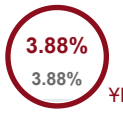
Ұқсастық туралы есеп

Метадеректер

Ұйымның атауы
International Kazakh-Turkish University named after Khoja Ahmed Yasawi
Тақырып
MODERN ASPECTS OF THE CONTROL OF METABOLIC SYNDROME IN OUTPATIENT CONDITIONS
Авторы Ғылыми жетекші
Нускабаева Г, Ок.м.н., ассоц.профессор Гульназ Нускабаева
Бөлімше
Әдістемелік жұмысты ұйымдастыру бөлімі

Көшіріп алу мөшірлемесі

Назар аударыңыз: жоғары коэффициенттер автоматты түрде плагиат емес. Баяндаманы уәкілетті адам талдауы керек.



ҰК 1

ҰК 2

25	34391	237947
Ұқсастық коэффициент 2 үшін фразаның ұзындығы	Сөздердің саны	Таңбалардың саны

Ескертулер

Бұл бөлімде мәтіннің бұрмалануына қатысты ақпаратты табасыз. Мәтіндегі бұл бұрмалаулар мәтіндегі МҮМКІН айла-шарғыларды көрсетуі мүмкін. Мәтіндегі бұрмалаулар әдейі болуы мүмкін, бірақ көбінесе бұл құжатты түрлендіру және оны сақтау кезіндегі техникалық қателер, сондықтан осы модульді талдауға толық жауапкершілікпен қарауды ұсынамыз. Сұрақтарыңыз болса, қолдау көрсету тобына хабарласыңыз.

Әріптерді ауыстыру		10
Аралықтар	A→	0
Шағын кеңістіктер		100
Ақ белгілер		0
Парафразалар (SmartMarks)	a	73

Ұқсастықтардың белсенді тізімдері

Тізім бойынша айналдырып, әсіресе ҰК 2-ден (бөлінген қалың шрифтпен) түскен үзінділерді талдаңыз. «Mark Fragment» сілтемесін пайдаланыңыз және олар құжатта (ұқсастықтармен) шашыраған қысқа фразалар, бір-біріне жақын көптеген қысқа сөйлемдер (мозаикалық плагиат) немесе дереккөзді (тікелей плагиат) көрсетпеген кең фрагменттерді қараңыз.

Топ 10 үзінділері

Мәтіннің түсі

РЕТТІК НӨМІР	ТАҚЫРЫП НЕМЕСЕ ДЕРЕККӨЗДІҢ URL (ДЕРЕККӨР)	БІРДЕЙ СӨЗДЕРДІҢ САНЫ
1	https://pdfs.semanticscholar.org/2539/520f36305c8ec1ba6a412cfb96983c6c31cb.pdf	35 0.10 %
2	Исправ_Садыкова_Турманбаева А.А. статья фармация_соңғы вариант [redacted] 5/30/2024 National Center for Expertise of Medicines and Medical Devices (National Center for Expertise of Medicines and Medical Devices)	26 0.08 %
3	https://www.ajol.info/index.php/ajhs/article/view/260493/245923	25 0.07 %

4	https://link.springer.com/article/10.1007/s40200-023-01213-5	24 0.07 %
5	https://cardiovascular.elpub.ru/jour/article/viewFile/2600/2088	23 0.07 %
6	https://www.medigraphic.com/pdfs/salpubmex/sal-2021/sal216e.pdf	23 0.07 %
7	https://pubmed.ncbi.nlm.nih.gov/30391988/	22 0.06 %
8	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10043912/	22 0.06 %
9	https://www.nature.com/articles/s41598-024-77928-z	21 0.06 %
10	https://www.medigraphic.com/pdfs/salpubmex/sal-2021/sal216e.pdf	21 0.06 %

RefBooks дерекқорынан (0.29 %)

РЕТТІК НӨМІР	ТАҚЫРЫП	БІРДЕЙ СӨЗДЕРДІҢ САНЫ
	Дереккөзі: Paperity	
1	The metabolic syndrome: time for a critical appraisal Jelte van Andel;	26 (4) 0.08 %
2	TSLP regulates mitochondrial ROS-induced mitophagy via histone modification in human monocytes Hung, Chih-Hsing,Lin, Yi-Ching, Tsai, Mei-Lan, Lin, Yu-Chih, Liao, Wei-Ting;	22 (2) 0.06 %
3	Metabolic syndrome: a population-based study of prevalence and risk factors Lotfi, Mohammad Amin, Ayoobi, Fatemeh, Bidaki, Reza,Jamali, Zahra, Esmaeili-Nadimi, Ali, Jalali, Zahra, Khalili, Parvin;	12 (2) 0.03 %
4	Risk of metabolic syndrome among children living in metropolitan Kuala Lumpur: A case control study Andrew P Hills, Bee K Poh,Bee S Wee, Abdul T Ruzita, Awang Bulgiba, Mohd N Ismail;	10 (1) 0.03 %
5	The Prevalence of the Metabolic Syndrome Among Arab Americans Donna Kritz-Silverstein PhD;	10 (2) 0.03 %
6	Determinants of metabolic syndrome among patients attending diabetes clinics in two sub-urban hospitals: Bono Region, Ghana Bandoh, Delia Akosua,Abagre, Timothy Agandah, Addo-Lartey, Adolphina Addoley;	6 (1) 0.02 %
7	Hypertension trials update Al Ghorani, Hussam, Mahfoud, Felix, Lauder, Lucas, Böhm, Michael, Kulenthiran, Saarraaken;	5 (1) 0.01 %
8	Association between triglyceride glucose-body mass index and cardiovascular outcomes in patients undergoing percutaneous coronary intervention: a retrospective study Zhang, Xinxin, Fang, Zhen, Wen, Yuchen, Lu, Jiaqi, Xu, Bing, He, Shenghu,Cheng, Yang;	5 (1) 0.01 %
9	The prevalence and risk factors of metabolic syndrome a suburban community in Pathum Thani province, Thailand Panthip Sangprasert,Kornanong Yuenyongchaiwat, Duangnate Pipatsitipong;	5 (1) 0.01 %

жергілікті дерекқордан (0.00 %)

РЕТТІК НӨМІР	ТАҚЫРЫП	БІРДЕЙ СӨЗДЕРДІҢ САНЫ

дерекқор алмасу бағдарламасынан (0.48 %)

РЕТТІК НӨМІР	ТАҚЫРЫП	БІРДЕЙ СӨЗДЕРДІҢ САНЫ
1	Исправ_Садыкова_Турманбаева А.А. статья фармация_соңғы вариант [redacted] 5/30/2024 **National Center for Expertise of Medicines and Medical Devices (National Center for Expertise of Medicines and Medical Devices)**	**56 (3) 0.16 %**

2	Atherogenic Index of Plasma in Metabolic Syndrome: A Systematic Review and Meta-analysis [redacted] 7/31/2025 Universitatea de Medicină şi Farmacie "Iuliu Hatieganu" din Cluj-Napoca (Universitatea de Medicină şi Farmacie "Iuliu Hatieganu" din Cluj-Napoca)	29 (4) 0.08 %
3	Cardiovascular risk in fatty liver disease: Pathogenic links [redacted] 12/6/2022 Universitatea de Medicină şi Farmacie "Iuliu Hatieganu" din Cluj-Napoca (Universitatea de Medicină şi Farmacie "Iuliu Hatieganu" din Cluj-Napoca)	20 (3) 0.06 %
4	FINAL 12.07. - Mitophagy – the “missing link” in ASD [redacted] 7/15/2024 Medical University - Plovdiv (Медицински факултет)	17 (3) 0.05 %
5	PISONI_UC13748_20230110_3139_c062.pdf [redacted] 1/16/2024 Universitat de València (UV)	17 (3) 0.05 %
6	Учебник Cultural Anthropology [redacted] 6/3/2024 International IT University (Медиакоммуникации и история Казахстана)	11 (1) 0.03 %
7	«Особливості перебігу первинної артеріальної гіпертензії в молодому віці з проявами метаболічного синдрому та шляхи корекції виявлених порушень» [redacted] 2/4/2025 Ukrainian Medical Stomatological Academy (UMSA) (UMSA)	5 (1) 0.01 %
8	SZYMANSKI_NI41965_20201112_3142_c062.pdf [redacted] 1/11/2024 Universitat de València (UV)	5 (1) 0.01 %
9	Factors Associated With Metabolic Syndrome In Type 1 Diabetes [redacted] 9/9/2020 Universitatea de Medicină şi Farmacie "Iuliu Hatieganu" din Cluj-Napoca (Universitatea de Medicină şi Farmacie "Iuliu Hatieganu" din Cluj-Napoca)	5 (1) 0.01 %

интернеттен (3.10 %)

РЕТТІК НӨМІР	ДЕРЕККӨЗДІҢ URL	БІРДЕЙ СӨЗДЕРДІҢ САНЫ
1	https://www.nature.com/articles/s41598-024-77928-z	77 (5) 0.22 %
2	https://www.medigraphic.com/pdfs/salpubmex/sal-2021/sal216e.pdf	67 (5) 0.19 %
3	https://edoc.site/cardiology-an-illustrated-textbook-jaypeepdftahir99-vrg-pdf-free.html	59 (10) 0.17 %
4	https://www.science.gov/topicpages/i/improving+metabolic+syndrome.html	54 (9) 0.16 %
5	**https://pdfs.semanticscholar.org/2539/520f36305c8ec1ba6a412cfb96983c6c31cb.pdf**	**46 (3) 0.13 %**
6	http://discovery.ucl.ac.uk/1470431/1/PhD_thesis_final_P_Huangfu_2015.pdf	43 (8) 0.13 %
7	https://link.springer.com/article/10.1007/s40200-023-01213-5	41 (3) 0.12 %
8	https://bmcmedicine.biomedcentral.com/articles/10.1186/1741-7015-9-48	40 (3) 0.12 %
9	https://cardiovascular.elpub.ru/jour/article/viewFile/2600/2088	39 (3) 0.11 %
10	https://mafiadoc.com/endocrine-abstracts-vol-49_5b7f64bd097c47450b8b46ef.html	36 (5) 0.10 %
11	https://mafiadoc.com/endocrine-abstracts-vol-56_5c189327097c47ab1a8b45f4.html	36 (6) 0.10 %
12	https://link.springer.com/content/pdf/10.1186/s12889-022-12753-5.pdf?pdf=button	33 (3) 0.10 %
13	https://www.ajol.info/index.php/ajnt/article/view/81808/71952	31 (3) 0.09 %

14	https://www.hindawi.com/journals/bmri/2021/6661457/	30 (3) 0.09 %
15	https://cardiab.biomedcentral.com/counter/pdf/10.1186/s12933-024-02145-x.pdf	29 (4) 0.08 %
16	https://ejim.springeropen.com/articles/10.1186/s43162-024-00375-9	28 (5) 0.08 %
17	https://pubmed.ncbi.nlm.nih.gov/30391988/	27 (2) 0.08 %
18	**https://www.ajol.info/index.php/ajhs/article/view/260493/245923**	**25 (1) 0.07 %**
19	https://pmc.ncbi.nlm.nih.gov/articles/PMC11416200/	23 (3) 0.07 %
20	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10043912/	22 (1) 0.06 %
21	https://pmc.ncbi.nlm.nih.gov/articles/PMC12055507/	22 (3) 0.06 %
22	https://ejmhr.com/index.php/journal/article/view/171	20 (1) 0.06 %
23	http://lib.dr.iastate.edu/cgi/viewcontent.cgi?article=2202&context=etd	20 (2) 0.06 %
24	https://www.nature.com/articles/s41366-020-00713-1	18 (3) 0.05 %
25	https://pmc.ncbi.nlm.nih.gov/articles/PMC8403373/	18 (2) 0.05 %
26	https://link.springer.com/article/10.1007/s12035-019-1533-2	18 (1) 0.05 %
27	https://link.springer.com/article/10.1007/s40200-025-01708-3	16 (1) 0.05 %
28	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4265590/	15 (1) 0.04 %
29	https://cyberleninka.ru/article/n/rasprostranennost-i-biomarkery-metabolicheskogo-sindroma	14 (1) 0.04 %
30	https://www.frontiersin.org/journals/public-health/articles/10.3389/fpubh.2024.1333910/full	12 (1) 0.03 %
31	https://www.eshonline.org/esh-content/uploads/2018/10/Download.pdf	11 (1) 0.03 %
32	https://pmc.ncbi.nlm.nih.gov/articles/PMC12106998/	11 (2) 0.03 %
33	https://springerplus.springeropen.com/articles/10.1186/s40064-016-3514-5	11 (1) 0.03 %
34	https://www.ajol.info/index.php/pamj/article/view/222156/209639	10 (1) 0.03 %
35	https://heart.bmj.com/content/91/suppl_5/v1	9 (1) 0.03 %
36	https://pubmed.ncbi.nlm.nih.gov/28109251/	9 (1) 0.03 %
37	https://journals.plos.org/plosone/article/file?id=10.1371/journal.pone.0196332&type=printable	9 (1) 0.03 %
38	https://koreascience.kr/article/JAKO202209461025984.page	8 (1) 0.02 %
39	https://www.frontiersin.org/articles/10.3389/fendo.2022.904001/full	7 (1) 0.02 %
40	https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0181039	6 (1) 0.02 %
41	https://cyberleninka.ru/article/n/osobennosti-etiopatogeneza-metabolicheskogo-sindroma	5 (1) 0.01 %
42	https://www.jcdronline.org/index.php/JCDR/article/download/718/699/1375	5 (1) 0.01 %
43	https://pmc.ncbi.nlm.nih.gov/articles/PMC9242664/	5 (1) 0.01 %
44	https://link.springer.com/chapter/10.1007/978-3-030-43027-6_11	2 (1) 0.01 %

Қабылданған үзінділер тізімі (үзінділер жоқ)

MINISTRY OF SCIENCE AND HIGHER EDUCATION OF THE REPUBLIC OF KAZAKHSTAN

KHOJA AKHMET YASSAWI INTERNATIONAL KAZAKH-TURKISH UNIVERSITY

Gulnaz Nuskabayeva

MODERN ASPECTS OF THE CONTROL OF METABOLIC SYNDROME IN OUTPATIENT CONDITIONS

Teaching manual

Turkistan

УДК 618.929 8

ББК 57.1

The educational material is presented in clear and accessible language, distinguished by a logical structure and practical orientation. It integrates both fundamental principles and contemporary data from biomedical science and clinical practice. The manual facilitates the development of professional competencies essential for independent clinical work in outpatient settings.
This tutorial can be recommended for broad application in the educational process of medical universities, in programs of continuing professional education, and as a practical resource for physicians engaged in primary health care.

REVIEWERS:

Sadykova K.Zh., PhD, associate professor, head of department of "Special clinical disciplines" Khoja Akhmet Yassawi International Kazakh-Turkish University

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The purpose of this manual is to present up-to-date information on metabolic syndrome, including its epidemiological features, pathogenesis, clinical manifestations, approaches to treatment and prevention. Special attention is given to issues of quality of life, treatment adherence, as well as the use of digital technologies and telemedicine in outpatient practice.
The material presented may be useful for medical university students, general practitioners, internists, cardiologists, and endocrinologists, as well as for all specialists interested in the problem of metabolic syndrome and its impact on public health.
Funding: This research was funded by the **Science Committee of the Ministry of Science and Higher Education of the Republic of Kazakhstan (Grant no. AP19676909)** and by the grant from the Best University Teacher-2024 competition, **Ministry of Science and Higher Education of the Republic of Kazakhstan.**

ISBN

Contain

NOTATIONS AND ABBREVIATIONS

ABPM Ambulatory blood pressure monitoring
AH - Arterial hypertension
AHA/NHLBI - American Heart Association and **National Heart, Lung, and Blood Institute**
AO - Abdominal obesity
ATP III - Third group on the treatment of adults
BMI - Body Mass Index
BP - Blood pressure
CRP C-reactive protein
DBP - Diastolic blood pressure
DNA - deoxyribonucleic acid
GLP-1 - glucagon-like peptide-1
HC - hip circumference
HyperTG - hypertriglyceridemia
HDLP - high-density lipoproteins
IDF - International Diabetes Federation
IR - insulin resistance
IL-6 - Interleukin-6
LDLP - low-density lipoproteins
MedDiet - Mediterranean Diet Adherence Screener
MHRK - Ministry of Health of the Republic of Kazakhstan
METS - **metabolic** syndrome
NADH - Nicotinamide Mononucleotide
NCEP-ATP **III - National Cholesterol Education Program** - The third group for the treatment of adults
RNA - ribonucleic acid
SBP - systolic blood pressure
TCH - Total cholesterol
T2 D - type 2 diabetes mellitus
TG - Triglycerides
VO - visceral obesity
VLDLP - very low-density lipoproteins
WC - waist circumference

INTRODUCTION

Metabolic syndrome is a complex cluster of interrelated metabolic disorders, including abdominal obesity, insulin resistance, dyslipidemia, and arterial hypertension. The combination of these factors significantly increases the likelihood of developing chronic non-communicable diseases-primarily cardiovascular and endocrine, as well as certain oncological pathologies-which is directly associated with an elevated risk of premature mortality. According to modern epidemiological studies, the prevalence of metabolic syndrome worldwide ranges from 20% to 30% of the adult population; however, in some regions, this figure exceeds these limits. The frequency of occurrence of the syndrome depends on a number of factors: geographical and ethnocultural characteristics, sex and age of patients, as well as the diagnostic criteria used, developed by various international associations [1].
It is believed that the increase in incidence in recent decades is mainly due to lifestyle changes. The so-called “westernization” of diet-dominated by high-calorie, refined, and fat-rich foods-in combination with low levels of physical activity contributes to the development of obesity and reduced tissue sensitivity to insulin. Socioeconomic shifts also exert a significant influence, especially in developing countries, where rising prosperity is accompanied by increased consumption of high-energy foods. The situation is further aggravated by population aging, the growing prevalence of obesity, and impaired glucose tolerance. Thus, if current trends persist, global healthcare will face an increasing burden of metabolic syndrome in the coming decades.
The key pathogenetic mechanism is insulin resistance-a reduction in the biological response of tissues to insulin action. This process is exacerbated under conditions of obesity, endothelial dysfunction, chronic subclinical inflammation, and alterations in the composition of the intestinal microbiota. Genetic factors also play a significant role: polymorphisms of several genes have been identified that are responsible for the regulation of lipid and carbohydrate metabolism, predisposition to cognitive impairments, and other clinical manifestations. International and national professional communities devote special attention to the study and treatment of metabolic syndrome, which is reflected in clinical guidelines and standards of medical care for obesity, arterial hypertension, diabetes mellitus, dyslipidemia, obstructive sleep apnea syndrome, and impaired glucose tolerance. The modern therapeutic strategy is based on an integrative approach: priority is given not to the isolated correction of individual manifestations of the syndrome, but to comprehensive interventions aimed at reducing overall cardiovascular risk, slowing the progression of complications, and improving patients’ quality of

life.
The earliest contact of an individual with the healthcare system in the case of metabolic syndrome occurs at the level of outpatient and primary care. Here, a leading role belongs to general practitioners and internists, whose competence determines the timeliness of diagnosis, the adequacy of therapeutic decision-making, and the effectiveness of preventive measures.
Based on this, the purpose of this study guide is to deepen knowledge and develop practical skills among healthcare professionals in the fields of epidemiology, etiopathogenesis, risk factors, clinical manifestations, diagnosis, and modern approaches to the treatment of metabolic syndrome. In addition, significant attention is given to mastering methods for assessing the quality of medical care at the outpatient stage.

The main objectives of the manual include:
Expansion of theoretical knowledge on the epidemiology, pathogenesis, risk factors, diagnosis, and treatment of patients with metabolic syndrome in primary healthcare settings.
Development of practical skills in history taking, physical examination, interpretation of laboratory and instrumental diagnostic results, establishing a clinical diagnosis, prescribing individualized therapy, and referring patients to specialized care.
Enhancement of clinical reasoning and analytical skills necessary for evaluating the course of the disease and the effectiveness of treatment in outpatient conditions.
The study guide covers key sections-from conceptual frameworks and epidemiological characteristics to modern strategies of diagnosis and treatment. Special attention is paid to practice-oriented tools: test assignments, clinical cases, and situational tasks that allow consolidation of acquired knowledge and the development of professional competencies.
The novelty and value of the manual lie in the integration of up-to-date scientific data, international and national guidelines, as well as the systematization of practical algorithms for patient management at the outpatient stage. The presented material is aimed at developing competencies necessary for providing high-quality and effective care to patients with metabolic syndrome, as well as at stimulating interest in further in-depth study of this multidisciplinary problem.

