ICD) 10 (WHO, 1998) does not have MS as a separate nosology. According to the national recommendations, all components of this symptom complex are

described in diagnostic conclusions [42]. To date this is the optimal solution of the problem.

The Russian recommendations describe in detail main diagnostic problems of separate MS components. The recommendations have the list basic and additional diagnostic methods. One should pay attention at differentiation between MS and disorders with similar symptoms (for example Cushing syndrome, pheochromocytoma). To differentiate these disorders from MS, adrenal and hypophysis CT and certain hormones level tests are necessary [2].

According to the experts MS treatment is multifactoral including medication and life style changes [142]. It is noteworthy that the recommendations cover in detail problems of diet, patient education, changes in dietary habits and physical activity. Medication in MS treatment depends upon the severity and manifestation of the symptoms. The recommendations discuss antihypertension, lipid lowering, antihyperglycemic, anti-obesity drugs as well as use of aspirin in MS patients. Russia accumulated a huge amount of data from many clinical trials of the efficiency and safety of these drugs, which allows the authors to share their experience in MS treatment. The new revision of the national MS treatment recommendations features new parts devoted to sleep apnoe, MS in children and adolescent, MS in menopause. The latter part analyses hormone substitution therapy in females with MS.

The important part of the national recommendations is the schematic algorithms of MS patients' treatment. The systematization of the up-to-date approaches to MS treatment increases the efficiency of the primary care facilities.

It is noteworthy that the Russian national recommendations do not have European or American analogs.

CONCLUSION

MS is a medical and social problem of the modern human civilization. MS is prevalent both in adult population and in children and adolescents. The meta-analysis of international and national studies shows that developed and developing countries are facing a new pandemic in the 21st century. The prevalence of MS is twice as high as T2DM prevalence. MS prevalence is expected to rise by 50% in the coming 25 years.

According to the Russian PRIMA study, 30% of adults in a town in Volga federal district have MS. The study revealed the peculiarities of MS. The MS prevalence is proportionate with age. There are females than males among MS patients. MS prevalence depends upon the nationality. Social factors affect MS prevalence: MS is significantly more prevalent in unemployed, widowers and females with high school education. In the studied population, no significant correlation was found between MS and behavioral risk factors as low physical activity, high stress, smoking, alcohol abuse. However, there was significant correlation between eating disorders and MS prevalence. Thus, certain demographic parameters, social and economic status and behavioral factors play an important role in MS. The important aspect of MS introduction in clinical practice is its atherogenic potential and contribution in CVD. Several prospective studies demonstrated that the risk of cardiovascular complications due to atherosclerosis is twice as high in MS patients as in patients without MS. Moreover, MS patients face 40% risk of T2DM in the coming 5 years. According to the Russian population study, every third MS patient had various CVD and complications at the moment of screening.

Emergence of international consensus on MS criteria allows standardizing of definitions and diagnostics. The leading experts come to

the agreement on four points out of five. The cut-off points of waist circumference for AO are the subject of discussion until new data are obtained. The Russian experts accepted the European norms for AO in MS diagnostics.

In the Russian population, the most prevalent MS components are AO, AH, low level of HDL-C and HTC. The typical features of MS clinical manifestation are the lipid triad, AO and stage I-II hypertension. However, we are planning a series of clinical trials including prospective observation of information and predictor capabilities of various MS definitions.

The clinical significance of MS is determined by the fact that to date MS is viewed as an interdisciplinary problem. The pathogenic link is found between MS and NAFLD, gout, polycystic ovary syndrome, erectile dysfunction and androgen deficiency state. Moreover, cardiologists, endocrinologists and neurologists encounter MS complications in everyday practice. Consolidation of efforts of health care community will allow developing of efficient measures of MS prevention.

MS treatment is multifactor and depends upon the manifestation of MS components and the total cardiovascular risk. Non-drug treatment is of great importance. Several authoritative studies demonstrated that life style changes and regular physical activity decreases the risk of MS complications. We understand that this task is rather difficult to implement in real practice. However, government, mass media and family play an important role in MS prevention programs. One should take individual social and behavioral factor of a patient.

Nowadays four groups of drugs are used to treat MS:

- IR and hyperglycemia correcting drugs
- Antihypertension drugs
- Lipid lowering drugs
- Anti-obesity drugs

Each drug group has the evidence base on efficiency and safety for long term administration in MS patients.

Efficient decrease of total cardiovascular events rate necessitates combined administration of drugs with different action. In future, we expect development of polypill drugs containing several active substances in a single pill that.

And finally, early diagnostics of MS necessitates the inclusion of MS tests in the dispensary examination of adult population (BP and waist circumference measurement, lipid and fasting glucose levels). This approach allows revealing early metabolic disorders and taking preventive measures. As a rule, preventive measures have good prognostic result and are justifiable in the economic dimension. One should keep in mind that the rehabilitation period needs much more resources and efforts to improve life quality and prognosis.

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Appendix 1

LIST OF DRUGS USED FOR CORRECTION OF METABOLIC SYNDROME

Drug group	Effect
Antihypertension drugs	
ACE inhibitors	↓ BP, neutral or weakly positive metabolic affect, organ protection
Sartans	↓ BP, neutral or weakly positive metabolic affect, organ protection
CCBs	↓ BP, anti-ischemic and neutral metabolic affect
Imidazoline receptors agonists	↓ BP, positive metabolic affect
Highly selective beta blockers	↓ BP, HR, peripheral sympathoadrenal system blocking, neutral metabolic affect
Thiazides	↓ BP, neutral metabolic affect, organ protection
Lipid lowering drugs	
Statins	↓ Cholesterol up to 55% depending of the dose, ↓TG up to 30%, depending of the dose pleiotropic affects
Fibrates	Preferential ↓ TG and HDL-C, additional metabolic affects
Antihyperglycemic drugs	
Metformin	↓ IR, glucose production in liver, body mass decrease and additional metabolic affects
Pioglitazone (Rosiglitazone)	↓ IR, anti-inflammatory and additional metabolic affects
Acarbose	↓ postprandial glucose level, body mass decrease and additional metabolic affects
Antiaggregants	
Aspirin	↓ platelets aggregation and adhesion, anti-atherosclerotic affect

Appendix 2

ALGORITHMS OF METABOLIC SYNDROME THERAPY