CHAPTER 1. EPIDEMIOLOGY AND PATHOGENESIS OF METABOLIC SYNDROME

1.1 Prevalence of metabolic syndrome in the world

Metabolic syndrome (METS) is one of the most important medical problems in the world today, and although there are numerous studies on this problem, some aspects are still being discussed in healthcare. The presence of components such as abdominal obesity (AO), insulin resistance (IR), lipid disorders, and high blood pressure (BP) **increases the risk of developing** cardiovascular disease, **type 2 diabetes mellitus (T2D)** and their complications [2]. According to epidemiological studies, in most countries, 20 to 30% of the adult population suffers from METS. However, the prevalence of METS varies around the world, for example, the incidence of METS varies, 32.9% in Turkey [3], 30.0% in Bangladesh [4], 45.3% in Mexico [5], 43.0% in Japan [6].
The following diagnostic criteria were used to study the **prevalence of METS in the** adult population of Iran, **the International Diabetes Federation (IDF), the National Cholesterol Education Program - Adult** Treatment Group III **(NCEP-ATP III),** Adult Treatment Group III (ATP III), and the American Heart Association **and the National Heart, Lung, and Blood Institute** (AHA/NHLBI). For the study, the interval from 2009 to 2017 was taken. 2009 showed **that the prevalence of METS** ranged from 16.6% (ATP III) to 23.70% (AHA/NHLBI). Over 8 years, there was an **increase in the prevalence** of METS from 5.2% to 7.3%, and thus the incidence of METS ranged from 21.8% (ATP III) to 31.0% (AHA/NHLBI). Moreover, according to NCEP-ATP III, it increased from 17.9% in 2009 to 24.3% in 2017 (by 6.4%) [7].
Other studies conducted in the United Arab Emirates using three criteria found **that the prevalence of METS was** 14.7%, 19.5%, and 22.4% **according to ATP III,** IDF, and JS, respectively [8]. Similar studies were conducted in 29 African countries, where the results were 44.8%, 39.7%, 33.1%, 31.6%, and 29.3% using diagnostic criteria [9].
In Latin America, the prevalence of METS varies, **in** Bolivia within **44.1%** [10], and **in Peru, according to** the **IDF and ATPIII** definitions, the **prevalence** of METS was **35.3% and 28.2%,** respectively. **A systematic review of the** region showed 24.5%, which is lower than in other studies conducted in Europe and Asia [11].
Thus, Table 1 presents the results of a study in recent years, which indicates the overall prevalence of METS using the IDF criterion and NCEP-ATP III. In the CIS countries, there is also a high prevalence of METS, for example, in 2017, **the population of** four regions of Russia (**Krasnodar** Territory, Meteorological **and Ryazan** Regions, Republic **of** Karelia) was **examined, men (n=3011) and women (n=3721) aged 25-64** years were selected for the study. METS was detected in 33% of the examined, and with age, **the proportion of people with** risk factors such as **smoking, insufficient consumption of vegetables and** fruits, lack of higher **education,** and below-average income [12]. The same trend is observed in Uzbekistan, according to the author, the growth of METS is due to an increase in obesity, changes in lifestyle and nutrition [13].

Table 1 - Prevalence of metabolic syndrome according to epidemiological studies

No	Prevalence %	Country	References
International Diabetes Federation (IDF)			
1	10,3	Iran	Jamali Z, **et al. Metabolic syndrome: a population-based study of prevalence and risk factors. Sci Rep., 2024**
2	22	Nigeria	**Bowo-Ngandji A, et al. Prevalence of the metabolic syndrome in African populations: A systematic review and meta-analysis. PLoS One.,** 2023
3	23,7	Ethiopia	Belete R, et all. **Global prevalence of metabolic syndrome among patients with type I diabetes mellitus: a systematic review and meta-analysis. Diabetol Metab Syndr., 2021**
4	35,0	Sri-Lanka	Ranasinghe P, et all. **Prevalence and trends of metabolic syndrome among adults in the asia-pacific region: a systematic review. BMC Public Health., 2017**
5	31,5	France	Prioux C, et al. Cross-sectional associations between healthy and **unhealthy plant-based diets** and metabolic **syndrome in** three distinct French populations: a meta-analysis. Br J Nutr., 2025	
6	51	Italy	Obeidat, A.A.; et al. Developmental Trends of Metabolic Syndrome in the Past Two Decades: A Narrative Review. J. Clin. Med, 2025
NCEP-ATP III			
1	32,9	Turkish	Abacı A, et all. **Data on prevalence of metabolic syndrome in Turkey: Systematic review, meta-analysis and**

meta-regression of epidemiological studies on cardiovascular risk factors. Turk Kardiyol Dern Ars., 2018

2 30,0 India **Krishnamoorthy Y,** et all. Prevalence **of metabolic syndrome among adult population in India: A systematic review and meta-analysis. PLoS One.,** 2020

3 37,3 и 29,8 Latin America Zila-Velasque J.P. **Prevalence of metabolic syndrome and its components according to altitude levels: a systematic review and meta-analysis. Sci** Rep., 2024

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Differences in the prevalence of METS in **the world can be explained by marked cultural differences,** lifestyle characteristics, genetic predisposition, hormonal factors and racial characteristics [14].

1.2 Prevalence of metabolic syndrome by sex and age

Gender differences are an important aspect of epidemiological research. The biological, behavioural and sociodemographic factors underlying gender differences require further integrated study [15].

Most studies have reported a higher prevalence of METS in women. For example, in Indonesia, the incidence of METS in women is 46%, which is significantly higher than in men (28%) [16]. In the analysis of each component of the METS, according to the IDF criteria, a difference between the sexes was found for all components of the METS, with the exception of blood glucose. However, when the METS was assessed **according to the criteria of Cook et al. and de Ferranti et al.,** these differences were found only in triglyceride (TG) and high-density lipoprotein (HDLP) levels, suggesting that the results were dependent on the diagnostic criteria used [17].

Karl Krupp et al. found a high prevalence of METS among women in rural areas, which amounted to 47.1%. Among those with MS, 56.5% met three of the five diagnostic criteria, 32.2% met 4 criteria and 11.2% met all 5 criteria. Among the entire sample, the most common criterion was low HDLP (88.4%), followed by elevated glucose (57.9%), TG (49.3%), elevated BP (41.5%) and increased waist circumference (WC) (15.3%). The prevalence of METS among older women and housewives was higher than in other groups, possibly due to physical inactivity, diet, and low levels of medical supervision [18].

The prevalence of METS in the central regions of the Krasnoyarsk Territory, according to the **revised NCEP/ATP-III criteria,** is 26.8%. **With age, the prevalence of** METS increased substantially, from 6.9% (25-34 years) to 45.2% (55-64 years). The frequency of METS detection was significantly higher in rural residents compared to urban residents. The level of education had a significant impact on the prevalence of METS, so in people with primary education, METS was found in 35.7%, with secondary education in 30.3%, with higher education in 17.8%. METS is more common among women than men and in rural areas compared to urban populations. With increasing levels of formation, METS is less common, although the prevalence of METS increases substantially with age. The correlation is not traced with all components of the METS and has gender differences [19].

A study of the prevalence of METS and its components in the city of Zahedan (southeastern Iran) between 2009 and 2017 using the IDF, NCEPATP III, ATP III, and AHA/NHLBI criteria revealed that two components of METS, including AO and T2D, showed an increasing trend, while elevated BP, hypertriglyceridemia (HyperTG), and low HDLP levels were reported less frequently. that the upward trend in METS was noticeable among women than among men, as well as among those aged <40 years compared to ≥40 years. In addition, over 8 years, the annual increase in prevalence was approximately 1% per year, and the overall prevalence of METS among women increased by 6-7.6% [20].

Similar results were found among patients in Northern India, where the prevalence of METS by sex was 59% among women and 26.2% among men. The authors also noted a marked increase in the prevalence of MS among women (0.75% to 0.95% per year) compared to men (0.13% to 0.46% per year) during the study period [21].

In a meta-analysis by Farmfarma K. et al., METS was more common in women, amounting to 34.8% compared to 25.7% in men. According to the authors, the higher prevalence of METS among women may be due to age-related hormonal changes, in particular a decrease in postmenopausal estrogen levels, which leads to an increase in visceral obesity (VO) and a decrease in metabolic regulation [22]. Although in the work of Mazloomzadeh et al., he high prevalence of METS among women may be due not only to hormonal changes, but also to behavioral factors such as lifestyle, low physical activity, nutrition [23].

A systematic review found that METS is widespread in Brazil at 33%, with a higher prevalence among women at 38% compared to men at 26%. In addition, significant differences were found depending on the diagnostic criterion used, the region of residence, ethnic groups, as well as urbanization, for

example, the highest rates were among indigenous peoples and in the central-western region of the country. The prevalence of METS was similar in males and females, while remaining highly heterogeneous [24].
Cross-sectional study has shown that the prevalence of METS depends on the diagnostic criterion used. Thus, when assessing METS by sex, female adolescents had a higher prevalence according to the IDF criteria (19) (p = 0.017). However, when METS was assessed using the Cook and de Ferranti criteria, the prevalence of METS was higher in males (p<0.05). Such results highlight the need to develop uniform standards for clinical practice and screening programs in order to improve prevention at the population level [25].
Although many studies have reported a higher prevalence of METS in women, there are a number of authors in whose studies METS is more common in men in individual populations and regions. The results of a cross-sectional study in high-altitude regions of China involving 5,053 people showed that the prevalence of METS is higher in men (5.9%) compared to women (1.8%) [26]. At the same time, the most common components were obesity and arterial hypertension (AG). The authors confirm that the height of residence can have a significant impact on the development of METS.
Sigit F.S. and et al., found that the prevalence of METS in men living in the Netherlands is higher (36%) than in women (24%) [27]. In addition, AO was found to be a significant predictor of METS.
Studies conducted in Kazakhstan revealed that the prevalence of METS among people of reproductive age was 18.1% (19.1% in men, 17.1% in women). The most common components of METS were AO (42.9%), hypoalphacholesterolemia (29.8%), HyperTG (9.5%), hyperglycemia (5.7%), and AG (40.3%). Among the components of METS, HyperTG (p=0.024) and AG (p<0.001) were found to be more common in men than in women [28].
In addition, according to many authors, the prevalence of METS among children and adolescents is increasing. In Figure 1, presented by Noubiap et al., the results showed that the highest rate among children was found in Mexico (12.3%), and among adolescents in Iran (9.0%), the UAE (9.8%) and Spain (9.9%) [29].

Figure 1 - **Prevalence of metabolic syndrome among children and adolescents** (adapted from [29])

The prevalence of METS in children and adolescents ranged from 0.3% to 26.4%, with the authors stating that the increase in the number with METS depended on the criterion used. For example, for IDF, the prevalence of METS ranged from 0.3% to 9.5%, while for de Ferranti from 4.0% to 26.4%. The authors analyzed sex differences due to differences in hormonal regulation during puberty, emphasizing that the variability in the level and action of sex hormones in boys and girls affects the pace, sequence, and severity of pubertal changes [30].
A study conducted as part of ERICA showed that the prevalence of METS, according to IDF criteria, is 2.1% among girls and 3.3% among boys in Brazilian adolescents aged 15 to 17 years [31].
According to the Ministry of Health of the Republic of Kazakhstan (MHRK), overweight before the age of 12 leads to a 14.86-fold increase in the risk of developing METS (27.2 in men, 18.9 in women) (p <0.001), physical inactivity in men in 2.06, and in women 3.3). It was also noted that having a family, moderate alcohol consumption, exercising, and avoiding fatty and sugary foods (p<0.05) were associated with a reduced risk of developing METS [28]. The data obtained need to be adapted to regional conditions for early liagnosis and prevention of METS in pediatrics.
A multivariate model using logistic regression showed that age is significantly associated with METS. For example, in a study of the prevalence of METS, it was noted that there was an association between age and METS among patients with severe mental pathology [32]. Elderly patients with such disorders may be exposed to antipsychotics for longer periods of time than younger patients and thus are more prone to the development of metabolic complications. Therefore, the authors consider age as a reason to evaluate patients with psychiatric disorders in individuals with METS and to introduce metabolic screening into psychiatric practice in order to develop national guidelines for the identification and control of metabolic disorders in such patients.
According to Aguilar et al., the prevalence of METS among U.S. adults increases significantly with age, from 18.3% in the 20-39 age group to 46.7% in those over 60 years of age [33].
According to Hirode et al., there was a high prevalence of METS in individuals over 60 years of age (48.6%) compared to 19.5% in groups under 40 years of age. In addition, there is an increasing trend of increasing prevalence for each year of middle age, indicating age as an independent prognostic factor [34].
The prevalence of MS was approximately twice as high in ≥40 years of age as in <40 years of age, based on different diagnostic criteria and the two study periods. Indeed, the incidence of METS changed from 24.7% (ATP III) to 32.6% (AHA/NHLBI) among patients aged ≥40 years in 2009, showing an increase of 1.2% to 3.7% during the two study periods. In 2009, between 9.30% and 15.9% of those under the age of 40 had METS. Interestingly, the prevalence of METS increased by 4.6% to 5.9% among patients aged <40 years based on various criteria [20]. Based on the data obtained, it can be noted that age is an independent and significant risk factor for the development of METS.
Thus, despite differences in diagnostic methods and criteria, there is a trend towards an increase in the prevalence of METS in all regions of the world. Data on gender and age characteristics of the prevalence of METS serve as a basis for the study and development of targeted prevention and monitoring programs.

1.3 Prevalence of components of metabolic syndrome

Based on the data of world studies, it has been established that METS and its components are risk factors for the development of cardiovascular diseases of atherosclerotic origin. Analysis of the results of experimental and clinical studies showed that the presence of a single link between the components of METS and the formation of clusters increases the atherogenic potential of each component, which ultimately accelerates the development of atherosclerosis by 2-3 times [35].
Studies on the prevalence of METS and its components report conflicting results due to differences in the diagnostic criteria used. However, it is generally recognized that the prevalence of this pathology is increasing in both developed and developing countries, accompanied by rise of T2D, hypertension, cardiovascular diseases and obesity. The prevalence of METS depends on many factors that contribute to its development, which explains the complexity of diagnosis and approaches to the prevention and treatment of this pathology. The adverse effects of such a combination as AO, AG, dyslipidemia (HyperTG) and a decrease in HDLP, elevated fasting glucose levels are so great that a number of authors have justified the rather gloomy term "silent killer" to METS. It has been proven that people with METS have a 2-3-fold increased risk of developing coronary heart disease in the next 10 years, T2D by 3.5-5 times, and overall mortality by 1.2-1.6 times compared to individuals who do not have this syndrome [36].
Analyzing data from 27,800 Mexican adults who took part in the study in 2006, 2012, 2016, and 2018, it was found that the prevalence of METS among Mexican adults was 40.2%, 57.3%, 59.99%, and 56.31% in 2006, 2012, 2016, and 2018, respectively (< 0.0001). In 2018, 7.62% of METS cases had a significant risk of developing T2D and 11.6% of cardiovascular disease cases. There are an estimated 36.5 million adults living with

METS in Mexico, of which 2 million and 2.5 million are at high risk of developing T2 D or cardiovascular disease, respectively, over the next 10 years [37].
Current demographic changes in South Korea, characterized by an increase in the share of single households, are accompanied by significant shifts in eating behavior and the health status of the population. Figure 2 shows the incidence of different combinations of METS components in adults in Korea depending on the type of housewife.
Thus, both groups are characterized by a combination of all five components, only single housewives are characterized by combinations that include AO and AG, while for family housewives an isolated increase in BP is typical [38].
The predominant components of METS in Indonesians were hypertension (61%) and hyperglycemia (51%), in the Dutch population - hypertension (62%) and AO (40%). South Asian Americans had a high incidence of AO. More than half of people with diabetes live in Southeast Asia and the Western Pacific. Over the next 25 years, the increase in the incidence of diabetes is expected to be particularly significant in Africa. The incidence of diabetes is higher in the indigenous peoples of the United States (15% among American Indians), but not among the Chinese (4.3%). Men, living in the Netherlands have higher rates (36%) than women (24%). In Indonesian women, this rate is higher than the incidence of METS components among males (46% and 28%, respectively) [39].
The prevalence of METS and its components in the Brazilian population was estimated, where WC (65.5%) and low HDLP (49.4%) were the most common components, including in the youngest people. METS and its components were more common among women (41.8%), those with low levels of education (47.5%) and the elderly (66.1%) [40].

Figure 2 - Frequency of occurrence of various combinations of components of metabolic syndrome (adapted from [38]).

The cumulative prevalence of METS components in the adult population in Vietnam was 16.1%, with a higher prevalence observed among women of 17.3%. Low HDLP was the most common component (34.1%), followed by high TG (33.3%). Female sex, living in urban areas, obesity, and a higher body mass index (BMI) or body fat percentage were associated with an increased likelihood of developing METS [41].
Another analytical study used a sample of university students from Iraq, between October 2021 and February 2022. As the results showed, 41.3% of participants had METS, with the highest incidence occurring in women (66.9%). The most common component was elevated fasting blood glucose (98.3%), followed by elevated WC (87.9%) and finally low HDLP (85.4%). that the following factors predispose to METS are female sex, age over 20 years, obesity, high consumption of fast food, and physical inactivity [42].
As a result of a survey conducted among the residents of the city of S. In Arkhangelsk, it was found that the most common component of METS was AG, occurring in 68-96% of all men and 38-94% of all women in the study. In addition to AG, an increase in glycated hemoglobin and HyperTG levels was more common in men, while an increase in glycated hemoglobin levels and a decrease in HDL-C levels were more common in women [43].
The prevalence of METS components was estimated using IDF 2005, 2009 and CDS 2013, the results showed significant differences in sex and body mass index. Since all components of METS are reversible, their early identification using data from medical examinations can lead to the development of effective approaches to the prevention of obesity, cardiometabolic diseases and T2D. Based on the findings, the researchers recommend the use of uniform international diagnostic criteria (METS) to determine exactly at which levels (e.g., BP, blood glucose, WC) can be diagnosed. This data is essential to understand and compare outcomes across countries and populations in the same way [44].

1.4. Relationship of metabolic syndrome with other diseases
Numerous studies have shown that the pathogenetic relationship between METS and other diseases is due to a number of mechanisms, such as endothelial dysfunction, chronic inflammation, oxidative stress, hormonal changes, and disruptions to the gut microbiota.
The relationship between METS and the development of many chronic diseases (cardiovascular pathology, non-alcoholic fatty liver disease, arthritis, chronic kidney disease) is noted in for many decades. The study determined the prevalence of METS and its components in people with and without chronic obstructive pulmonary disease. Thus, the results of prospective epidemiological studies showed that the prevalence of METS in patients with chronic obstructive pulmonary disease was 28.4% and 31%, respectively. of people with chronic obstructive pulmonary disease had low levels of HDLP (47.4%), WC (43.9%) and high fasting plasma glucose (39.3%). There was a statistically significant difference in the incidence of respiratory dysfunction between people with and without METS. Age over 60 years (OR = 2.20, 95% CI: 1.72-2.80), women (OR = 1.36, 95% CI: 1.49-1.97), obesity (OR = 11.17, 95% CI: 9.02-13.62) and lack of education (OR = 1.80, 95% CI: 1.49-2.17), as well as living in urban areas, are stronger predictors of METS in this population [45].
The results of studies suggest that non-alcoholic fatty liver disease shows a strong bidirectional association with METS. Non-alcoholic fatty liver disease significantly increases the risk of METS and can also be considered as an independent risk factor for the development of certain cardiovascular diseases [46]. Given that non-alcoholic fatty liver disease is often combined with metabolic diseases such as obesity, T2D, hyperlipidemia, and hypertension, it may have negative prognostic effects. In addition, BMI and nonalcoholic fatty liver disease show a strong correlation [47]. Interestingly, non-alcoholic fatty liver disease also occurs in people without obesity, with most of these findings occurring in Asian countries, although they have been described worldwide. Despite phenotypic differences, non-alcoholic fatty liver disease patients who were not obese had similar severity of histological liver injury [48].
Currently, there are limited studies that have evaluated the association of thyroid antibodies with METS components in adults, especially from regions where iodine concentrations are sufficient. The study determined the prevalence of METS components in Chinese adults with autoimmune thyroid disease. A higher prevalence of thyroid antibodies was observed in women than in men (30.6% versus 23.7%) (p=0.034) [49].
In an analysis of data from the U.S. National Health and Nutrition Examination Survey (NHANES) from 2011 to March 2020, which included 10,175 individuals examined, hyperuricemia was classified as a serum uric acid concentration greater than 7.0 mg/dL in men and 5.7 mg/dL in women, according to the diagnostic criteria adopted by NHANES III. the prevalence of METS was 45.9% and hyperuricemia was 20.7%. Between 2011 and 2020, a significant increase in the prevalence of METS was observed in the Hispanic and Asian populations, and the prevalence of hyperuricemia increased significantly only in the Hispanic population. After adjusting for mixed factors in METS patients Higher hyperuricemia was observed in women than in men. Elevated BP was the strongest factor in hyperuricemia [50].
There have been studies that have shown that hyperuricemia is associated with insulin resistance. Li Y et al. showed that elevated uric acid levels are strongly associated with IR in patients without diabetes. Established statistical associations (including HOMA index, glycated hemoglobin, and HDLP TG-to-C ratio index indicate a potential role for hyperuricemia as a marker of early metabolic dysfunction [51].
Other authors have suggested that there is an ethnically specific pattern of METS and hyperuricemia. There are rapid changes in the prevalence of METS components and hyperuricemia depending on socioeconomic status and food intake [52].

A retrospective cohort study found that patients with myeloma had a higher prevalence of diabetes at baseline and had a higher risk of developing diabetes at 1 year, AG at 5 years, and dyslipidemia at 1, 3, and 5 years of follow-up compared to patients without myeloma. In addition, myeloma patients were more likely to develop dyslipidemia after 1, 3 and 5 years of follow-up compared to the control group. This supports the view that the characteristics of myeloma itself may be associated with an increased risk of various components of METS, and warrant future prospective studies of these components [53].

It was proven that almost half of patients (53.3%) with endometrial cancer were diagnosed with METS. The features of the course of endometrial cancer against the background of METS were a moderate degree of differentiation (in 71.8% of cases) and the depth of tumor invasion up to 1/2 of the myometrium (in 65.3%). At the same time, the most common version of METS was a 4-component one. Significant factors in the 3-year recurrence-free survival of patients were the presence or absence of METS, TG level and fasting blood glucose, which once again emphasizes the impact of METS not only on the development of endometrial cancer, but also on the survival of patients. The analysis and the results of early studies suggest the need to develop strategies to reduce the prevalence of METS components that can have an impact on both morbidity reduction and long-term survival rates [54].

Thus, the analysis of epidemiological data shows a trend towards an increase in the prevalence of METS in different ethnic, age, gender groups, in addition, the presence of metabolic syndrome increases the risk of adverse outcomes, accelerates progression and reduces the quality of life of people. An integrated approach, namely early diagnosis, lifestyle changes, and correction of risk factors, are the main condition for reducing the negative impact of metabolic syndrome on public health.

CHAPTER II. CURRENT UNDERSTANDING OF THE PATHOGENESIS OF METABOLIC SYNDROME

2.1. The Role of Insulin Resistance in the Development of Metabolic Syndrome

The development of METS is closely linked to the influence of modifiable environmental and lifestyle factors, which are currently regarded as the key determinants of this pathological condition. Rapid urbanization, changes in dietary habits, the widespread availability of high-calorie “fast” food, and chronic psycho-emotional stress create conditions for persistent disruptions of the body’s adaptive mechanisms, thereby explaining the high prevalence of METS in the population.

Among the most significant exogenous factors are excessive caloric intake, particularly from saturated fats, refined carbohydrates, and highly processed foods. Such dietary patterns lead to a positive energy balance, promote fat accumulation, and contribute to obesity. The modern shift toward the so-called “Western diet” is characterized by a deficiency of dietary fiber, vitamins, and antioxidants, which impairs carbohydrate and lipid metabolism, exacerbates inflammatory processes, and plays an important role in the development of IR.

Low levels of physical activity represent another major pathogenic factor. A sedentary lifestyle reduces tissue sensitivity to insulin, decreases mitochondrial activity, and promotes the accumulation of visceral fat. Visceral adipose tissue is metabolically active, producing a wide range of pro-inflammatory cytokines and adipokines that sustain chronic subclinical inflammation and aggravate metabolic disturbances.

Chronic stress and disruption of circadian sleep rhythms also play a crucial role in the pathogenesis of METS. Prolonged exposure to stress activates the hypothalamic-pituitary-adrenal axis, resulting in hypersecretion of cortisol. This hormone stimulates lipogenesis in visceral fat, decreases tissue sensitivity to insulin, and thereby contributes to obesity. Sleep disturbances further exacerbate these effects by disrupting leptin and ghrelin secretion, which increases appetite, raises caloric intake, and ultimately worsens metabolic disorders [55].

The schematic illustration (Figure 3) reflects the key pathogenetic interrelationships in the development of METS. At the center of this system lies IR, which is closely associated with obesity. Excess adipose tissue amplifies IR, promotes oxidative stress, and sustains chronic inflammation, all of which damage the vascular wall. This leads to endothelial dysfunction, accompanied by elevated BP. Collectively, obesity, IR, chronic inflammation, endothelial dysfunction, AG, and autonomic nervous system imbalance form a vicious pathological cycle, in which each factor reinforces the others, shaping the clinical picture of METS.

Figure 3. Relationship between the components of metabolic syndrome (adapted from [56]).

It was previously believed that IR is the primary factor in the initiation of METS. Under hyperglycemia, excess glucose accumulates in endothelial cells and, together with glycation products and free fatty acids, induces pronounced oxidative stress that damages the vascular wall. Excessive fatty acid oxidation results in the accumulation of acetyl-CoA and reduced forms of nicotinamide adenine dinucleotide (NADH), which activate pyruvate dehydrogenase kinase 4 and inhibit pyruvate oxidation.

Under normal conditions, insulin binds to receptors on the cell surface and initiates a signaling cascade, including phosphorylation of insulin receptor substrates, activation of PI3K/Akt, and translocation of glucose transporters (GLUT4) to the cell membrane. This ensures glucose uptake into cells and lowers its plasma concentration. In IR, this process is impaired, leading to reduced glucose utilization and compensatory hyperinsulinemia [57].

According to G.I. Shulman et al., an important mechanism of IR development is the accumulation of lipid metabolites, particularly diacylglycerols and ceramides, in the liver and muscle tissue. These molecules activate serine/threonine kinases (e.g., PKC), which inhibit insulin receptor substrate activity and disrupt further signal transduction [58]. Additionally, visceral adipose tissue secretes pro-inflammatory cytokines such as tumor necrosis factor- α (TNF-α), interleukin-6 (IL-6), and others that promote IR progression by activating inflammatory pathways and suppressing GLUT4 expression. Chronic inflammation is further amplified by macrophage infiltration of adipose tissue [59].

In IR, the liver becomes resistant to the insulin-mediated suppression of gluconeogenesis. As a result, hepatic glucose production continues even in hyperinsulinemia, leading to fasting hyperglycemia-an early marker of T2D. At the same time, hepatic synthesis of triglycerides and very-low-density lipoproteins (VLDL) is enhanced, contributing to an atherogenic dyslipidemia profile.

Chronic hyperglycemia and excess fatty acid influx exert multifactorial metabolic effects, including impaired vascular smooth muscle cell proliferation, reduced antioxidant defense, and enhanced lipid peroxidation. Endothelial dysfunction is accompanied by hypercoagulation, increased vascular permeability, subendothelial lipoprotein migration, and accelerated atherosclerotic plaque formation. Elevated free radicals reduce nitric oxide levels, aggravating endothelial dysfunction. In MS, these processes often lead to endothelial cell apoptosis and impaired intracellular energy metabolism.

The cardiovascular system is one of the most vulnerable targets of IR. Normally, insulin stimulates endothelial nitric oxide synthase (eNOS) activity, ensuring vasodilation and improved tissue perfusion. In IR, eNOS activity decreases, while the expression of vasoconstrictors (e.g., endothelin-1) increases, predisposing to atherosclerosis. An additional role is played by adipokine imbalance: reduced adiponectin levels, which have anti-inflammatory and anti-atherogenic properties, are associated with adverse outcomes in patients with abdominal obesity [60].

Beyond exogenous factors, genetic and epigenetic mechanisms are also crucial in IR development. Mutations in insulin receptor genes, PI3K/Akt pathway proteins, as well as polymorphisms affecting lipid metabolism and inflammation, reduce tissue insulin sensitivity. Epigenetic modifications,

including DNA methylation and histone modifications, further regulate the expression of key metabolic genes, forming an individual predisposition to METS.

Thus, IR represents a universal mechanism underlying most pathological manifestations of METS. A deep understanding of the molecular and systemic aspects of IR not only clarifies the pathogenetic basis of METS but also defines strategic targets for developing effective preventive and therapeutic interventions.

2.2. The Role of Visceral Obesity

VO is a central component in the pathogenesis of METS (Figure 4).

VO establishes a characteristic endocrine-inflammatory background that triggers a cascade of disturbances in carbohydrate and lipid metabolism, development of IR, endothelial dysfunction, and chronic subclinical inflammation. Unlike subcutaneous adipose tissue, which primarily serves as an energy depot, visceral fat is highly metabolically active and functions as an endocrine organ. It secretes a wide spectrum of biologically active molecules, including adipokines, pro-inflammatory cytokines, stress-axis hormones, and microRNAs. This accounts for its specific contribution to IR, atherogenic dyslipidemia, and, consequently, cardiovascular and endocrine complications.

Figure 4. Pathogenetic role of visceral obesity in the development of metabolic syndrome

Anatomically, visceral fat is located within the abdominal cavity, surrounding the liver, pancreas, and intestines. Venous drainage occurs mainly through the portal vein, exposing the liver directly to free fatty acids and inflammatory mediators. This explains the early development of hepatic IR, progression of non-alcoholic fatty liver disease, and the emergence of atherogenic dyslipidemia. Moreover, visceral adipocytes exhibit increased lipolytic activity, enhancing free fatty acid release into the portal circulation, maintaining hyperlipidemia, and worsening glucose metabolism disorders.

VO is closely associated with chronic low-grade inflammation. Visceral adipocytes and infiltrating macrophages produce pro-inflammatory mediators:

- TNF-α, IL-6 - impair insulin signaling (via serine/threonine kinase activation) and disrupt insulin receptor function;
- IL-1β, IL-18 - sustain the inflammatory cascade and contribute to atherogenesis;
- C-reactive protein (CRP) - its concentration correlates with VO severity and clinical manifestations of MS.

Systemic inflammation accelerates endothelial dysfunction and the progression of atherosclerosis, thereby increasing the risk of cardiovascular events.

VO is an active source of hormone-like molecules, which are summarized in Table 2.

Table 2 - Major Adipokines of Visceral Adipose Tissue

No	Adipokine	Mechanism of Action	Change in VO	Consequences
1	Adiponectin	Improves insulin sensitivity, exerts anti-inflammatory effects	↓	Increased IR and inflammation
2	Leptin	Regulates appetite and energy metabolism	↑	Appetite dysregulation, obesity
3	Resistin	Participates in glucose metabolism regulation	↑	Insulin resistance
4	Visfatin	Mimics insulin action	↑	Dysregulation of glucose homeostasis
5	RBP-4	Retinol transport	↑	Impaired carbohydrate metabolism, IR
6	TNF-α, IL-6	Minimal expression under normal conditions	↑	Chronic inflammation, endothelial dysfunction

Adiponectin. One of the key links connecting obesity, IR and inflammation. Its receptors - AdipoR1 (predominantly expressed in skeletal muscle, skin, and subcutaneous adipose tissue) and AdipoR2 (mainly in the liver) - mediate tissue-specific effects. For example, through AMPK activation, adiponectin enhances glucose utilization in muscles and suppresses hepatic gluconeogenesis, improves the lipid profile by increasing HDL cholesterol and reducing TG, downregulates pro-inflammatory cytokine expression, and protects the endothelium [61]. The adiponectin gene locus (3q27) is associated with an unfavorable metabolic phenotype, and its polymorphisms are linked to variability in the risk of cardiometabolic disorders.

Adiponectin also enhances mitochondrial biogenesis in adipocytes, reduces their size, promotes esterification of free fatty acids, and in several models demonstrates a protective effect against MS [62]. Its action is largely antagonistic to leptin: whereas leptin increases TNF-α and IL-6 production and thereby promotes IR, adiponectin suppresses inflammatory signaling pathways, being associated with better glycemic control and a more favorable lipid profile [63].

Hypoadiponectinemia, in contrast, is linked to the development of cardiovascular pathology and increased cardiovascular risk. In patients with AG, adiponectin levels are significantly lower than in normotensive individuals [64]. Moreover, an inverse association between adiponectin and smoking has been demonstrated, showing that the intensity of smoking correlates with a loss of adipose tissue’s ability to synthesize this cardioprotective adipokine, thereby contributing to elevated cardiovascular risk in smokers.

Several clinical studies in patients with acute myocardial infarction revealed an inverse correlation between adiponectin and troponin I levels, as well as an association of low adiponectin with more pronounced insulin resistance (HOMA-IR) and metabolic destabilization; however, the findings across different studies are inconsistent [65].

Increasing adiponectin levels is considered a potential therapeutic target: weight loss, adherence to a Mediterranean diet, higher intake of fish and omega-3 fatty acids, and moderate coffee consumption are all associated with elevated adiponectin. Among pharmacological agents, increases in adiponectin have been reported with certain hypoglycemic drugs (thiazolidinediones, SGLT-2 inhibitors), lipid-lowering agents (fenofibrate), and antihypertensive drugs (ACE inhibitors, angiotensin receptor blockers). However, the effect is not uniform within classes, as shown, for example, for azilsartan compared with other ARBs.

Resistin. The hormone’s name reflects its ability to induce IR in mice, where it is mainly secreted by visceral adipocytes. In humans, however, most studies indicate that macrophages are the primary source, underscoring its close association with inflammation. Human oligomeric resistin stimulates pro-inflammatory cytokine production, sustaining chronic low-grade inflammation. Clinical data show that in patients with T2DM, elevated resistin levels are associated with increased risk of major cardiovascular events and overall mortality. The contribution of resistin to atherogenesis is mediated via endothelium-dependent mechanisms: promotion of endothelial and smooth muscle cell proliferation and migration, increased endothelial permeability, and leukocyte adhesion. Accordingly, resistin levels correlate with recurrent coronary events in patients after acute coronary syndrome [66], with similar findings reported by local researchers [68]. A hyperresistinemia threshold >8.5 ng/mL is considered a risk factor for long-term cardiovascular complications after acute coronary syndrome and stenting.

Apelin. A relatively novel adipokine, apelin levels increase with obesity and are strongly linked to abdominal (visceral) fat distribution. Plasma apelin concentration rises proportionally with the severity of AO and correlates with WC and WC/hip ratio. Elevated levels are also recorded in obesity with

hyperinsulinemia; multiple studies in T2D have shown increased apelin [68]. Interestingly, in T1D, the rise in apelin is even more pronounced, suggesting regulation beyond fat mass alone. In T2D cohorts, apelin has been shown to negatively correlate with glycated hemoglobin, implying its role in glycemic control and insulin sensitivity [69].

Beyond carbohydrate metabolism, apelin contributes to AG pathogenesis [70]. In obese patients, apelin levels are lower in those with AG compared to normotensive individuals. Apelin concentration varies by AG grade: higher in stage 2 compared to stage 1, but decreasing again in stage 3, possibly reflecting breakdown of compensatory mechanisms. Lower apelin levels in patients with combined AG and T2D compared with non-hypertensive patients correlate with disease duration and diastolic blood pressure (DBP), suggesting depletion of apelin production with chronic disease. The relationship between apelin and DBP supports its vasodilatory role. A meta-analysis confirmed that reduced circulating apelin is strongly associated with increased AG risk [71].

The adipokine imbalance characteristic of VO-elevated resistin and leptin alongside reduced adiponectin and variable apelin-creates a distinctive endocrine-inflammatory profile that sustains IR, endothelial dysfunction, and atherogenesis, thereby accelerating MS development.

Portal hypothesis. One of the fundamental mechanisms of VO pathogenesis is the direct portal influx of adipose-derived mediators to the liver. Excess free fatty acids and cytokines from visceral fat, delivered through the portal vein:

1. induce hepatic IR;
2. activate gluconeogenesis;
3. promote progression of non-alcoholic fatty liver disease (NAFLD);
4. contribute to an atherogenic dyslipidemia.

This explains the stronger association of visceral, rather than subcutaneous, obesity with systemic metabolic disturbances.

Neurohormonal and enzymatic pathways. VO is accompanied by activation of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system: elevated cortisol and catecholamines enhance lipolysis, hyperglycemia, hypertension, and dyslipidemia. High tissue activity of 11β-HSD1 increases local active cortisol production in adipose tissue, worsening metabolic dysregulation.

Molecular regulators and potential targets. Dysregulation of microRNAs targeting genes of inflammation and lipid/carbohydrate metabolism disrupts insulin signaling and contributes to atherogenesis; several microRNAs are under consideration as potential biomarkers of METS. Incretins, particularly GLP-1, have attracted additional attention due to their antihyperglycemic and cardioprotective properties, with dysfunction of the incretin axis possibly representing another mechanism in METS progression.

2.3. Mitochondrial Dysfunction and Oxidative Stress

Mitochondrial dysfunction and oxidative stress are interrelated processes that form the basis of MS pathogenesis (Figure 5).

In recent years, mitochondrial dysfunction has been recognized as one of the key elements in the pathogenesis of METS. Mitochondria generate up to 90% of cellular energy through oxidative phosphorylation, regulate lipid and carbohydrate metabolism, calcium homeostasis, apoptosis, and cellular adaptation pathways. Their impairment leads to energy deficit, overproduction of reactive oxygen species, activation of inflammatory cascades, and development of systemic IR, hypertension, dyslipidemia, and chronic inflammation.

Figure 5 - Pathogenetic Mechanisms of Mitochondrial Dysfunction in Metabolic Syndrome

Mitochondrial Overload and Energy Deficiency

In obesity and hypercaloric nutrition, mitochondria receive an excessive influx of substrates (glucose and free fatty acids), leading to their incomplete oxidation and accumulation of lipotoxic metabolites. This disrupts insulin signaling in the liver and skeletal muscles. Additional contribution comes from mitochondrial DNA damage, which is highly vulnerable to reactive oxygen species and reduces the efficiency of the respiratory chain. At the same time, expression of biogenesis factors is suppressed, the number of functioning organelles decreases, and the energy deficit worsens.

Oxidative Stress

Oxidative stress is defined as an imbalance between reactive oxygen species production and antioxidant defense. Major reactive oxygen species sources in metabolic syndrome (MS) include the mitochondrial respiratory chain (complexes I and III), NADPH oxidase, xanthine oxidase, and activated immune cells.

Excess reactive oxygen species trigger:

5. lipid peroxidation,
6. protein and DNA damage,
7. activation of transcription factors that induce pro-inflammatory cytokines (TNF-α, IL-6, CRP). This maintains chronic inflammation and aggravates tissue dysfunction.

Oxidative stress is a complex biological condition arising from an **imbalance between** the excessive generation **of reactive oxygen species (ROS) and the** limited capacity of endogenous and exogenous antioxidants to counteract their harmful effects. This disequilibrium is widely recognized as a critical factor in cellular dysfunction and tissue injury, and it has been implicated in the pathogenesis of numerous chronic and degenerative diseases, including cancer, cardiovascular pathology, diabetes, and neurodegenerative disorders such as Alzheimer's and Parkinson's disease. Over the past few decades, the concept of oxidative stress has gained considerable prominence in biomedical research, as it not only provides a mechanistic explanation for aging and chronic disease development but also highlights potential preventive and therapeutic strategies.

While ROS are often regarded solely as damaging byproducts of metabolism, they also perform essential physiological functions. At controlled concentrations, they serve as crucial signaling molecules, modulate immune responses, and participate in redox-sensitive transcriptional regulation. However, when their production exceeds the neutralizing capacity of antioxidant defenses, ROS accumulation triggers oxidative damage to lipids, proteins, and nucleic acids, thereby undermining cellular integrity and accelerating pathological processes.

Reactive Oxygen Species

Reactive oxygen species are chemically reactive derivatives of molecular oxygen that emerge as natural byproducts of metabolic processes. They encompass both **free** radicals (e.g., **superoxide** anion [O_2^-], **hydroxyl radical [-OH]) and** non-radical oxidants such **as hydrogen peroxide (H_2O_2).** Free radicals, characterized by the presence of unpaired electrons, are particularly unstable and prone to initiating chain reactions that propagate cellular injury.

Mitochondrial oxidative phosphorylation remains the principal endogenous source of ROS, where the electron transport chain occasionally leaks electrons that reduce oxygen prematurely, forming superoxide. Other cellular processes-such as peroxisomal fatty acid oxidation, cytochrome P450 activity, and inflammatory cell activation (notably neutrophils and macrophages during the respiratory burst)-further contribute to ROS production.

Importantly, ROS generation is not confined to endogenous metabolism. Exogenous stressors, including environmental pollution, ionizing radiation, ultraviolet exposure, alcohol consumption, cigarette smoke, and certain xenobiotics, also markedly elevate oxidative burden.

Sources of Oxidative Stress

Oxidative stress originates from the interplay of multiple internal and external factors.

1. Endogenous sources:
 - Mitochondria: The most significant contributors, where electron leakage during respiration generates superoxide radicals.
 - Endoplasmic reticulum stress: Protein misfolding can activate ROS-generating pathways.
 - Enzymatic systems: Enzymes such as NADPH oxidases, xanthine oxidase, and nitric oxide synthase under pathological conditions are potent ROS producers.
2. Exogenous sources:
 - Lifestyle and environment: Cigarette smoking, chronic alcohol use, and excessive dietary fats stimulate ROS accumulation.
 - Pollutants: Heavy metals (e.g., cadmium, lead, mercury), pesticides, and air pollutants contribute to oxidative load.
 - Physical factors: Ultraviolet radiation and ionizing radiation directly produce free radicals within tissues.

Antioxidant Defense Systems

To mitigate oxidative injury, organisms have evolved a sophisticated network of antioxidants that act synergistically to neutralize ROS and repair damage. These defense systems are broadly categorized into enzymatic and non-enzymatic components:

1. Enzymatic antioxidants:
 - Superoxide dismutase (SOD) converts superoxide into hydrogen peroxide.
 - Catalase (CAT) rapidly decomposes hydrogen peroxide into water and oxygen.
 - Glutathione peroxidases (GPx) reduce hydrogen peroxide and lipid hydroperoxides using reduced glutathione (GSH).
2. Non-enzymatic antioxidants:
 - Endogenous molecules: Uric acid, bilirubin, melatonin, and coenzyme Q10.
 - Dietary antioxidants: Vitamin C, vitamin E (α-tocopherol), carotenoids, flavonoids, and polyphenols from fruits and vegetables.

The adequacy of these antioxidant defenses determines the degree of oxidative damage and, consequently, the extent of disease progression.

Cellular Consequences of Oxidative Stress

When antioxidant defenses are overwhelmed, ROS accumulation disrupts cellular homeostasis and initiates a cascade of deleterious events:

1. DNA damage: ROS attack nucleic acids, leading to single- and double-strand breaks, base modifications, and cross-linking. Hydroxyl radicals are particularly destructive, promoting mutations that compromise genome stability and predispose to oncogenesis.
2. Lipid peroxidation: Polyunsaturated fatty acids in membranes are highly susceptible to peroxidation, generating toxic aldehydes such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE). These byproducts disrupt membrane integrity and amplify inflammation.
3. Protein oxidation: Amino acids such as cysteine and methionine undergo oxidative modifications, altering protein structure, impairing enzymatic activity, and destabilizing signaling cascades.

ROS can also activate **transcription factors such as nuclear factor-κB (NF-κB) and activator protein-1 (AP-1),** which drive pro-inflammatory gene expression. Chronic activation of these pathways fosters persistent low-grade inflammation, a central mechanism in many chronic diseases.

Pathophysiological Implications

1. Aging: The free radical theory of aging posits that cumulative oxidative damage to cellular macromolecules is a major driver of senescence and age-related diseases. Although modified by more recent hypotheses, oxidative stress remains a central theme in gerontology.
2. Diabetes mellitus: Type 2 diabetes exemplifies a vicious cycle between oxidative stress and metabolic dysfunction. Chronic hyperglycemia promotes mitochondrial overproduction of ROS, while ROS themselves impair insulin signaling through oxidative modification of insulin receptor substrates. This contributes to worsening insulin resistance, β-cell dysfunction, and heightened cardiovascular risk. Notably, emerging therapies such as sodium-glucose co-transporter-2 (SGLT2) inhibitors improve glycemic control while simultaneously reducing oxidative stress and cardiovascular mortality.
3. Neurodegenerative diseases: In conditions like Parkinson's disease, oxidative stress exacerbates dopaminergic neuron degeneration via mitochondrial dysfunction and impaired antioxidant defenses. In Alzheimer's disease, ROS accelerate amyloid-β aggregation and tau phosphorylation, perpetuating neurotoxicity.
4. Cancer: The role of ROS in carcinogenesis is dualistic. On one hand, ROS promote mutagenesis and tumor initiation by damaging DNA. On the other, high ROS levels can induce apoptosis, a feature exploited in some chemotherapeutic approaches. This paradox underscores the complexity of ROS-targeted therapies.

Hormesis and Adaptive Responses

An important nuance in oxidative biology is the concept of hormesis, which suggests that mild, transient elevations in ROS may activate protective signaling pathways. For example, exercise-induced ROS generation enhances antioxidant capacity and mitochondrial biogenesis through redox-sensitive transcription factors such as Nrf2 (nuclear factor erythroid 2-related factor 2). This adaptive response illustrates that not all ROS exposure is detrimental; rather, a balance between ROS and antioxidants is essential for health.

Therapeutic Considerations and Controversies

The therapeutic manipulation of oxidative stress remains an area of intense investigation but also considerable debate. Clinical trials of antioxidant supplementation have yielded inconsistent results:

1. Positive outcomes: In certain contexts, antioxidants such as vitamin E have shown modest benefits in reducing cardiovascular risk.
2. Negative or neutral outcomes: Other large-scale studies have failed to demonstrate protective effects, and in some cases, supplementation has worsened outcomes, especially in cancer, where antioxidants may interfere with ROS-mediated tumor suppression.

This inconsistency likely reflects the multifactorial nature of oxidative stress and the context-dependent effects of antioxidants. Future strategies may involve targeted modulation of ROS rather than blanket antioxidant therapy-for instance, enhancing endogenous antioxidant gene expression via Nrf2 activators or employing mitochondria-specific ROS scavengers.

Oxidative stress represents a fundamental biological phenomenon at the intersection of physiology, pathology, and aging. While excessive ROS accumulation drives tissue injury and chronic disease, tightly regulated ROS levels are indispensable for cellular communication and defense. The dual nature of ROS underscores the complexity of therapeutic interventions, where both deficiency and excess may be harmful. Ongoing research into redox biology will be pivotal for developing precision-based strategies that harness the beneficial aspects of oxidative signaling while mitigating its destructive potential.

Mitochondrial Dynamics Impairment

The imbalance between mitochondrial fusion and fission is a critical pathogenic link. In MetS, fission is enhanced (via hyperactivation of dynamin-related protein 1), while fusion is suppressed (due to reduced activity of mitofusins 1/2 and optic atrophy protein). This results in mitochondrial fragmentation, functional insufficiency, and increased reactive oxygen species generation.

Mitochondria, often referred to as the "powerhouses of the cell," are dynamic organelles essential for energy production, metabolic regulation, and programmed cell death. Their functional integrity relies heavily on a delicate balance between two opposing but complementary processes: mitochondrial fission (division) and fusion (joining). Together, these processes are collectively termed mitochondrial dynamics and serve as critical regulators of organelle morphology, distribution, and quality control.

When mitochondrial dynamics are properly regulated, cells maintain energy homeostasis, adapt to fluctuating metabolic demands, and preserve viability under stress conditions. Conversely, disruption of this equilibrium-whether due to genetic mutations, environmental insults, or metabolic disturbances-leads to mitochondrial dynamics impairment, a condition now recognized as central to the pathophysiology of numerous diseases. Disorders linked to impaired mitochondrial dynamics span a wide spectrum, including neurodegenerative diseases (Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis), metabolic syndromes (obesity, type 2 diabetes), and cancer.

At the molecular level, impaired mitochondrial dynamics promote excessive oxidative stress, accumulation of reactive oxygen species (ROS), defective mitophagy, and loss of mitochondrial DNA (mtDNA) integrity. These changes, in turn, contribute to neuronal degeneration, metabolic dysfunction, and systemic decline associated with aging.

Regulatory Mechanisms of Mitochondrial Dynamics

Mitochondrial morphology is tightly regulated by a specialized group of GTPases and associated proteins:

1. Fusion proteins: **Mitofusins (Mfn1 and Mfn2)** on the outer mitochondrial membrane and **optic atrophy protein 1 (OPA1)** **on the inner mitochondrial membrane** mediate mitochondrial fusion. These proteins ensure mixing of mitochondrial contents, thereby promoting functional complementation and maintenance of mtDNA stability.
2. Fission proteins: Dynamin-related protein 1 (Drp1) is the central mediator of fission. Its activity is modulated by post-translational modifications, including phosphorylation, ubiquitination, and S-nitrosylation. When recruited to mitochondria by adaptor proteins such as Fis1, Mff, and MiD49/51, Drp1 facilitates scission of the mitochondrial network.

The balance between these opposing forces is highly responsive to cellular energy status and stress signaling pathways. For instance, phosphorylation of Drp1 at specific serine residues enhances its mitochondrial recruitment and promotes fission during high-energy demand or cellular stress. Similarly, OPA1 undergoes proteolytic processing under stress conditions, altering inner membrane fusion and cristae organization.

Mitochondrial Dynamics in Health and Disease

Under physiological conditions, mitochondrial dynamics serve multiple roles:

1. Energy production: By regulating organelle morphology, dynamics optimize mitochondrial function under varying energy demands.
2. Apoptosis: Mitochondrial fragmentation is an early hallmark of apoptosis, facilitating cytochrome c release.
3. Quality control: Fusion allows for the dilution of damaged mitochondrial components, while fission segregates dysfunctional mitochondria for selective elimination via mitophagy.

When dysregulated, however, these processes contribute to pathogenesis:

1. Neurodegenerative disorders: Abnormal fragmentation or hyperfusion has been observed in Alzheimer's, Parkinson's, and Huntington's disease, where it exacerbates neuronal injury, synaptic dysfunction, and eventual cell death.
2. Metabolic syndromes: In obesity and diabetes, disrupted dynamics interfere with insulin signaling, amplify oxidative stress, and reduce mitochondrial bioenergetic efficiency.
3. Inflammatory diseases: Aberrant mitochondrial fission enhances the release of mitochondrial DNA and ROS, which act as danger-associated molecular patterns (DAMPs) to activate innate immune pathways and perpetuate chronic inflammation.

Mechanisms of Impairment

1. Excessive oxidative stress: Impaired dynamics often lead to ROS accumulation, which further damages mitochondrial proteins, lipids, and mtDNA, creating a vicious cycle of dysfunction. For example, ROS-mediated oxidation of Drp1 enhances its activity, leading to excessive fission and mitochondrial fragmentation.
2. Defective mitophagy: Failure to eliminate dysfunctional mitochondria allows the persistence of bioenergetically inefficient organelles, promoting further ROS release and triggering apoptotic or necrotic pathways.
3. Genetic contributions:

- Mutations in OPA1 cause autosomal dominant optic atrophy, underscoring the role of inner membrane fusion in neuronal survival.
- Mutations **in Mfn2 are associated with Charcot-Marie-Tooth disease type** 2A, a peripheral neuropathy characterized by impaired mitochondrial transport and dynamics.
- MtDNA mutations, such as the m.11778G>A substitution in ND4, cause Leber's hereditary optic neuropathy, with penetrance influenced by nuclear haplogroups such as haplogroup J.

4. Post-translational modifications: Dysregulated phosphorylation or ubiquitination of Drp1 and Mfn2 alters their activity, leading to either excessive fragmentation or hyperfusion.

Mitochondrial Dysfunction and Oxidative Stress

Mitochondrial impairment and oxidative stress reinforce one another in a self-perpetuating cycle. In neurodegenerative diseases, accumulation of ROS contributes to dopaminergic neuronal death (Parkinson's) or amyloid-β aggregation and tau hyperphosphorylation (Alzheimer's). Similarly, in amyotrophic lateral sclerosis (ALS), ROS-driven mitochondrial fragmentation accelerates motor neuron degeneration.

Genetic and Metabolic Interplay

The genetic basis of mitochondrial dynamics disorders is complex, involving both nuclear-encoded genes and mtDNA variants. In addition to well-established mutations in OPA1 and Mfn2, bi-allelic variants in nuclear genes modulate susceptibility to mitochondrial impairment, influencing phenotypic severity and disease progression.

In metabolic diseases, mitochondrial fragmentation has been strongly linked to impaired insulin signaling. Studies demonstrate that in type 2 diabetes, abnormal dynamics increase β-cell vulnerability to apoptosis and impair glucose-stimulated insulin secretion. Obesity-related metabolic stress similarly enhances fission, promoting systemic insulin resistance and inflammation.

Therapeutic Perspectives

Restoring mitochondrial dynamics has emerged as a promising therapeutic avenue. Current strategies under investigation include:
1. Pharmacological modulation of fission/fusion proteins: Inhibitors of Drp1, such as mdivi-1, have shown preclinical efficacy in reducing neuronal apoptosis and improving mitochondrial function.
2. Mitophagy enhancement: Agents that activate PINK1/Parkin pathways to facilitate clearance of dysfunctional mitochondria may reduce oxidative damage.
3. Mitochondrial transfer therapy: Experimental approaches using stem cell-derived mitochondrial transplantation aim to replenish functional organelles in damaged tissues.
4. Lifestyle interventions: Regular exercise has been shown to beneficially modulate mitochondrial dynamics, in part through hormetic ROS signaling and upregulation of antioxidant defenses.
Mitochondrial dynamics are fundamental to cellular adaptation, survival, and energy metabolism. Impairments in the balance of fission, fusion, and mitophagy contribute to a wide array of pathological states, ranging from neurodegeneration to metabolic syndromes. While genetic mutations, oxidative stress, and post-translational modifications play key roles in disrupting these processes, emerging research suggests that targeted therapeutic strategies may restore mitochondrial homeostasis and improve disease outcomes. Further elucidation of the molecular underpinnings of mitochondrial dynamics will be crucial for translating these insights into effective clinical interventions.

Calcium Overload and Apoptosis Activation
Damaged mitochondrial DNA is released into the cytoplasm, where it acts as a danger-associated molecular pattern and activates the innate immune response. This occurs via Toll-like receptor 9 (TLR9) and NOD-like receptor family pyrin domain-containing 3, leading to secretion of IL-1β and IL-18 and perpetuating chronic low-grade inflammation. Additionally, ROS interact with nitric oxide to form peroxynitrite, which damages the endothelium and reduces vasodilation, linking mitochondrial dysfunction to accelerated atherogenesis.
Calcium overload refers to the pathological accumulation of calcium ions (Ca2+) within the intracellular compartment, leading to disruption of calcium homeostasis. This dysregulation is of particular importance in neurodegenerative disorders (e.g., amyotrophic lateral sclerosis, Alzheimer's disease) and oncological diseases, where aberrant calcium signaling contributes to cell death and disease progression.
Beyond its established role in apoptosis (programmed cell death), calcium overload also influences alternative cell death modalities such as pyroptosis and necroptosis, highlighting its broad impact on cellular health and disease outcomes.
Mechanisms of Calcium Overload
1. Excessive Calcium Influx
- Overactivation of glutamatergic N-methyl-D-aspartate (NMDA) receptors, often due to excitotoxicity, facilitates uncontrolled calcium entry into neurons.
- Dysregulation of transient receptor potential (TRP) channels amplifies intracellular calcium signaling.
- A process known as calcium-induced calcium release further propagates calcium waves from the endoplasmic reticulum (ER), worsening overload.
2. Disruption of Calcium Transport Systems
- Key transporters-including plasma membrane Ca2+-ATPases, sodium-calcium exchangers (NCX), and sarco/endoplasmic reticulum Ca2+-ATPases (SERCA)-work together to preserve calcium balance.
- Dysfunction of these systems (e.g., via oxidative damage, genetic mutations, or metabolic stress) impairs calcium clearance, leading to pathological accumulation.
3. Oxidative Stress and ER Stress
- Oxidative stress promotes calcium overload by impairing ER function and altering protein folding, triggering the unfolded protein response (UPR).
- Dysregulated UPR links ER dysfunction with mitochondrial apoptosis pathways, reinforcing calcium-mediated cell death.
Pathophysiological Consequences
1. Neurodegeneration:
In neurons, sustained calcium overload damages mitochondria, enhances ROS production, and triggers apoptosis or pyroptosis. This contributes to motor decline in amyotrophic lateral sclerosis and cognitive impairment in Alzheimer's disease.
2. Cancer:
Calcium signaling demonstrates a dual role in cancer biology. Moderate elevations in Ca2+ promote tumor cell proliferation and survival, while excessive accumulation facilitates apoptosis, which has inspired calcium-targeted cancer therapies.
3. Cardiovascular and Metabolic Disorders:
Iron overload, by aggravating intracellular calcium levels, activates calcineurin, influencing synaptic plasticity and contributing to both vascular and metabolic dysfunction.
Therapeutic Perspectives and Controversies
The dualistic role of calcium signaling remains one of the central controversies in redox biology and cancer research. While mild elevations support survival pathways, uncontrolled accumulation triggers death cascades.
Emerging therapies include:
1. Ion interference therapy: Manipulating ionic homeostasis to selectively induce calcium overload in malignant cells.
2. Nanotechnology-based calcium formulations: Targeted delivery systems designed to induce tumor apoptosis while sparing healthy tissue.
Although promising, clinical application is still limited by the challenge of achieving tissue-specific targeting and avoiding systemic toxicity.
Vascular Dysfunction and Neurodegenerative Disorders
Cerebrovascular health is increasingly recognized as a pivotal determinant of cognitive function and resilience against neurodegeneration.
Epidemiological studies show that vascular risk factors-hypertension, diabetes, obesity, and hypercholesterolemia-substantially increase the likelihood of developing dementia and related disorders.
Mechanisms of Vascular Damage
1. Atherosclerosis and Hypoperfusion
- Atherosclerotic plaque deposition, particularly in the carotid arteries and circle of Willis, narrows cerebral vessels and impairs blood flow.
- Chronic cerebral hypoperfusion leads to ischemia and hypoxia, reducing ATP availability and promoting ROS generation within mitochondria.
2. Oxidative Stress and Inflammation
- Interaction of ROS with nitric oxide (NO) forms peroxynitrite, a potent oxidant that reduces endothelial function and vasodilation.
- Pro-inflammatory cytokines and chemokines perpetuate vascular damage and contribute to neuroinflammation, which accelerates neurodegenerative processes.

3. Blood-Brain Barrier Dysfunction
- Vascular inflammation and oxidative stress weaken the integrity of the blood-brain barrier (BBB).
- Increased permeability allows infiltration of neurotoxic molecules and immune cells into the brain parenchyma, amplifying neuronal injury.

Links to Neurodegenerative Diseases

1. Alzheimer's disease (AD): Vascular dysfunction precedes amyloid pathology in many cases, with reduced cerebral blood flow and BBB breakdown exacerbating amyloid-β deposition and tau pathology.
2. Parkinson's disease (PD): Alterations in cerebral perfusion contribute to both motor and non-motor symptoms. Vascular compromise may potentiate neuroinflammation and dopaminergic neuron loss.
3. Vascular dementia (VaD): The second most common form of dementia, VaD arises from cumulative ischemic insults, microinfarcts, and chronic hypoperfusion, often coexisting with AD pathology.

Clinical and Epidemiological Evidence

1. Patients with a history of stroke or cardiovascular disease have a markedly increased risk of developing dementia.
2. Shared risk factors such as hypertension, diabetes, and hyperlipidemia underscore the intertwined nature of vascular and neurodegenerative disease progression.
3. Some clinical studies suggest that aggressive management of vascular risk factors delays cognitive decline, while others report progression of neurodegeneration despite optimized vascular health-reflecting ongoing controversy in the field.

Therapeutic Implications

1. Preventive strategies: Control of vascular risk factors (blood pressure, glucose, lipid levels) is central to dementia prevention.
2. Anti-inflammatory and antioxidant therapies: Targeting chronic inflammation and oxidative stress may reduce vascular-mediated neuronal injury.
3. Neurovascular unit-targeted therapies: Strengthening BBB integrity and restoring endothelial function represent promising future directions.

Calcium overload and vascular dysfunction represent two interconnected hallmarks of cellular and systemic pathology. While calcium overload drives neuronal death and contributes to cancer biology, vascular insufficiency exacerbates cognitive decline and neurodegeneration through hypoperfusion, oxidative stress, and inflammation. Understanding these processes in tandem underscores the complexity of brain aging and highlights opportunities for integrated therapeutic strategies. Ongoing research must focus on precise modulation of calcium signaling and comprehensive management of vascular health, both of which hold promise for reducing the burden of neurodegenerative diseases.

Dysregulation of Cellular Sensors and Mitophagy

Reduced AMP-activated protein kinase (AMPK) activity limits mitochondrial biogenesis, impairs cellular adaptation to metabolic stress, and aggravates insulin resistance. At the same time, impaired mitophagy leads to accumulation of defective organelles that serve as additional ROS sources. Thus, a vicious cycle is formed, where mitochondrial dysfunction is both a consequence and a cause of insulin resistance:

8. In muscle tissue → reduced glucose utilization,
9. In the liver → steatosis and excessive lipid production,
10. In adipose tissue → chronic hyperlipidemia and inflammation.

This creates a self-perpetuating loop: obesity → mitochondrial overload → ROS → mtDNA damage → ↓ ATP → insulin resistance → further obesity.

Mitochondria are central regulators of cellular energy metabolism, apoptosis, and stress responses. Given their importance, eukaryotic cells rely on robust quality control systems to maintain mitochondrial integrity. One of the most critical of these systems is mitophagy, a selective **form of autophagy that eliminates dysfunctional mitochondria.** This process is orchestrated by a network of cellular sensors, particularly PTEN-induced kinase **1 (PINK1) and the E3 ubiquitin ligase Parkin,** which monitor mitochondrial health and initiate the clearance of damaged organelles.

When functioning properly, mitophagy preserves mitochondrial fitness, prevents the accumulation of reactive oxygen species (ROS), and protects tissues with high energy demands, such as the brain and heart. However, dysregulation of mitophagy leads to the persistence of defective mitochondria, contributing to oxidative stress, inflammation, and neuronal vulnerability. This dysfunction is increasingly recognized as a hallmark of neurodegenerative diseases including Parkinson's disease (PD), Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD).

Mechanisms of Mitophagy

The PINK1/Parkin Pathway

Under normal conditions, PINK1 is continuously imported into the inner mitochondrial membrane and degraded by mitochondrial proteases. In damaged or depolarized mitochondria, PINK1 fails to translocate and instead accumulates on the outer mitochondrial membrane (OMM). This stabilization recruits Parkin, which ubiquitinates OMM proteins such as Mfn1/2, thereby labeling the mitochondrion for autophagic degradation.

This process not only clears defective mitochondria but also signals for mitochondrial biogenesis via transcriptional co-activators such as PGC-1α, thereby maintaining a healthy mitochondrial pool.

Alternative Pathways

Although the PINK1/Parkin axis is the best-characterized, mitophagy can also be mediated by receptor proteins such as BNIP3, NIX, and FUNDC1, particularly under hypoxic conditions. These receptors directly interact with LC3 on autophagosomes, bypassing the need for ubiquitination. This redundancy illustrates the evolutionary importance of mitophagy across different stress contexts.

Mechanisms of Dysregulation

1. Genetic Mutations
- Mutations in PINK1 and Parkin (PARK2) are strongly linked to familial forms of early-onset PD. Loss-of-function mutations impair ubiquitination and clearance of defective mitochondria, resulting in neurotoxic accumulation.
- Variants in OPA1 and Mfn2, which regulate mitochondrial fusion, indirectly impair mitophagy by destabilizing mitochondrial networks.
- In AD, presenilin (PS1 and PS2) mutations hinder mitophagosome-lysosome fusion, preventing clearance of defective mitochondria.
- In HD, mutant huntingtin protein interferes with autophagy initiation and mitochondrial quality control, compounding energy deficits in neurons.

2. Post-Translational Modifications (PTMs)
- Phosphorylation of PINK1 is necessary for Parkin activation, while defective phosphorylation impairs mitophagy initiation.
- Ubiquitination by Parkin is crucial for autophagosome recruitment. Loss of this function stalls clearance, creating a buildup of dysfunctional organelles.
- Crosstalk with calcium signaling has been observed, where Ca2+ fluxes modulate mitophagic responses, although the precise mechanisms remain under investigation.

3. Oxidative Stress and Inflammation
- ROS damage mitochondrial proteins and DNA, amplifying the need for mitophagy. However, oxidative modification of mitophagy regulators (e.g., Parkin

oxidation) disrupts their function.
- Pro-inflammatory cytokines exacerbate mitochondrial injury while simultaneously suppressing autophagy-related pathways, creating a feedback loop of neuroinflammation and impaired clearance.

Mitophagy in Neurodegenerative Disorders

1. Parkinson's disease (PD): Mutations in PINK1 and Parkin account for up to 50% of familial early-onset PD cases. Loss of mitophagy results in accumulation of dysfunctional mitochondria, increased ROS, and selective degeneration of dopaminergic neurons in the substantia nigra.
2. Alzheimer's disease (AD): Tau protein interacts with Parkin, preventing its recruitment to mitochondria. This, together with presenilin mutations, leads to impaired mitophagy and persistence of damaged mitochondria. Elevated oxidative stress and defective clearance further exacerbate amyloid and tau pathology.
3. Amyotrophic lateral sclerosis (ALS): Mitophagy dysfunction contributes to motor neuron degeneration, with evidence of abnormal expression of autophagy-related proteins in ALS models.
4. Huntington's disease (HD): Mutant huntingtin disrupts autophagy initiation, indirectly impairing mitochondrial clearance. This accelerates energy deficits and neurodegeneration.

Interplay with Other Cellular Pathways

Mitophagy operates in coordination with:

1. Macroautophagy: Broader autophagic processes that clear aggregated proteins and organelles.
2. Mitochondrial biogenesis: Controlled by transcriptional regulators such as PGC-1α and NRF1/2, ensuring replenishment of the mitochondrial pool.
3. Energy sensors: The AMP-activated protein kinase (AMPK) pathway enhances mitophagy by stabilizing PGC-1α and promoting autophagosome formation.

Thus, impaired mitophagy has ripple effects across multiple aspects of cellular homeostasis, amplifying vulnerability in high-energy tissues.

Implications for Pathophysiology

The inability to clear dysfunctional mitochondria results in:

1. Persistent oxidative stress, due to accumulation of ROS-producing organelles.
2. Release of mitochondrial DNA into the cytosol, which acts as a danger signal and triggers innate immune pathways.
3. Chronic neuroinflammation, further promoting neuronal death and glial activation.
4. Progressive impairment of tissue health, particularly in organs that cannot easily regenerate, such as the brain and heart.

Therapeutic Perspectives

Given its central role in neurodegeneration, mitophagy is an attractive therapeutic target. Potential strategies include:

1. Pharmacological activators: Compounds that stimulate PINK1/Parkin signaling or alternative receptor-mediated mitophagy.
2. AMPK activators: Agents such as metformin, which promote autophagy and mitochondrial biogenesis.
3. Gene therapy approaches: Correction of PINK1 or Parkin mutations to restore functional mitophagy pathways.
4. Antioxidant-autophagy combinations: Dual-targeted approaches to simultaneously reduce oxidative stress and enhance clearance of damaged mitochondria.

While preclinical studies show promise, translation into effective therapies is complicated by the need to balance mitophagy activity: both insufficient and excessive mitophagy can be detrimental.

Dysregulation of cellular sensors such as PINK1 and Parkin represents a pivotal mechanism in the pathogenesis of neurodegenerative diseases. Impaired mitophagy allows dysfunctional mitochondria to accumulate, fueling oxidative stress, inflammation, and neuronal degeneration. Understanding the nuanced regulation of mitophagy-spanning genetics, PTMs, and environmental stressors-is essential for identifying therapeutic windows. Future research will focus on selective mitophagy enhancers, personalized therapies for genetic variants, and integrated approaches targeting both mitochondrial clearance and biogenesis. Such interventions hold significant potential to slow, or even halt, the progression of neurodegenerative diseases.

2.4. Chronic Inflammation and Cytokine Imbalance

Chronic subclinical inflammation is now recognized as one of the key mechanisms in METS pathogenesis. Its hallmark is prolonged, moderately elevated levels of inflammatory mediators, insufficient to reach acute inflammation, yet capable of causing systemic damage to target organs. Unlike classical inflammation, which plays a protective role, chronic inflammation in METS creates a destructive, self-sustaining pathological cycle. It is driven by adipose tissue dysfunction, cytokine imbalance, and activation of innate immunity.

Adipose Tissue as a Source of Inflammation

In obesity and MEtS, adipose tissue shifts from a passive energy depot to an active endocrine-inflammatory organ. Adipocyte hypertrophy is accompanied by impaired microcirculation, local hypoxia, and apoptosis. These changes promote infiltration of macrophages and T-lymphocytes. Morphologically, "crown-like structures" around necrotic adipocytes are markers of chronic inflammation. Macrophages adopt a pro-inflammatory phenotype, secreting TNF-α, IL-6, IL-1β, chemokines, and adhesion molecules. Meanwhile, production of anti-inflammatory adipokines, particularly adiponectin, decreases, tipping the balance toward pro-inflammatory signaling and establishing systemic cytokine imbalance.

Role of Individual Cytokines

1. IL-6: secreted by macrophages and adipocytes. Elevated in obesity and IR. It regulates carbohydrate and lipid metabolism, induces hepatic synthesis of acute-phase proteins (including CRP). High CRP strongly correlates with type 2 diabetes and cardiovascular complications. IL-6 also activates vascular walls, increasing adhesion molecule expression and stimulating the local renin-angiotensin system (RAS), accelerating atherogenesis.
2. TNF-α: produced by adipose tissue macrophages, correlates with adipose mass and IR. It disrupts insulin signaling through serine phosphorylation and inactivation of IRS-1, reducing insulin effects in adipocytes and hepatocytes. It also enhances lipolysis and elevates free fatty acids, worsening IR.
3. IL-1β and IL-18: promote pancreatic β-cell apoptosis and reduce insulin secretion, accelerating diabetes progression.

Role of Toll-like Receptors (TLRs)

Innate immunity activation via TLRs, especially TLR2 and TLR4, plays a major role in METS. Their ligands include pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs). Endogenous DAMPs include saturated fatty acids, modified LDL, advanced glycation end-products (AGEs), heat shock proteins, and extracellular matrix fragments. Binding to TLRs activates pro-inflammatory cascades.

In MetS patients, expression of TLR2 and TLR4 on monocytes is increased, even after adjustment for abdominal obesity. Additional evidence includes elevated endotoxin levels and gut permeability changes linked to microbiota imbalance and lipopolysaccharide influx - classical TLR4 ligands. This sustains systemic inflammation and metabolic disruption.

Imbalance of Pro- and Anti-inflammatory Factors

The cytokine profile in METS is marked not only by overproduction of pro-inflammatory mediators but also by decreased anti-inflammatory signaling. Adiponectin levels drop significantly, reducing insulin sensitivity and anti-atherogenic protection. IL-10 deficiency, which normally inhibits macrophage activity, further promotes inflammation chronicity.

Thus, chronic inflammation and cytokine imbalance in METS form a closed system where innate immunity activation, adipose tissue immune cell infiltration, elevated pro-inflammatory cytokines, and reduced protective factors maintain IR, endothelial dysfunction, and atherogenesis.

Chronic inflammation and cytokine imbalance are central pathogenetic mechanisms of MS, tightly linking obesity, IR, and vascular complications. They underlie metabolic disease progression and represent promising therapeutic targets. Correcting inflammatory status and restoring cytokine balance are considered crucial strategies in METS prevention and treatment.

2.5. Gut Microbiota and Its Role in Metabolic Syndrome Development

In recent decades, the gut microbiota has emerged as a key determinant of human health and the pathogenesis of chronic diseases. Once viewed mainly as a digestive aid, it is now considered a dynamic, metabolically active “organ” that regulates metabolism, immune responses, energy balance, and epigenetic gene expression.

Under normal conditions, the gut microbiota is characterized by high diversity and relative stability. The dominant taxa are Firmicutes and Bacteroidetes, which together account for more than 80% of the total gut microbial community. Maintaining a balanced ratio between them is critical for sustaining eubiosis. Of particular importance are Faecalibacterium prausnitzii, Roseburia spp., and Akkermansia muciniphila, which synthesize short-chain fatty acids such as butyrate, propionate, and acetate. These metabolites play a central role in regulating both energy balance and immune homeostasis.

Role of Short-Chain Fatty Acids

Butyrate - the primary energy source for colonocytes, it maintains intestinal barrier integrity and exhibits strong anti-inflammatory properties. Its epigenetic action is mediated through inhibition of histone deacetylases, leading to activation of antioxidant defense genes and suppression of inflammatory signaling.

Propionate - regulates hepatic gluconeogenesis, contributes to lipid metabolism, and exerts modulatory effects on immune function.

Acetate - participates in lipogenesis and appetite regulation through the gut-brain axis.

Thus, SCFAs provide a critical link between the composition of the gut microbiota and systemic metabolic processes.

In patients with METS, the following alterations are observed:

Reduced microbial diversity,

Decreased abundance of butyrate-producing bacteria,

Expansion of opportunistic pathogenic microorganisms,

An altered Firmicutes/Bacteroidetes ratio, associated with obesity and IR.

One of the key consequences of dysbiosis is impaired intestinal barrier function. Butyrate deficiency and reduced expression of tight junction proteins (occludin, claudin) lead to increased mucosal permeability. This results in systemic translocation of lipopolysaccharides (LPS) from Gram-negative bacteria, which activate TLR4 on macrophages and adipocytes. The downstream NF-κB cascade triggers secretion of pro-inflammatory cytokines (TNF-α, IL-6, IL-1β). This condition, known as metabolic endotoxemia, is considered a central mechanism driving chronic low-grade inflammation.

Dysbiosis, or imbalance of its composition and functions, is recognized as a critical mechanism in METS pathogenesis (Figure 6).

Figure 6 - Pathogenetic role of gut microbiota in the development of metabolic syndrome (adapted from [72]).

Dysbiosis shifts the immune balance toward pro-inflammatory responses. The number of regulatory T cells (Tregs) with suppressive properties decreases, while Th1 and Th17 lymphocytes, producing IFN-γ and IL-17, become more active. This sustains chronic inflammation and promotes endothelial dysfunction. Simultaneously, activation of the NLRP3 inflammasome in the presence of LPS and mitochondrial DAMP signals further enhances secretion of IL-1β and IL-18. These cytokines damage pancreatic β-cells, promote apoptosis, and contribute to the progression ofT2D.

A deficiency of SCFAs reduces the activity of energy sensors such as AMP-activated protein kinase (AMPK) and Sirtuin-1 (SIRT1, NAD+-dependent deacetylase). This impairs mitochondrial biogenesis, increases oxidative stress, and worsens IR. Dysregulated bile acid metabolism disrupts signaling through farnesoid X receptors (FXR) and TGR5, thereby promoting atherogenesis.

The epigenetic effects of the microbiota are mediated through metabolites (butyrate, propionate, acetate) that modulate chromatin structure and histone deacetylase activity. These mechanisms directly influence the expression of genes involved in inflammation, antioxidant defense, and energy metabolism.

The gut microbiota is a key regulator of metabolic and immune processes. Dysbiosis disrupts intestinal barrier integrity, promotes translocation of bacterial components, activates innate and adaptive immune responses, induces epigenetic alterations, and suppresses energy metabolism. Collectively, these mechanisms drive chronic low-grade inflammation, reinforce insulin resistance, and perpetuate the pathological cycle of METS.

CHAPTER III. CLINICAL MANIFESTATIONS AND DIAGNOSIS OF METABOLIC SYNDROME

3.1. Abdominal obesity as a clinical component of metabolic syndrome

In modern medicine, AO is considered not only as one of the diagnostic criteria of METS, but also as its central pathogenetic link. Visceral accumulation of adipose tissue forms a complex cascade of metabolic, hormonal, and inflammatory disorders that combine into a single continuum: obesity, IR, dyslipidemia, AH, and T2D.

Historically, the identification of the concept of AO in clinical medicine began in the second half of the 20th century, when it became clear that patients with the central type of obesity had a significantly higher risk of cardiovascular complications compared with individuals with an even distribution of fat mass. In the 21st century, thanks to data from large population-based cohort studies (NHANES, EPIC-Europe, KNHANES), this phenotype was finally recognized as the leading clinical marker of METS.

Metabolic and endocrine mechanisms

The main feature of AO lies in the fact that visceral adipose tissue is not a passive depot but an active endocrine and immunometabolic organ. Hypertrophied adipocytes are characterized by increased lipolytic activity and reduced insulin sensitivity. This leads to an excessive influx of free fatty acids into the systemic circulation, which, through the portal vein, enter the liver. There they stimulate intrahepatic lipogenesis, synthesis of triglycerides

(TG) and very-low-density lipoproteins (VLDL), forming an atherogenic type of dyslipidemia.

At the same time, hepatic macrophages (Kupffer cells) are activated, which enhances local inflammation and impairs insulin signaling. Thus, already at the early stages, AO triggers a chain of metabolic disturbances combining lipid and carbohydrate imbalance.

Role of adipokines

Visceral adipose tissue actively secretes adipokines - biologically active substances regulating energy metabolism, inflammation, and vascular tone:

Leptin, whose level is elevated in obesity, loses effectiveness due to the development of leptin resistance, leading to impaired control of appetite and energy expenditure.

Adiponectin, which has anti-inflammatory and anti-atherogenic properties, is significantly reduced in AO.

Resistin, visfatin, and retinol-binding protein-4 (RBP-4) contribute to the intensification of IR and maintenance of chronic inflammation.

Modern studies also point to the involvement of exosomes and microvesicles secreted by adipocytes, which contain microRNAs and proteins regulating gene expression in distant target organs. These intercellular signals give metabolic disorders a systemic character.

A morphological feature of VO is the infiltration of adipose tissue by macrophages with the formation of “crown-like structures” around necrotizing adipocytes. They serve as a source of production of pro-inflammatory cytokines (TNF-α, IL-6, MCP-1), which enhance systemic inflammation and form a state of chronic metabolic stress. Chronic low-grade inflammation is recognized as one of the key mechanisms linking obesity **with the development of IR, endothelial dysfunction, and atherosclerosis.**

The close association of AO with nonalcoholic fatty liver disease confirms the systemic nature of this disorder. nonalcoholic fatty liver disease is considered the hepatic manifestation of MS and reflects the combination of IR, lipotoxicity, and inflammation. In patients with AO, nonalcoholic fatty liver disease is detected in more than 60% of cases [73]. According to the meta-analysis by Xue et al., an increase in waist circumference by every 10 cm is associated with a 4.0% increase in cardiovascular risk in men and 3.4% in women [74]. These data emphasize the importance of early detection and correction of AO.

AO is not just one of the symptoms but a fundamental component of METS pathogenesis. It integrates endocrine, metabolic, and inflammatory mechanisms, forming the basis for the development of T2D, dyslipidemia, and cardiovascular complications. Simple anthropometric methods, such as measuring **WC and waist-to-hip** ratio, are of crucial importance for diagnosing MS, risk stratification, and developing preventive strategies.

3.2. Arterial hypertension in metabolic syndrome

AH is one of the most frequent and clinically significant manifestations of MetS. The mechanisms of AH formation in MetS are multifactorial and reflect the complex interaction of metabolic, neurohumoral, and inflammatory processes (Table 3). A key role is played by IR, VO, and the associated activation of hormonal and mediator cascades.

Table 3 - Main mechanisms of arterial hypertension development in metabolic syndrome

Mechanism	Key factors	Clinical consequences
Insulin resistance and hyperinsulinemia	↑ Sympathetic activity, ↑ Na+ reabsorption	Increased cardiac output, volume-dependent hypertension
RAAS activation	Angiotensin II, aldosterone	Vasoconstriction, Na+ and water retention, vascular remodeling
Endothelial dysfunction	↓ NO, ↑ peroxynitrite	Reduced vasodilation, increased vascular tone
Chronic inflammation and ROS	TNF-α, IL-6, CRP, ROS	Vascular stiffness, atherosclerosis, hypertension progression

Its presence significantly increases the risk of severe cardiovascular complications, including coronary heart disease, stroke, and chronic heart failure. Historically, in the 1980s-1990s, when the concept of METS was just being formed, the combination of AO and AH was regarded as the “core” of the pathological process. Currently, it has been established that more than 60-70% of patients with METS have elevated BP levels, and in a significant proportion of them, AH precedes disturbances of carbohydrate and lipid metabolism. This indicates that hypertension is not only a component of the syndrome but also an important predictor.

The diagnostic thresholds of AH have been repeatedly revised by leading international organizations. According to the criteria of WHO and the International Society of Hypertension (1999), the diagnosis is established at BP ≥140/90 mmHg. Modern ESC/ESH guidelines (2018) retain these values, whereas the American Heart Association (AHA, 2017) proposed stricter criteria - ≥130/80 mmHg. For patients with MS, this latter threshold has particular significance, since even moderate BP elevation in them is accompanied by a substantial increase in cardiovascular risk.

The pathogenesis of AH in MS is multifactorial and reflects the complex interplay of metabolic, neurohormonal, and inflammatory processes. The key mechanisms include:

4. Hyperinsulinemia occurring on the background of IR activates the nervous system, leading to tachycardia, increased cardiac output, and generalized vasoconstriction. Additionally, insulin stimulates renal sodium reabsorption, which increases circulating blood volume and contributes to volume-dependent hypertension.

5. RAAS activation. Visceral adipocytes produce angiotensinogen, renin, and angiotensin II, promoting systemic aldosterone activation. The RAAS causes sustained vasoconstriction, sodium and water retention, as well as smooth muscle cell proliferation in the vascular wall, resulting in remodeling.

6. Endothelial dysfunction. In M METS, both the production and bioavailability of nitric oxide - the main physiological vasodilator-are reduced. Elevated levels of reactive oxygen species inactivate nitric oxide and generate peroxynitrite, which has cytotoxic effects. As a result, vessels lose their ability to dilate adequately, thereby sustaining chronic hypertension.

7. Chronic inflammation and oxidative stress. Pro-inflammatory cytokines (TNF-α, IL-6, CRP) upregulate adhesion molecules, attract macrophages to the vascular wall, stimulate intimal thickening, and increase vascular stiffness. These processes result in persistent blood pressure elevation and further endothelial injury.

Epidemiological data over recent decades confirm the extremely high prevalence of hypertension among patients with METS. According to the NHANES (USA), more than 65% of individuals with METS have hypertension [75]. Similar findings have been reported in Asia: for example, in South Korea, the KNHANES survey showed HTN in more than 70% of METS patients [76].

A key feature of hypertension in METS is its asymptomatic course at early stages and frequent BP variability. Many patients demonstrate exercise-induced hypertension and nocturnal hypertension, identified through 24-hour ambulatory blood pressure monitoring (ABPM). The “non-dipper” phenomenon-absence of normal nocturnal BP decline-is common, significantly increasing the risk of target organ damage.

Long-standing hypertension leads to structural remodeling of the heart and vessels, including concentric left ventricular hypertrophy, increased myocardial mass, and higher vascular stiffness. These changes contribute to the progression of chronic heart failure and coronary artery disease. In the

kidneys, hypertension accelerates glomerulosclerosis and reduces filtration function, promoting chronic kidney disease progression.
Hypertension is therefore a fundamental clinical manifestation of METS and a key determinant of its poor prognosis. Its pathogenesis is rooted in insulin resistance, RAAS activation, endothelial dysfunction, inflammation, and oxidative stress. Given its high prevalence and strong association with organ damage, early diagnosis and comprehensive BP management are crucial. Effective control of hypertension largely determines the success of cardiovascular prevention in METS.

3.3. Dyslipidemia in Metabolic Syndrome

Dyslipidemia occupies a central place in the structure of METS, as it defines its atherogenic potential and represents a major factor driving cardiovascular disease.
Back in 1988, J. Reaven, describing the “syndrome X,” emphasized that the combination of IR, hyperinsulinemia, and lipid metabolism disorders forms a single continuum of risk. Today, dyslipidemia is considered one of the principal clinical criteria of METS in WHO, IDF, and AHA/NHLBI classifications, and its timely detection is essential for preventing atherosclerosis and its complications.

The pathogenesis of dyslipidemia in METS is multifaceted, rooted in lipid metabolism dysregulation caused by IR and VO. Hypertrophied adipocytes release excess free fatty acids, which enter the liver via the portal vein. In response, the liver increases synthesis of TG) and (VLDL), initiating atherogenic dyslipidemia.
Elevated VLDL levels disrupt lipid transport balance by activating cholesteryl ester transfer protein, which exchanges TG between VLDL, LDL and HDL. As a result, HDL particles become TG-depleted and undergo accelerated catabolism → reduced plasma HDL. LDL particles are transformed into small dense LDL, which readily penetrate the vascular intima and initiate atherogenesis.
In addition, IR is associated with reduced activity of lipoprotein lipase, the key enzyme responsible for hydrolyzing TG in chylomicrons and VLDL. Decreased LPL activity slows clearance of TG-rich lipoproteins, further elevating plasma TG levels. Apolipoproteins also play an important role. ApoB-100, present in each VLDL and LDL particle, is considered a marker of an atherogenic lipid profile. Elevated apoB levels are strongly associated with accelerated atherosclerosis in METS patients.
Chronic inflammation and oxidative stress aggravate dyslipidemia. Pro-inflammatory cytokines (TNF-α, IL-6) suppress expression of lipid-regulating genes and stimulate the liver to overproduce VLDL. At the same time, they reduce synthesis of ApoA-I-the major protein of HDL-thereby lowering HDL levels and impairing reverse cholesterol transport. Reactive Oxygen Specie modify LDL particles, producing oxidized LDL (oxLDL), which are highly atherogenic and trigger endothelial immune-inflammatory responses. Dyslipidemia and inflammation create a vicious cycle that drives METS and atherosclerosis progression.
Dyslipidemia in MS has direct prognostic value. Small dense LDL are more permeable through the endothelium and prone to oxidation, inducing vascular inflammation, adhesion molecule expression, and macrophage activation, leading to foam cell formation. Reduced HDL levels weaken anti-atherogenic mechanisms, impair reverse cholesterol transport, and diminish antioxidant protection of the endothelium. HyperTG is associated with hypercoagulation and increased thrombotic risk.
Altogether, these changes explain the high incidence of coronary heart disease, stroke, and peripheral atherosclerosis in METS patients. Characteristic lipid profile alterations in METS and their clinical implications are summarized in Table 4.

Table 4 - Characteristic changes in the lipid profile in metabolic syndrome and their clinical significance

Changes in Lipid Profile	Mechanism	Clinical Significance
↑ Triglycerides	Excessive influx of FFAs into the liver, ↑ VLDL synthesis	Hypertriglyceridemia, thrombogenicity, high risk of CAD
↓HDL-C	Accelerated catabolism due to lipid exchange (CETP), ↓ apoA-I synthesis	Reduced reverse cholesterol transport, accelerated atherogenesis
↑Small dense LDL	Lipid redistribution, CETP activity	High atherogenicity, penetration into the vascular wall
↑ Oxidized LDL	Oxidative stress, ROS	Induction of inflammation, foam cell formation
↑ apoB-100	Overproduction of VLDL and LDL	Marker of atherogenic profile, predictor of CVD

Modern studies show that in patients with MetS, the levels of atherogenic indices, including the Atherogenic Index of Plasma (AIP), are significantly higher compared to individuals without the syndrome. These indicators demonstrate a clear correlation with the risk of cardiovascular diseases. A recent meta-analysis involving multiple prospective cohorts demonstrated that dyslipidemia in MetS increases the risk of major cardiovascular outcomes and mortality, even after adjusting for such factors as age, hypertension, and glucose levels [77].
In addition, dyslipidemia is closely **associated with the development** of nonalcoholic **fatty liver disease,** which is considered **the hepatic manifestation of MetS.** Their interaction is bidirectional: disturbances in lipid metabolism aggravate steatosis, while **progression of nonalcoholic fatty liver disease** intensifies systemic dyslipidemia.
Dyslipidemia in MetS represents a complex multilevel disturbance of lipid metabolism, including hypertriglyceridemia, reduced HDL-C, the formation of small dense and oxidized LDL, as well as elevated apoB-100 levels. These alterations are closely linked to IR, chronic inflammation, and oxidative stress, forming an atherogenic lipid profile. Epidemiological data confirm its high prevalence and association with increased mortality, while clinical observations emphasize its key role in the progression of coronary artery disease, stroke, and nonalcoholic fatty liver disease. Thus, early detection and correction of dyslipidemia in patients with MetS should be regarded as one of the most important tasks of modern clinical practice and preventive cardiology.

3.4. Hyperglycemia in Metabolic Syndrome

Hyperglycemia is one of the most significant clinical components of MetS. It reflects systemic disturbances of carbohydrate metabolism that develop against the background of IR, obesity, and chronic inflammation. Even moderate elevations in glucose levels are associated with a substantial increase in the risk of T2D, cardiovascular disease, and microangiopathies. The inclusion of hyperglycemia in the diagnostic criteria of MetS (WHO, NCEP ATP III, IDF) underscores its fundamental role in the pathogenesis and prognosis of this condition.
The concept of hyperglycemia within the structure of MetS developed in parallel with the evolution of the “syndrome X” hypothesis. In 1988, J. Reaven identified it as a key element of the pathological cluster, alongside IR and dyslipidemia. In the WHO classification (1999), hyperglycemia was established as an obligatory diagnostic criterion of MetS. Later, according to the NCEP ATP III (2001) and IDF (2005) guidelines, it was included among the core components along with central obesity, hyperTG, low HDL-C, and hypertension. The establishment of stricter diagnostic thresholds (≥5.6 mmol/L)

revealed that even minimal glycemic abnormalities significantly increase cardiovascular risk.

The development of hyperglycemia in MetS is the result of a complex interplay of IR, β-cell dysfunction, lipotoxicity, chronic inflammation, and disturbances in gut microbiota.

Insulin resistance. In IR, glucose uptake by target tissues, primarily skeletal muscle (normally accounting for up to 80% of glucose disposal), is impaired. At the same time, adipose tissue releases excessive free fatty acids, enhancing lipotoxicity and stimulating hepatic gluconeogenesis.

β-cell dysfunction. Chronic hyperinsulinemia induces glucotoxicity, accompanied by mitochondrial dysfunction, accumulation of reactive oxygen species, and β-cell apoptosis. Lipotoxicity further aggravates the damage through accumulation of toxic lipid intermediates (ceramides, diacylglycerols). Ultimately, compensatory hypersecretion of insulin is replaced by its deficiency, driving the transition from prediabetes to overt T2D.

Islet amyloidosis. In MetS, deposits of islet amyloid polypeptide (IAPP) accumulate within β-cells, disrupting the islet microenvironment and worsening secretory failure.

Incretin resistance. Impaired action of GLP-1 and GIP reduces their stimulatory effect on insulin secretion and suppression of gluconeogenesis, contributing to pronounced postprandial hyperglycemia.

Role of the liver and skeletal muscles. In MetS, the liver becomes an active source of hyperglycemia due to increased gluconeogenesis and the presence of NAFLD. In skeletal muscle, decreased GLUT-4 expression limits glucose utilization.

Chronic inflammation and microbiota. Visceral adipocytes and macrophages produce cytokines (TNF-α, IL-6, MCP-1) that suppress expression of insulin signaling proteins (IRS-1, PI3K, GLUT-4). Gut dysbiosis reduces production of short-chain fatty acids (butyrate, propionate), which normally improve insulin sensitivity, and enhances endotoxemia through translocation of lipopolysaccharides that activate TLR4 and the NF-κB cascade.

In early stages, hyperglycemia is asymptomatic and typically detected via oral glucose tolerance testing or measurement of glycated hemoglobin (HbA1c), which remains a universal marker of chronic hyperglycemia:

5.7-6.4% - prediabetes

≥6.5% - T2D.

Postprandial hyperglycemia plays a particularly important role, as it is associated with endothelial dysfunction and accelerated atherogenesis.

Even at prediabetic glycemic levels, the risk of both **microvascular and macrovascular** complications rises markedly. Microvascular **complications include retinopathy, nephropathy, and** peripheral neuropathy; **macrovascular complications include coronary artery** disease, stroke, and chronic kidney disease.

Meta-analyses indicate that hyperglycemia within the framework MetS significantly increases the risk of cardiovascular mortality, independent of other syndrome components.

Hyperglycemia is an integral clinical feature of MetS and a critical predictor of its adverse outcomes. Its development arises from the combination of IR, β-cell dysfunction, chronic inflammation, incretin resistance, hepatic abnormalities, and gut microbiota imbalance. The high prevalence of hyperglycemia and its central role in complication development highlight the importance of early detection, monitoring, and correction of carbohydrate metabolism disorders. A deeper understanding of the molecular mechanisms will allow refinement of preventive and therapeutic strategies for patients with MetS.

3.5. Diagnostic Criteria for Metabolic Syndrome

The relevance of the problem of MetS is determined not only by its high prevalence among both adult and pediatric populations but also by the wide spectrum of associated disorders affecting the cardiovascular system, endocrine organs, and metabolic processes. The presence of MetS **significantly increases the risk of developing T2** D, **coronary artery disease, stroke, and** chronic heart failure. Consequently, the unification of diagnostic criteria for MS has become a priority task for leading international health organizations.

Historically, the concept of MetS has relatively recent origins. In 1988, Gerald Reaven introduced the term “Syndrome X,” considering IR as the central link of the pathological cascade. According to him, IR triggers hyperinsulinemia, activation of the sympathoadrenal system, the development of AH, atherogenic dyslipidemia, and AO. Thus, Reaven was the first to systematize previously described heterogeneous clinical and metabolic phenomena, integrating them into a single syndromic complex.

In subsequent decades, numerous cohort and population-based studies confirmed the close interrelation among the components of MetS and their role in the development of T2D and cardiovascular disease. This determined the need for the development of unified diagnostic criteria, enabling standardized approaches to patient identification, risk stratification, and the selection of management strategies.

World Health Organization (WHO) Criteria (1999)

The first official attempt to formalize the diagnosis of MetS belongs to the WHO. In 1999, WHO proposed to use IR as a mandatory diagnostic component, determined by oral glucose tolerance test, fasting insulin measurement, or confirmed T2D. For diagnosis, at least two additional factors were required:

11. Obesity (**BMI >30 kg/m2 or increased waist-to-hip ratio),**
12. Dyslipidemia (TG ≥ **1.7 mmol/L and/or** HDL- C < 0.9 **mmol/L in men and** <1.0 mmol/L in women),
13. Arterial hypertension (≥140/90 mmHg),
14. Microalbuminuria.

Despite its strong pathophysiological rationale, these criteria proved to be of limited applicability in mass screening due to the need for loading tests and laboratory measurements, which are difficult to implement in primary healthcare settings.

NCEP ATP III Criteria (2001)

A breakthrough stage came with the recommendations of the **Adult Treatment Panel III (ATP III) of** the U.S. National **Cholesterol Education Program.** According to NCEP ATP III, the diagnosis can be made if any three out of five **criteria** are present:

15. **Abdominal obesity** (WC > 102 **cm in men and >88 cm in women),**
16. Hypertriglyceridemia (TG ≥1.7 mmol/L),
17. Low HDL-C (< **1.0 mmol/L in** men and <1.3 mmol/L **in women),**
18. Arterial hypertension (≥130/85 mmHg or antihypertensive therapy),
19. Hyperglycemia (**fasting glucose ≥6.1** mmol/L).

The main innovation was that IR was no longer mandatory, which made the diagnosis simple and feasible for routine clinical practice and facilitated large-scale epidemiological studies.

IDF Criteria (2005)

The IDF proposed a more sensitive approach, making AO a mandatory criterion. In addition, IDF was the first to take ethnic differences in fat distribution into account, establishing different WC thresholds:

20. **For Europeans - ≥94 cm in men and ≥80 cm in** women,
21. For **South** Asian populations - ≥ **90 cm in men and ≥80 cm in women.**

This version improved the detection of MetS in Asian countries, where even moderate obesity significantly increases **the risk of T2** D and cardiovascular disease. However, the emphasis on mandatory AO faced criticism, since patients with pronounced metabolic disturbances but without obesity could be left undiagnosed.

JIS Criteria (2009)

The Joint Interim Statement (JIS), endorsed by leading international organizations (IDF, AHA/NHLBI, WHF, IAS, IASO), combined the strengths of previous systems. According to JIS, the diagnosis requires the presence of any three out of five components (AO, AH, hyperglycemia, hyperTG, low HDL-C), without any obligatory criterion, while taking into account ethnicity-specific WC thresholds.

Thus, JIS became the most balanced option, ensuring diagnostic simplicity, adaptation to various populations, and international comparability of data.

The evolution of diagnostic criteria for MetS reflects a gradual transition from pathogenetically oriented to more practical and universal systems. Differences among them significantly affect prevalence estimates of MetS, which must be considered in interpreting epidemiological data and in planning public health measures. In clinical practice, the NCEP ATP III and JIS criteria have gained the widest acceptance due to their simplicity, reproducibility, and prognostic value.

3.5.1. Impact of Diagnostic Criteria Choice on the Prevalence of Metabolic Syndrome

One of the key challenges in studying MS is the high variability in prevalence estimates depending on the diagnostic criteria applied. This phenomenon clearly demonstrates how the choice of diagnostic system influences not only epidemiological indicators but also the organization of preventive healthcare programs, assessment of disease burden, and risk prediction.

A classic example is provided by **data from the National Health and Nutrition Examination Survey** (NHANES, 2001-2002, USA). **According to NCEP ATP III criteria,** the prevalence of MetS among adults was about 34%. However, when IDF criteria were applied, prevalence increased to 39-41%, primarily due to the mandatory inclusion of AO and the use of lower WC cutoffs. Thus, switching from one system to another can increase the number of diagnosed patients by several million at the national level.

A similar situation is observed in Europe. In the large Spanish EPIC-Espaṅa cohort, the prevalence of MetS was about 30%, comparable with other Southern European countries [78]. Meanwhile, data from the international MetS and Arterial Stiffness consortium demonstrated an average prevalence of 24-25% across European populations, with notable inter-country and age-group differences [79]. This highlights that even within one continent, MetS prevalence can vary depending on ethnocultural factors, dietary structure, and diagnostic criteria applied.

Particular attention should be paid to Asian data. In 2024, the updated report “Metabolic Syndrome Fact Sheet 2021: Korea,” based on the national survey KNHANES VIII (2019-2021), was published. The study included more than 23,000 adults aged 19 years and older. The prevalence of MetS in South Korea was 24.9% (28.1% in men and 21.7% in women). Analysis revealed marked gender and age differences: in men, prevalence increased from the age of 30-39 years, whereas in women, the main rise occurred in the postmenopausal period. The most common components were AO and low HDL-C. The authors emphasize that in recent years there has been a steady upward trend in MetS prevalence, requiring revised prevention strategies and risk factor management [80].

Advantages and Limitations of Different Systems

22. WHO (1999).

Advantages: high pathophysiological validity; emphasis on the central role of IR.

Limitations: difficult application in routine practice; requirement for Oral Glucose Tolerance Test and insulin measurements; low reproducibility in mass surveys.

23. NCEP ATP III (2001).

Advantages: simplicity, reproducibility, absence of mandatory components; applicable in any clinical setting and large-scale surveys.

Limitations: insufficient consideration of ethnic differences; risk of underestimating patients with normal body weight but marked IR.

24. IDF (2005).

Advantages: consideration of ethnic obesity patterns; high diagnostic sensitivity; improved identification of patients in Asian populations.

Limitations: mandatory AO increases risk of overdiagnosis; reduced specificity; exclusion of metabolically unhealthy normal-weight individuals.

25. JIS (2009).

Advantages: optimal compromise; unification of leading organizations’ approaches; ethnicity-specific WC cutoffs; high applicability for international epidemiological studies.

Limitations: absence of a mandatory criterion reduces pathogenetic rigor; some experts consider JIS overly “broad” and less selective.

Thus, the choice of diagnostic criteria directly influences MetS prevalence estimates, which must be considered both in scientific research and clinical practice. For assessing global trends and ensuring data comparability across countries, NCEP ATP III and JIS criteria have received the greatest recognition, while WHO and IDF criteria remain valuable primarily in scientific and ethnospecific contexts.

3.5.2. Features of Diagnosis in Outpatient Practice

Diagnosis of MS in outpatient settings relies on three main pillars:

1. Identification of AO,
2. Documentation of elevated blood pressure,
3. Laboratory confirmation of dyslipidemia and hyperglycemia. The physician’s key task is to measure accurately, confirm findings outside the office (when required), and avoid both overdiagnosis and underdiagnosis.

1. Abdominal obesity: clinical verification of the visceral phenotype

Anthropometry (Basic Screening)

1. WC: the most reproducible and prognostically significant indicator of visceral fat. Technique: measured in standing position, at the midpoint **between the** lower margin of **the rib cage and the iliac crest,** at the end of expiration, without excessive tape tension. Ethnicity-specific cutoffs (IDF/JIS):
2. Europeans: ≥94 cm (men), ≥80 cm (women)
3. Asians: ≥90 cm (men), ≥80 cm (women)
4. Some subgroups (e.g., South Asian women): ≥80 cm
5. Waist-to-hip ratio: unfavorable if >0.90 (men) and >0.85 (women). Useful for describing fat distribution but less reproducible due to variability in hip measurements.

6. Waist-to-height ratio: universal predictor; cutoff ≥0.5 is associated with increased risk of T2D and cardiovascular disease, independent of ethnicity. Convenient for population screening.
7. BMI: remains an entry-level filter but does not reflect fat distribution. Important to consider the “metabolically unhealthy normal-weight” phenotype: normal BMI with elevated WC.

Instrumental Assessment of Visceral Fat (when clinically indicated)
8. Ultrasound (US): measurement of visceral fat thickness/visceral-to-subcutaneous fat ratio; operator-dependent.
9. CT: the “gold standard” for quantitative assessment and mapping of fat compartments; limited by radiation dose and cost.
MRI: highly informative, no radiation exposure; limited by availability and cost.
Biomarkers (supportive markers of visceral phenotype)
1. Elevated leptin/resistin, reduced adiponectin, high-sensitivity C-reactive protein (hs-CRP), pro-inflammatory cytokines. These indicators do not replace anthropometry but aid in risk stratification and in explaining the phenotype to patients.
2. Blood Pressure: From Office Measurement to Circadian Profile
Diagnostic threshold for MetS (NCEP/IDF/JIS): ≥130/85 mmHg or ongoing antihypertensive therapy. However, clinicians must distinguish between the “MS criterion” and the diagnosis of AH, which in modern guidelines may use different or lower thresholds depending on the context and measurement method.
Office measurement technique (minimum quality requirements):
Rest for 5 minutes; no caffeine/nicotine/exercise for 30 minutes before measurement. Cuff appropriate for arm circumference; back and arm supported, legs uncrossed. At the first visit: measure on both arms; obtain ≥2 readings 1-2 minutes apart, average the results; repeat visit if borderline values are found.
Out-of-office control (confirmation standard in MS patients):
1. ABPM: diagnostic thresholds - 24h mean ≥130/80, daytime ≥135/85, nighttime ≥120/70 mmHg. Circadian profile is crucial: absence of nocturnal dipping (non-dipping) or nighttime BP elevation (riser) is more frequent in MS, associated with microalbuminuria, left ventricular hypertrophy, carotid intima-media thickening, and carries additional prognostic risk.
2. Home BP monitoring: morning/evening measurements over 7 days (first day for adaptation), cutoff ~135/85 mmHg. Useful for detecting masked hypertension, typical in MetS.
BP patterns in MetS:
1. Masked hypertension: common in patients with obesity, sleep apnea, high psychosocial stress, or high daytime activity; office values normal, but ABPM/home readings elevated.
2. White-coat effect: less common in MetS but possible in highly anxious patients; must be distinguished from true AH to avoid overdiagnosis.
3. Non-dipping/riser profile & morning surge: linked with sympathetic and RAAS overactivity and sleep apnea; require targeted detection via ABPM.
Special groups:
1. Adolescents: assess by percentiles (sex/age/height); in presence of AO, acanthosis, or family history of T2D - prefer ABPM and repeat screening.
2. Perinatal/perimenopausal women: often parallel increase in visceral fat, reduced adiponectin, history of GDM/GH requires heightened vigilance.
3. Elderly: more often isolated systolic AH, increased arterial stiffness; orthostatic testing is mandatory (SBP drop ≥20 mmHg or DBP ≥10 mmHg within 1-3 min of standing).
3. Dyslipidemia as a Criterion of MetS: Formal thresholds (NCEP ATP III / IDF / JIS):
1. Triglycerides ≥1.7 mmol/L, and/or HDL-C <1.0 mmol/L (men) or < 1.3 mmol/L (women).
Practical rules:
1. Test performed fasting, after 12h of no food.
2. Avoid alcohol and strenuous exercise the day before.
3. If borderline, repeat testing within 2-4 weeks.
In patients on lipid-lowering therapy (statins, fibrates, ezetimibe), dyslipidemia is recorded as present, even if corrected.
Beyond TG and HDL-C:
1. LDL-C: remains the main therapeutic target; elevation increases risk even if TG normal.
2. Non-HDL-C: reflects all atherogenic lipoproteins; shown to be a stronger predictor of events than LDL-C in some studies.
3. Apolipoprotein B (ApoB): direct measure of particle number; elevated ApoB confirms risk even with normal LDL-C.
4. Hyperglycemia: Early Detection of Carbohydrate Metabolism Disorders
Criteria (NCEP/IDF/JIS):
26. **Fasting plasma glucose ≥5.6 mmol/L** (**or previously diagnosed T2DM,** or ongoing glucose-lowering therapy). (In NCEP 2001 the cutoff was 6.1 mmol/L, later reduced to 5.6 mmol/L for better sensitivity to prediabetes.)
Diagnostic methods:
1. Fasting glucose: first-level screening. May miss postprandial disorders.
2. Oral glucose tolerance test (OGTT, 75 g): gold standard for early detection of prediabetes/T2DM in MetS patients.
3. Normal: <7.8 mmol/L (2h)
4. Impaired glucose tolerance: 7.8-11.0 mmol/L
5. Diabetes: ≥11.1 mmol/L
6. glycated hemoglobin: useful for stratification and monitoring.
7. 5.7-6.4% - prediabetes
8. ≥6.5% - diabetes. (Not formally included in MS criteria but widely applied in practice.)
9. HOMA-IR: not part of formal criteria, but commonly used in research; elevated values confirm hidden disturbances in glucose metabolism in normoglycemic individuals.
Special groups:
1. Children/adolescents (with obesity/family history of T2D):
2. Start screening at age 10.
3. OGTT if uncertain.
4. glycated hemoglobin ≥5.7% - intensify follow-up.

5. Elderly: combine fasting glucose + HbA1c, and if necessary OGTT.

3.5.3. Practical Relevance in Outpatient Diagnosis

Basic screening and extended evaluation:

1. Minimum at first visit: fasting plasma glucose.
2. Transition to extended evaluation if ≥1 risk factor (AO, family history of T2D, hypertension, hyperuricemia, dyslipidemia, OSA, gestational diabetes/hypertension):
3. OGTT (75 g),
4. glycated hemoglobin,
5. Full lipid profile (TG, HDL-C/LDL-C, non-HDL-C; ApoB if available),
6. Creatinine/eGFR and urine albumin/creatinine (early kidney damage),
7. Uric acid,
8. hs-CRP (as indicated).

Additional Diagnostic Criteria of MetS

Although not part of the core definitions, several markers remain valuable for risk stratification:

Insulin resistance (IR):

1. Gold standard: euglycemic hyperinsulinemic clamp (research only).
2. Oral Glucose Tolerance Test with insulin measurement: evaluates dynamics of insulin and glucose.
3. HOMA-IR: (fasting glucose × fasting insulin) / 22.5; ≥2.5-3.0 indicates IR.
4. QUICKI index: inverse of HOMA-IR, also based on fasting glucose and insulin.

Microalbuminuria:

Microalbuminuria is defined as urinary albumin excretion in the range of 30-300 mg/day or an albumin-to-creatinine ratio of 30-300 mg/g in a morning urine sample. In MetS, microalbuminuria is considered a marker of generalized endothelial dysfunction. It is associated with early stages of kidney damage, as well as with a high risk of cardiovascular diseases and overall mortality.

Methods of assessment:

1. 24-hour urinary albumin excretion (accurate method, but inconvenient for the patient).
2. Morning spot urine sample with albumin-to-creatinine ratio determination.
3. Semi-quantitative dipstick tests for screening.

Hyperuricemia:

Hyperuricemia is defined as an increase in serum uric acid levels above 360 μmol/L in women and 420 μmol/L in men. According to epidemiological studies, hyperuricemia is observed in 25-40% of patients with MetS. It is strongly associated with AO, hypertension and IR.

Although these three indicators are not included in universal diagnostic criteria, they are useful for:

1. identifying a “truly high” risk in patients with a “borderline” set of basic criteria;
2. justifying early preventive interventions;
3. planning the frequency of monitoring and the intensity of risk factor management.

Stepwise Outpatient Algorithm (Checklist)

- Anthropometry: WC (ethnic cutoffs), BMI, if possible WC/height.
- Blood pressure: ≥2 office measurements (repeat if borderline) → ABPM/home BP to confirm phenotype (masked HTN, non-dipping common).
- Laboratory (fasting, 12h):

4. Glucose ± OGTT (per risk factors), HbA1c
5. Lipids (TG, HDL-C, LDL-C, non-HDL-C; ApoB if available)
6. Creatinine/eGFR, urine ACR
7. Uric acid; hs-CRP if indicated
8. HOMA-IR

4) OSA screening: questionnaire, cardio-respiratory monitoring if indicated.
5) Exclude secondary causes (early onset, resistant AH, hypokalemia, etc.).
6) MetS criteria: presence of ≥3 out of 5 components → confirm diagnosis, stratify overall CV risk.
7) “Plus-components” (IR/microalbuminuria/hyperuricemia): note to intensify prevention strategy and monitoring frequency.

3.5.6. Specific Features of Metabolic Syndrome Diagnosis in Outpatient Practice

In the outpatient setting, the diagnosis of MetS requires a stepwise and structured approach that integrates anthropometric, clinical-instrumental, and laboratory methods. The sequence of patient evaluation should ensure high reproducibility of measurements, minimize interpretation errors, and allow for the early detection of preclinical stages of metabolic disturbances.

The most rational strategy involves the use of an algorithm that begins with basic screening (anthropometry, office blood pressure measurement, fasting glucose and lipid profile), followed by an in-depth assessment in the presence of risk factors or borderline abnormalities.

The outpatient stage of MetS diagnosis is of fundamental importance, since it is at the primary care level that the majority of patients at high risk of developing T2D, cardiovascular diseases, and chronic kidney disease are identified. Unlike inpatient settings, where a wide range of specialized methods is available, outpatient practice relies on standardized, reproducible, and at the same time cost-effective approaches. Their goal is to ensure high diagnostic sensitivity while minimizing resource expenditure.

Modern international and national guidelines emphasize the necessity of integrating clinical assessment, anthropometric measurements, and basic laboratory tests into a unified diagnostic algorithm. This comprehensive approach not only confirms the presence of MetS but also enables early risk stratification, which is crucial for timely prevention of complications.

The diagnostic algorithm for patients in outpatient practice is presented in Figure7.

Figure 7 - Algorithm for Outpatient Diagnosis of Metabolic Syndrome

1. Initial Stage: Clinical and Anamnestic Assessment

At the first visit, special attention is paid to history taking and risk factor assessment. The main elements include:

Family history: obesity, T2D, premature cardiovascular events (myocardial infarction, stroke in men <55 years and women <65 years).
Lifestyle: dietary habits, physical activity level, smoking, alcohol abuse, sleep patterns.
Endocrine-gynecological factors: in women - polycystic ovary syndrome, history of gestational diabetes, or preeclampsia.
Already at this stage, a primary care physician can identify patients at increased risk, justifying the need for further examination.
2. Physical Examination and Anthropometry
The phenotypic marker of MS is recognized as AO, which highlights the importance of anthropometric methods:
BMI: reflects overall body mass, but does not always correlate with metabolic risk.
WC: the most representative indicator of visceral obesity. Ethnicity-specific thresholds:
Europeans: ≥94 cm in men, **≥ 80 cm in women.**
Asians: ≥ 90 **cm in** men, **≥ 80 cm** in **women.**
WC/height ratio: a universal risk index; threshold ≥0.5 is associated with high cardiometabolic risk.
WC/hip ratio (WHR): used less frequently, but remains relevant in epidemiological studies.
3. Blood Pressure Assessment
Hypertension is one of the most common components of MetS. For correct diagnosis it is necessary to:
27. measure BP after 5 minutes of rest, at least twice per visit;
28. use a cuff appropriate to arm circumference;
29. recommend repeated visits in borderline cases;
- use **ambulatory blood pressure monitoring (ABPM) or home blood pressure monitoring (HBPM)** to exclude “white coat hypertension” and confirm persistent elevation.
4. Laboratory Diagnostics
The basic set of laboratory tests for MetS diagnosis includes:
Fasting plasma glucose: threshold ≥5.6 mmol/L.
Lipid profile: TG ≥1.7 mmol/L; HDL-C <1.0 mmol/L in men and <1.3 mmol/L in women.
Additional indicators: total cholesterol (TC), LDL-C, non-HDL-C - for more detailed risk stratification.
Uric acid: often elevated in MS patients, reflecting purine metabolism disturbances.
5. Advanced Methods
In cases of borderline or doubtful results, or with additional risk factors, it is advisable to use:
Oral glucose tolerance test: “gold standard” for detecting impaired glucose tolerance and latent type 2 diabetes.
Glycated hemoglobin: reflects mean glycemia over the past 2-3 months.
Microalbuminuria: marker of early nephropathy and endothelial dysfunction.
HOMA-IR: indicator of insulin resistance, used more in research and specialized practice than in routine care.
6. Outpatient Diagnostic Algorithm
The stepwise diagnostic approach can be presented as follows:
Initial visit: history taking; anthropometry (BMI, WC, WC/height ratio); BP measurement.
Basic laboratory tests: fasting glucose, lipid profile, uric acid.
If suspected or borderline results: OGTT; HbA1c; microalbuminuria.
Conclusion: diagnosis established if ≥3 out of 5 criteria are present; documentation of additional risk factors (insulin resistance, hyperuricemia); determination of referral pathway (endocrinologist, cardiologist, nephrologist).
Summary. Outpatient diagnosis of MetS is a multistep process based on the comprehensive evaluation of clinical, anthropometric, and laboratory parameters. Use of a unified algorithm increases disease detection, allows patient risk stratification, and forms the basis for early prevention of complications. This approach is consistent with evidence-based medicine principles and makes the outpatient level a key element in the fight against cardiometabolic diseases.

CHAPTER IV. TREATMENT AND MANAGEMENT OF METABOLIC SYNDROME IN OUTPATIENT SETTINGS

4.1. Non-pharmacological approaches

Proper nutrition in metabolic syndrome
Nutrition is the leading factor determining the course and outcome of MetS. Rational dietary therapy is considered not as an auxiliary, but as a key component of both prevention and treatment of MetS. A properly structured diet can significantly improve tissue sensitivity to insulin, reduce body weight, normalize lipid and carbohydrate metabolism, and decrease the severity of chronic inflammation. Table 5 presents the impact of nutritional components on the risk of developing MetS.
Basic principles of nutrition in MetS
Energy balance and calorie control: Daily caloric intake should correspond to the patient’s energy expenditure. In cases of obesity, a hypocaloric diet with a deficit of 500-700 kcal per day is recommended, which allows gradual (0.5-1 kg/week) and safe weight loss. Even a reduction in body weight by 5-10% improves glycemic indices, lipid profile, and lowers BP.
Optimization of macronutrient composition.
Fats: ≤30% of total caloric intake, with saturated fats ≤7-10%; trans fats must be completely eliminated. Preference should be given to mono- and polyunsaturated fatty acids (fish, nuts, olive and flaxseed oil).
Carbohydrates: 45-50% of total caloric intake, mainly from complex carbohydrates with a low glycemic index (whole grains, vegetables, legumes). Sugar and refined products are excluded.
Proteins: 15-20% of total caloric intake, preferably from fish, poultry, legumes, and low-fat dairy products.
Increased fiber intake: Dietary fiber (≥25-30 g/day) improves postprandial glycemia, lowers cholesterol levels, promotes satiety, and facilitates weight reduction.
Limitation of salt and sodium: Daily salt intake ≤5 g (WHO recommendation). This reduces the risk of hypertension, which is a key component of MetS.
Fractional eating regimen: 4-5 meals per day in small portions prevent sharp fluctuations in glucose and insulin levels and reduce the risk of overeating.
Recommended dietary patterns
Nutrition **plays a crucial role in the** prevention and correction of MetS. Dietary therapy is aimed not only at reducing body weight but also at modulating

the metabolic processes involved in the pathogenesis of the disease: insulin resistance, dyslipidemia, hyperglycemia, and chronic inflammation.
The most studied and recommended dietary patterns are:
Mediterranean diet.
Characterized by a high intake of vegetables, fruits, whole grains, legumes, nuts, fish, and olive oil as the primary source of fat. Dairy products and red wine are moderately allowed. Numerous studies (PREDIMED, Lyon Diet Heart Study) have proven its effectiveness in reducing the risk of T2D, cardiovascular disease, stroke and overall mortality. The antioxidant and anti-inflammatory potential of this diet makes it one of the most pathogenetically justified nutritional models for MetS.

Table 5 - The Impact of Dietary Components on the Risk of Developing Metabolic Syndrome

Dietary Component	Source	Impact on Metabolic Risk	Clinical Effects
Saturated fats	Animal fats, butter, palm oil	↑ LDL-C, ↑ visceral obesity	Increased risk of atherosclerosis, MS
Trans fats	Margarine, industrial baked goods, fast food	↑ Inflammation, insulin resistance	Increased incidence of T2DM and CVD
Mono- and polyunsaturated fatty acids (omega-3, omega-9)	Fish, nuts, olive oil, flaxseed oil	↓ TG, ↑ insulin sensitivity, ↓ inflammation	Reduced risk of MS, CVD
Simple carbohydrates	Sugar, sweets, carbonated drinks	↑ Glycemia, ↑ hyperinsulinemia	Formation of IR and T2DM
Complex carbohydrates (low GI)	Whole-grain bread, cereals, legumes	↓ Postprandial glycemia, ↑ satiety	Prevention of obesity and T2DM
Fiber	Vegetables, fruits, whole-grain products	↓ Cholesterol, ↓ postprandial glycemia	Reduced risk of MS and obesity
Proteins (plant-based)	Legumes, soy, nuts	↑ Insulin sensitivity, ↓ body weight	Protective effect in MS
Red meat (excess)	Beef, pork	↑ Hyperuricemia, ↑ oxidative stress	Increased risk of MS, gout
Antioxidants (vitamins C, E, polyphenols)	Berries, citrus fruits, green tea	↓ Oxidative stress, ↓ inflammation	Improved vascular health
Minerals (Mg, K, Ca)	Nuts, greens, dairy products	↓ BP, ↑ glucose metabolism	Reduced risk of HTN and T2DM
Mediterranean diet	Fish, olive oil, vegetables, nuts	Comprehensive risk reduction for MS	↓ T2DM, ↓ CVD, ↑ life expectancy
DASH diet	Vegetables, fruits, low-fat dairy products, sodium restriction	↓ BP, ↓ body weight, ↑ lipid profile	Prevention of MS and HTN

DASH diet (Dietary Approaches to Stop Hypertension).
Originally developed for the management of hypertension, it has also demonstrated positive effects on other components of MS. The main principles include sodium restriction, high consumption of vegetables, fruits, low-fat dairy products, legumes, and nuts. Clinical trials (DASH trial) have confirmed its effectiveness in reducing blood pressure, improving lipid profile, and carbohydrate metabolism.
Low-calorie and low-carbohydrate diets.
Reducing total caloric intake contributes to weight normalization and improvement of metabolic profile. In some cases, limiting carbohydrates to 40-45% of daily calories is recommended, especially in patients with pronounced hyperglycemia or non-alcoholic fatty liver disease. However, such approaches require medical supervision, as excessive carbohydrate restriction may lead to ketosis and other adverse effects.
Practical dietary recommendations:
Eliminate or minimize processed foods: fast food, sugary soft drinks, confectionery, products high in salt and trans fats.
Increase the consumption of vegetables and fruits (at least 400-500 g per day), giving preference to fresh and seasonal products.
Include fish in the diet at least 2-3 times per week, especially marine fish (salmon, sardines, mackerel) rich in omega-3 fatty acids.
Use predominantly plant-based oils (olive, flaxseed, canola) instead of animal fats.
Limit red meat consumption, preferring poultry, legumes, and plant-based proteins.
Thus, dietary recommendations should be individualized, taking into account cultural and ethnic characteristics of the patient, as well as their social resources. Proper nutrition in MetS is not only a tool for weight reduction but also a powerful factor in correcting the key pathogenetic mechanisms of the disease.
Physical Activity
Table 6 describes the effects of various types of physical activity on the components of metabolic syndrome.
Physical activity is the second cornerstone in the prevention and treatment of MetS, complementing rational nutrition. Its significance goes beyond weight control: regular aerobic and resistance training improves tissue sensitivity to insulin, normalizes lipid profile, lowers BP and reduces the severity of chronic inflammation.

Table 6 - The Impact of Different Types of Physical Activity on Components of Metabolic Syndrome

Type of Physical Activity	Examples	Main Metabolic Effects	Clinical Significance
Aerobic Exercise	Brisk walking, jogging, swimming, cycling	↓ Fasting glucose, ↓ TG, ↑ insulin sensitivity, ↓ SBP and DBP	Reduced risk of T2DM and hypertension; improved cardiorespiratory fitness
Resistance Training	Weight lifting, resistance band exercises, gym equipment	↑ Muscle mass, ↑ glucose utilization, ↑ basal metabolism, ↓ visceral fat	Reduced risk of sarcopenic obesity; prevention of MS in the elderly
Combined Programs	Combination of aerobic and resistance training	Cumulative effect: ↓ IR, improved lipid profile, ↓ body weight	Greatest effectiveness in long-term prevention of MS
Low-Intensity Daily Activity	10-15 min walks after meals, stair climbing, standing work	↓ Postprandial glycemia, ↓ hyperinsulinemia, improved endothelial function	Realistic option for patients with low adherence or limitations
Flexibility and Balance	Yoga, Pilates, stretching	↓ Stress levels, improved sleep, moderate weight reduction	Support of psycho-emotional health and indirect reduction of MS risk

Physiological mechanisms of the beneficial effects of physical activity:
Enhanced glucose utilization by muscle tissue independently of insulin levels.
Increased expression of glucose transporters (GLUT-4).
Activation of mitochondrial apparatus and enhancement of substrate oxidation.
Reduction of plasma free fatty acid concentration and mitigation of lipotoxicity.
Improvement of endothelial function through increased nitric oxide production and vasodilation.

Decrease in pro-inflammatory cytokine levels (TNF-α, IL-6), thereby reducing chronic sterile inflammation.
Practical aspects:
At least 150 minutes of moderate aerobic activity per week (walking, swimming, cycling) or 75 minutes of vigorous activity is recommended.
Incorporation of resistance exercises 2-3 times per week helps increase muscle mass, improve glycemic control, and enhance fat metabolism.
It is important to consider individual characteristics such as age, comorbid conditions, and level of physical fitness.
Regular physical activity, combined with dietary therapy and psychosocial support, forms the foundation for long-term and sustainable control of MetS.
Aerobic exercise
Aerobic physical activity (walking, jogging, swimming, cycling, Nordic walking) is the fundamental form of preventive intervention. International guidelines (WHO, American Heart Association) indicate that the minimum required volume is 150 minutes of moderate-intensity activity per week or 75 minutes of vigorous activity.
Resistance Training
Resistance (strength) training complements aerobic activity, acting primarily on muscle tissue. Performing 2-3 sessions per week increases muscle mass, which leads to enhanced peripheral glucose utilization and a rise in basal metabolic rate. Clinical studies have demonstrated that in middle-aged individuals who combined resistance training with aerobic exercise, **the risk of developing T2D** decreased by 35% **compared with the control group.**
In addition, resistance exercise helps prevent sarcopenia, which, when combined with obesity (sarcopenic obesity), increases the risk MetS in older adults.

Even small volumes of physical activity distributed throughout the day exert significant metabolic effects. Short walks of 10-15 minutes after each meal result in a marked reduction in postprandial glycemia and insulin levels. This approach is especially important in outpatient practice, as it allows tailoring of recommendations for individuals with low adherence or limited capabilities.
Physical activity should be regarded not as optional, but as an essential component of primary prevention of MetS. It exerts multifaceted effects-from improving carbohydrate and lipid metabolism to reducing systemic inflammation and preventing vascular complications-making it equally important as rational nutrition.

Psychosocial Interventions in Metabolic Syndrome
Modern research increasingly demonstrates that psychosocial factors (stress level, anxiety, depression, sleep quality, social support, and behavioral habits) **play a key role in the development and progression of** MetS. Chronic stress, through activation of the hypothalamic-pituitary-adrenal axis, leads to hypersecretion of cortisol, which contributes to the development of VO, IR, dyslipidemia and hypertension. Depressive and anxiety disorders reduce treatment adherence and worsen prognosis in patients with MetS.
Therefore, psychosocial interventions should be considered not as supplementary, but as an essential component of comprehensive prevention and treatment of MetS.
Stress Management
Chronic stress is associated with elevated levels of pro-inflammatory cytokines (IL-6, TNF-α, CRP), activation of the sympathetic nervous system, and increased catecholamine levels. All of these factors enhance vascular dysfunction and accelerate atherogenesis.
Stress management methods:
- Cognitive-behavioral therapy aimed at changing maladaptive beliefs;
- Relaxation practices (breathing exercises, meditation, yoga, mindfulness);
- Biofeedback with heart rate and respiration control;
- Workplace stress management programs.
Studies show that regular meditation reduces glycated hemoglobin, SBP, and improves quality of life in patients with MetS.
2. Correction of Sleep Disorders
Sleep deficiency (<6 hours) or poor sleep quality is associated with obesity, insulin resistance, and increased risk of T2D. Sleep disorders, including obstructive sleep apnea, occur in 40-60% of patients with MetS.

Interventions:

- Sleep hygiene education (consistent schedule, avoidance of caffeine and screen time before bed);
- Cognitive-behavioral therapy for insomnia (CBT-I);
- Screening and treatment of obstructive sleep apnea (CPAP therapy)
Sleep normalization has been proven to improve insulin sensitivity and reduce body weight.
3. Mental Health Support
Depression and anxiety disorders increase the risk of low treatment adherence and worsen the course of MetS.
Main approaches:
- Psychotherapy (CBT, interpersonal therapy, group therapy);
- Pharmacotherapy if needed (SSRIs, anxiolytics) under psychiatric supervision;
- Self-help programs (online courses, mobile apps).

4. Social Support and Educational Programs

Patients with support from family, friends, and healthcare providers demonstrate significantly higher adherence to lifestyle changes.
Interventions include:
- Health schools for patients with MetS;
- Group sessions with dietitians, trainers, and psychologists;
- Involvement of family members in educational and motivational programs

The effectiveness of such approaches is confirmed by meta-analyses, showing weight reduction and improvement in lipid profile among participants in group support programs.
Behavioral Interventions to Improve Adherence
Even the most effective pharmacological and non-pharmacological interventions lose their impact without patient adherence to recommendations.

Methods to improve adherence:

- Setting specific and achievable goals (SMART technique);
- Keeping diaries of diet, physical activity and self-monitoring;
- Use of digital technologies (mobile applications, reminders, telemedicine);

- Regular brief consultations with a doctor/nurse (5-10 minutes every 1-2 months).

Psychosocial interventions are an essential component in the management of patients with MetS. They address key pathogenetic links such as chronic stress, hypercortisolism, depression, and sleep disorders, while simultaneously improving adherence to therapy. Their implementation in outpatient practice requires a multidisciplinary approach involving physicians, psychologists, social workers, and the patient.

4.2. Pharmacological Treatment of Metabolic Syndrome

The primary method of treating MetS is lifestyle modification-weight reduction, dietary changes, increased physical activity, and stress control. However, numerous clinical observations show that for most patients these measures are insufficient. In such cases, pharmacotherapy is required to correct the key components of the syndrome.

Modern clinical guidelines (European Society of Cardiology, 2021; **American Diabetes** Association, 2023; European **Association for the Study of Diabetes,** 2022; International Diabetes Federation, 2022) emphasize that pharmacological therapy should be multilevel, targeting all major components of MS.

Treatment goals include:

- Achieving target blood pressure levels;
- Improving glycemic control and reducing insulin resistance;
- Correcting atherogenic dyslipidemia;
- Reducing the risk of cardiovascular events and overall mortality;
- Improving patients' quality of life

Thus, pharmacological treatment of MetS is not monotherapy but rather a combination of pharmacological approaches targeting different pathogenetic mechanisms. In this chapter, we will examine in detail the modern principles of prescribing antihypertensive, glucose-lowering, and lipid-lowering agents, as well as strategies for combination therapy.

4.2.1. Antihypertensive Therapy in Metabolic Syndrome: Modern Aspects

Hypertension is one of the most significant components of MetS, forming the basis for cardiovascular complications. Pathogenetically, elevated BP in patients with MetS is caused not only by increased peripheral vascular resistance but also by specific metabolic disturbances:

- Activation of the renin-angiotensin-aldosterone system (RAAS;
- Sympathetic hyperactivity;
- Endothelial dysfunction (reduced bioavailability of nitric oxide, NO);
- Chronic subclinical inflammation and elevated cytokine levels (TNF-α, IL-6), which affect vascular tone

Therefore, the choice of antihypertensive drugs in patients with MetS should consider not only their ability to reduce BP but also their effects on IR, lipid metabolism and endothelial function.

ACE inhibitors and angiotensin II receptor blockers (ARBs)

These classes of drugs have the strongest pathophysiological justification in MetS. Their action is not limited to antihypertensive effects but also includes:

- Reduction of RAAS activity, which decreases vasoconstriction and myocardial and vascular hypertrophy;
- Effects on carbohydrate metabolism: ACE inhibitors and ARBs increase tissue sensitivity to insulin, preventing worsening of IR;
- Nephroprotection: reduction of microalbuminuria and slowing of diabetic nephropathy progression;
- Anti-inflammatory and antioxidant effects mediated through angiotensin II blockade and reduced production of free radicals.

Calcium channel blockers (CCBs)

The use of calcium channel blockers in MetS therapy is justified by their metabolic neutrality and proven efficacy in stroke prevention. CCBs do not adversely affect carbohydrate and lipid metabolism, which makes them preferable compared with thiazide diuretics and beta-blockers.

Diuretics

Thiazide and thiazide-like diuretics (indapamide, chlorthalidone) have high antihypertensive efficacy and proven effects in stroke prevention. However, in patients with MS, their use requires caution. The problem is that thiazide diuretics may worsen metabolic disturbances-increasing glucose, triglycerides, and LDL cholesterol levels-which raises the risk of developing diabetes.

To address this, it is necessary to:

- Prescribe low doses (e.g., indapamide SR at 1.5 mg/day);
- Combine with ACE inhibitors or ARBs, which counterbalance negative effects on carbohydrate metabolism

Beta-blockers

Classical beta-blockers (atenolol, metoprolol) are considered less preferable in MetS due to their negative impact on metabolism:

- Reduced insulin sensitivity;
- Increased body weight;
- Elevated triglycerides and reduced HDL cholesterol;

However, modern agents (nebivolol, carvedilol) have a more favorable profile:

- Stimulate NO release and improve endothelial function;
- Have less impact on carbohydrate metabolism;
- Possess antioxidant properties

Their use is justified in cases of concomitant coronary artery disease or heart failure.

Thus, the pathogenesis of hypertension in MetS is closely linked to RAAS, endothelial dysfunction, and insulin resistance, which explains the priority use of ACE inhibitors and ARBs as drugs that act not only on BP but also on metabolic components of the syndrome.

Calcium channel blockers enhance the antihypertensive effect without disturbing metabolism. Diuretics remain valuable but should be prescribed in small doses and only in combination with RAAS blockers. Beta-blockers are used selectively, mainly in the form of new-generation drugs.

Table 7 presents the clinical evidence base (RCTs/meta-analyses).

As shown in Table 7, in populations close to the MetS phenotype (obesity/T2DM/multiple risk factors), the best balance of efficacy and metabolic safety is demonstrated by RAAS blocker-based regimens with the addition of CCBs; diuretics are useful but preferable in small doses under the "umbrella" of RAAS blockade; classical β-blockers are inferior in metabolic profile (except in cases where they are vitally indicated), while carvedilol/nebivolol are more acceptable.

This strategy reflects modern views on comprehensive cardiometabolic protection in patients with MS, where therapy is chosen taking into account not only target blood pressure levels but also the overall risk of diabetes and atherosclerosis.

4.2.2. Glucose-lowering Therapy in Metabolic Syndrome

The central pathogenetic mechanism of MetS is IR, which leads to chronic hyperinsulinemia and impaired glucose metabolism. Prolonged IR results in β-cell overload, their functional exhaustion, and, consequently, the development of T2D.

Key pathophysiological processes requiring pharmacological correction:

- Reduced sensitivity of muscle and adipose tissue to insulin → fasting hyperglycemia and impaired glucose tolerance;
- Lipo- and glucotoxicity, which damage β-cells and accelerate progression to T2D;
- Activation of inflammatory cascades and oxidative stress, aggravating endothelial dysfunction;
- Increased levels of free fatty acids, worsening insulin resistance, provoking hepatic steatosis, and inducing atherogenic changes in lipid profile;
- Formation of a “cardiometabolic risk” phenotype - a combination of hyperglycemia, atherogenic dyslipidemia, endothelial dysfunction, and hypertension.

Thus, glucose-lowering therapy in patients with MetS should simultaneously address several objectives:

1. Improve insulin sensitivity and reduce glucotoxicity.
2. Promote weight reduction (or at least avoid exacerbating obesity).
3. Provide pleiotropic effects (cardio-, nephro-, and vasculoprotection, anti-inflammatory action).
4) Minimize the risk of hypoglycemic episodes.

Study Population/Risk Comparison Primary Endpoint Key Result Practical Relevance for MS
HOPE High CV risk, many with diabetes/metabolic disorders Ramipril vs placebo (on top of standard therapy) Composite: MI/stroke/CV death −22% events on ramipril RAAS blockade provides cardio- and nephroprotection beyond BP lowering; pathogenetically justified in MS
LIFE Hypertension + LVH, some with metabolic disorders Losartan vs atenolol Stroke −25% strokes on losartan ARB better than β-blocker for vascular outcomes and metabolic profile
ADVANCE T2DM (typical cardiometabolic phenotype) Perindopril/indapamide vs placebo Micro- and macrovascular events Significant reduction in overall risk Combo RAAS blockade + low-dose diuretic is effective and metabolically acceptable
ASCOT-BPLA Hypertension + ≥3 risk factors (often MS) Amlodipine+perindopril vs atenolol+thiazide Mortality/CV events Superiority of CCB+ACEI regimen CCB+ACEI superior to β-blocker+thiazide in ‘metabolically heavy’ patients
ALLHAT Mass hypertension (some with MS) Chlorthalidone vs amlodipine/lisinopril CHD/Death Diuretic not worse than CCB/ACEI; ↑ new diabetes Diuretics effective for outcomes, but worsen glycemic control in MS
ACCOMPLISH High risk (many with diabetes/obesity) Benazepril+amlodipine vs benazepril+HCTZ Composite CV CCB combo superior to diuretic combo In MS, prefer RAAS+CCB as baseline fixed combination

Table 7 - Clinical Evidence Base (RCTs/Meta-Analyses) - Focus on Relevance to MetS

Main classes of glucose-lowering agents

1. Metformin - the first-line drug for both prediabetes and manifest T2D within the structure of MetS. Mechanisms of action:

Activation of AMPK and reduction of hepatic gluconeogenesis.
Enhancement of peripheral insulin sensitivity.
Moderate weight reduction through appetite suppression.
Anti-inflammatory and antioxidant effects.
Metformin is recommended for most patients with MetS, especially those with AO.

2. GLP-1 receptor agonists (liraglutide, semaglutide, dulaglutide)

Incretin-based agents with proven efficacy in MS complicated by obesity and high cardiovascular risk. Mechanisms of action:
Stimulation of insulin secretion and suppression of glucagon.
Delayed gastric emptying, reduced appetite → marked weight loss.
Improved insulin sensitivity.
Anti-inflammatory and anti-atherogenic effects.
GLP-1 receptor agonists are the optimal choice for patients with obesity and high risk of cardiovascular events.

3. SGLT2 inhibitors (empagliflozin, dapagliflozin, canagliflozin)

Agents that lower blood glucose by inducing glucosuria.
Mechanisms of action:
Inhibition of renal glucose reabsorption → urinary excretion.
Weight reduction (on average 2-4 kg).
Moderate blood pressure reduction (by 3-5 mmHg).
Cardio- and nephroprotective effects demonstrated in large RCTs (EMPA-REG, DAPA-HF).
SGLT2 inhibitors are indicated in patients with MS and heart failure, chronic kidney disease, or high cardiovascular risk.

4. Thiazolidinediones (PPARγ agonists, pioglitazone)

Used less frequently, but with pathogenetic justification.
Mechanisms of action:
Activation of PPARγ → increased tissue insulin sensitivity.
Reduction of free fatty acid levels.
Improvement of lipid profile (increase in HDL, reduction in TG).
Anti-atherogenic and anti-inflammatory effects.
Limitations: weight gain, fluid retention, risk of heart failure.

5. Insulin therapy Indicated only in cases of decompensated T2D or inefficacy of oral agents.

Advantages: rapid control of severe hyperglycemia and ketosis.
Disadvantages: weight gain, risk of hypoglycemia, reduced treatment adherence.

Practical Therapeutic Algorithms in MS

Prediabetes + obesity:
First line: metformin.

If ineffective: add a GLP-1 receptor agonist.
MS + type 2 diabetes without complications:
Start: metformin.
Next: combine with GLP-1 or SGLT2 inhibitor (choice depends on phenotype - obesity vs HF/CKD).
MS + type 2 diabetes + cardiovascular risk (CAD, stroke):
Combination: metformin + GLP-1 (liraglutide, semaglutide).
MS + type 2 diabetes + heart failure or CKD:
Combination: metformin + SGLT2 inhibitor (empagliflozin, dapagliflozin).
Elderly patients:
Avoid agents with high hypoglycemia risk (sulfonylureas, insulin).
Prefer: metformin and SGLT2 inhibitors.
Future Directions
Dual GIP/GLP-1 agonists (tirzepatide) - SURPASS trials (2021-2023) showed HbA1c reduction up to −2.5% and weight loss up to −20%.
SGLT2 + GLP-1 combination - provides maximal cardiometabolic effect (weight reduction + heart and kidney protection).
Pharmacogenetics - personalization of therapy based on genetic polymorphisms (e.g. SLC5A2 for SGLT2 response).
Glucose-lowering therapy in MetS - is not just about glycemic control, but a multi-level strategy for cardiometabolic protection. Metformin remains first-line, but modern drugs - GLP-1 receptor agonists and SGLT2 inhibitors - have radically changed the therapeutic approach, since they simultaneously affect body weight, cardiovascular, and renal risk.
Therapy choice should be personalized:
In obesity → GLP-1 preferred.
In HF/CKD → SGLT2 preferred.
In severe IR and prediabetes → metformin and possibly pioglitazone.
Thus, glucose-lowering therapy in the context of MetS should be regarded as a multi-organ strategy, integrating both endocrinological and cardiological objectives.
4.2.3. Lipid-Lowering Therapy in Metabolic Syndrome
Atherogenic dyslipidemia is a key component of MS. Its features include:
1. Moderate elevation of LDL-C, but with predominance of small, dense particles, which are highly atherogenic.
2. Reduced HDL-C levels (typically < 1.0 **mmol/L in men and** <1.2 mmol/L in women).
3. Hypertriglyceridemia (often >1.7 mmol/L), associated with insulin resistance.
4. Postprandial hyperlipidemia and accumulation of apoB-containing remnants.
5. Activation of inflammatory pathways promoting the progression of atherosclerosis.
This combination forms the "lipid triad of MS" phenotype (↑TG, ↓HDL-C, ↑sdLDL), which substantially increases the risk of cardiovascular events, even when total cholesterol levels are only moderately elevated.
The goal of lipid-lowering therapy in MS is not only to reduce LDL-C but also to correct the entire atherogenic profile: normalize triglycerides, raise HDL-C and improve LDL particle quality.
Main Classes of Lipid-Lowering Agents
Statins (HMG-CoA reductase inhibitors)
Mechanisms:
Powerful reduction of LDL-C (by 30-55%, depending on dose and molecule).
Pleiotropic effects: improvement of endothelial function, reduction of inflammation, stabilization of atherosclerotic plaques.
Statins are first-line therapy for all patients with MS at high and very high risk, regardless of baseline lipid levels.
Fibrates (PPARα agonists)
Mechanisms:
Activation of lipoprotein lipase → triglyceride reduction by 30-50%.
Increase in HDL-C by 5-15%.
Reduction in small dense LDL particles.
Fibrates are indicated for severe hypertriglyceridemia (>2.3-5.6 mmol/L), especially with low HDL-C. Important: consider the risk of myopathy when combined with statins.
Omega-3 polyunsaturated fatty acids (PUFAs, EPA/DHA)
Mechanisms:
Reduction of triglycerides by 20-30% at doses ≥2-4 g/day.
Anti-inflammatory and anti-arrhythmic effects.
Modification of cell membranes.
Ezetimibe (cholesterol absorption inhibitor)
Mechanisms:
Blockade of NPC1L1 in the intestine → reduced cholesterol absorption.
LDL-C reduction by 18-22%.
PCSK9 inhibitors (evolocumab, alirocumab)
Mechanisms - suppression of LDL receptor degradation → powerful LDL-C reduction (−50-60%).
Lipid-lowering therapy in MetS is the cornerstone of preventing cardiovascular complications, along with BP and glycemic control. Statins remain first-line drugs, but in patients with atherogenic dyslipidemia, a combination approach is required (statins + fibrates or omega-3, ezetimibe, PCSK9 inhibitors). Modern strategy should be personalized: the choice of agents depends on the predominant phenotype (hypertriglyceridemia, low HDL-C, statin resistance) and overall cardiometabolic risk.
4.2.4. Combined Approaches in Pharmacotherapy of Metabolic Syndrome
MetS is not a single disease but a cluster of interrelated disorders: hypertension, abdominal obesity, insulin resistance, and atherogenic dyslipidemia. It is their combination that sharply increases cardiovascular risk. Attempting to treat only one component (e.g., BP or glycemia alone) does not reduce risk to an acceptable level. A classic example is the UKPDS and ACCORD trials: improving glycemic control without parallel lipid and BP correction did not

lead to a significant reduction in myocardial infarction and stroke.
Therefore, MetS requires integrative pharmacotherapy that simultaneously targets all components of the syndrome. This concept is known as "cardiometabolic protection."
Rational drug combinations in specific scenarios:
Hypertension + Dyslipidemia
1. ACEI/ARB + statin
2. ACEI/ARB reduce BP and inflammation.
3. Statins stabilize atherosclerotic plaques.
4. Proven synergistic effect: reduced risk of stroke and MI (ASCOT, HOPE).
Disorders of carbohydrate metabolism + Obesity
1. Metformin + GLP-1 agonist
2. Metformin improves insulin sensitivity.
3. GLP-1 reduces body weight and appetite.
4. Combination demonstrated efficacy in DPPOS and LEADER.
T2DM + Heart failure/CKD
Metformin + SGLT2 inhibitor + ACEI/ARB
Reduces risk of HF hospitalizations (EMPA-REG, DECLARE, DAPA-HF).
Nephroprotection is provided.
RAAS blockers additionally reduce proteinuria.
Dyslipidemia with hypertriglyceridemia
1. Statin + fenofibrate (or highly purified EPA)
2. Statin controls LDL-C.
3. Fibrate lowers TG and raises HDL-C.
4. In the high TG/low HDL subgroup (ACCORD-Lipid), the combination reduced event risk by 31%.
Future directions
- Polypills (single-pill combinations drugs combining statins, antihypertensives, and antiplatelets are already being tested in large trials (TIPS-3, 2020);
- New molecules dual GIP/GLP-1 agonists (tirzepatide) show 15-20% weight loss and improved metabolic profile;
- Pharmacogenetics individualized therapy selection based on gene polymorphisms (PPAR, SLC5A2, CETP, PCSK9);
- Digital medicine integration of mobile apps and telemonitoring to control adherence and safety.
Combined pharmacotherapy in MetS is a strategic necessity Only simultaneous action on all pathogenetic components (BP, glycemia, lipids, body weight) can significantly reduce mortality and improve quality of life.
Current evidence confirms:
The basic triad (RAAS blocker + statin + metformin) should be prescribed to most patients with MetS.
Further therapy is personalized depending on phenotype (obesity, heart failure, kidney disease, hypertriglyceridemia).
The future lies with multi-organ drugs and integrative regimens ("cardiometabolic protection").
4.3. Monitoring and Control in Outpatient Practice for Metabolic Syndrome
Importance of outpatient monitoring.
The outpatient stage of managing patients with MetS is key, since it is here that long-term follow-up, risk factor control, and therapy adjustment are carried out. Most patients with MetS do not require hospitalization but remain chronically at risk of disease progression: hypertension, T2D, ischemic heart disease, and chronic heart failure.
Current guidelines (ESC/ESH 2021; ADA 2023; IDF 2022) recommend structured outpatient monitoring on several levels:
1. Monthly during the first 3-6 months of therapy monitoring BP, body weight, WC, heart rate.
2. Every 3-6 months assessment of the effectiveness of antihypertensive, hypoglycemic, and lipid-lowering therapy; adherence analysis; physical examination.
3. Every 6-12 months laboratory monitoring (glycated hemoglobin, lipids, creatinine, eGFR, microalbuminuria), ECG, and when necessary, ultrasound of target organs (heart, kidneys).
4. Annually in-depth evaluation of cognitive and psycho-emotional status, screening for depression and anxiety, ophthalmologic examination.
Scales and questionnaires in outpatient practice
The use of validated scales not only objectifies the patient's condition but also improves compliance.
5. SF-36 (Short Form-36 the most widely used quality-of-life assessment tool. In MS patients, the greatest changes are seen in the physical health component, correlating with the severity of obesity and hypertension. Several studies have shown that low SF-36 scores in MetS patients are associated with worse prognosis and poor adherence [76].
6. MMAS-8 (Morisky Medication Adherence Scale tool for assessing treatment adherence. A low MMAS-8 score predicts a high likelihood of decompensated BP and T2DM, as confirmed in meta-analysis [41].
7. PHQ-9 (depression scale and MoCA/MMSE (cognitive function tests useful for identifying hidden psycho-emotional and cognitive impairments, often accompanying MS.
Digital technologies and telemedicine
Healthcare digitalization not only increases the accuracy of monitoring but also improves adherence, as it engages patients in active self-management. The era of digital health has opened new opportunities in MetS control: telemedicine consultations, mobile applications, wearable devices (fitness trackers, smartwatches), and artificial intelligence in big data analysis allow prediction of hospitalization risk in MS patients.

4.4. Primary Prevention of Metabolic Syndrome
Primary prevention of MetS is aimed at preventing its onset in individuals with risk factors but without clinically manifest metabolic disorders. It plays a central role in public health strategies, as the development of MS begins long before clinical diagnosis and is associated with the cumulative impact of behavioral, social, and biological factors.
Lifestyle modification as the foundation of prevention
Rational nutrition is the key factor in preventing MS.

Main principles:
Limiting saturated fats and trans fats.
Increasing the share of vegetables, fruits, whole grains.
Regular consumption of fish and legumes.
Limiting salt (<5 g/day), sugar, and refined carbohydrates.
Physical activity
WHO (2020) and American Heart Association (2021) recommendations:
≥150 minutes of moderate aerobic activity per week or ≥75 minutes of vigorous activity.
Additionally, strength training 2-3 times per week.
The large Finnish Diabetes Prevention Study (DPS, 2001-2015) showed that in individuals with prediabetes, regular physical activity reduced the risk of type 2 diabetes by 58%.
Weight control
Even moderate weight reduction (5-10% of baseline body mass) is associated with:
1. Improved insulin sensitivity.
2. Reduction in TG levels and blood pressure.
3. Decrease in WC and visceral fat.
Psychosocial interventions
Chronic stress, depression, and low social support are independent risk factors for MetS.
Incorporating cognitive behavioral therapy and stress management training reduces cortisol levels, improves sleep quality, and enhances compliance.
Group support programs and “health schools” increase adherence to preventive measures by 1.5-2 times.
Screening and early detection
Effective primary prevention is impossible without early diagnosis.
Recommendations:
1. Screening of WC and BMI in all adults ≥18 years (IDF, 2022).
2. Fasting glucose measurement every 3 years starting at age 40, or earlier if risk factors are present.
3. Regular lipid profiling in cases of obesity, hypertension, or family predisposition.
The use of risk scores (e.g., FINDRISC for diabetes) makes it possible to identify groups with a high likelihood of MS even before symptoms appear.
Population-level measures
1. Primary prevention is effective only when individual and population-level strategies are combined:
2. Government programs to combat obesity and promote healthy eating (e.g., taxes on sugary drinks, food labeling).
3. Creation of infrastructure for physical activity (bike paths, parks, sports grounds).
4. Implementation of school-based programs for obesity prevention and healthy eating habits.
5. Media campaigns to raise public awareness.
Primary prevention of MetS is not only about individual measures but also about a systemic approach that includes government policy, healthcare, and society.
Main directions remain:
1. Rational nutrition.
2. Regular physical activity.
3. Weight control.
4. Stress reduction and psychosocial support.
5. Early identification of risk factors.
6. Use of digital technologies and population-level strategies.
The implementation of these measures has proven effective in international studies and should become a public health priority in countries with high prevalence of obesity and cardiovascular diseases, including Kazakhstan.

4.5. Prognosis in Metabolic Syndrome and Risk Factors for Adverse Outcomes
The prognosis in MetS is determined by the combined influence of its components - AO, AH, dyslipidemia, and impaired glucose metabolism. Each of these conditions independently increases the risk of cardiovascular disease and T2D but their coexistence creates a synergistic effect, significantly raising the probability of adverse outcomes.
Patients with MetS have a less favorable prognosis compared to individuals without MS, even when the levels of individual risk factors are comparable.
This is explained by several features:
1. Cumulative effect - the simultaneous presence of obesity, hypertension, and dyslipidemia generates a higher risk than the sum of risks from each condition separately.
2. Chronic subclinical inflammation (elevated CRP, IL-6, TNF-α) accelerates atherogenesis.
3. Endothelial dysfunction and reduced bioavailability of nitric oxide (NO) predispose to earlier development of coronary artery disease.
4. IR contributes not only to diabetes progression but also to vascular wall and myocardial damage.
Thus, the prognosis in MetS directly depends on the degree of compensation of each of its components.
Risk Factors for an Unfavorable Prognosis
Non-modifiable factors
1. Age >50 years - the risk of cardiovascular events doubles every 7-8 years.
2. Male sex - higher risk of coronary heart disease and sudden death, whereas women more often present with obesity and T2D.
3. Genetic predisposition (polymorphisms of FTO, MC4R, PPARγ, APOE genes).
Modifiable factors
1. Waist circumference >102 cm (men) / >88 cm (women) - a marker of AO and a predictor of cardiovascular disease.
2. Hypertension (>140/90 mmHg) - doubles the risk of stroke and coronary artery disease.
3. Hyperglycemia (HbA1c ≥7.0%) - associated with a 25% increase in overall mortality.
4. Hypertriglyceridemia (>2.3 mmol/L) and reduced HDL-C.

5. Low adherence to therapy (MMAS-8 ≤6 points).
6. Chronic stress and depression, which reduce compliance and intensify the inflammatory background.

CONCLUSION

MetS remains one of the most serious challenges of modern clinical medicine and public health. Its global prevalence continues to rise: according to NHANES (2020) and EPIC-Europe (2019), signs of MetS are identified in 20-35% of the adult population, and in more than half of individuals over the age of 60. In Kazakhstan and other Central Asian countries, a similar trend is observed: high rates of obesity, low levels of physical activity, and specific dietary traditions create a favorable environment for the development of this syndrome complex.

MetS negatively affects not only individual health but also demographic and socioeconomic indicators of society as a whole. It contributes to increasing disability, premature mortality, and substantially raises the burden on healthcare systems. This underscores the urgent need to develop and implement multi-level strategies for the diagnosis, prevention, and treatment of MetS at both individual and population levels.

A review of the literature and epidemiological studies indicates that MetS is a global phenomenon, but its clinical manifestations vary depending on regional characteristics. In European countries, the “dyslipidemic” phenotype is more common, characterized by pronounced atherogenic dyslipidemia; in the United States, obesity combined with carbohydrate metabolism disorders predominates; in Kazakhstan and CIS countries, AO and AH are most prominent, largely due to low physical activity and dietary habits (excessive salt, bakery products, and animal fats). These differences emphasize the need for personalized preventive and therapeutic strategies that take into account ethnocultural and socioeconomic factors.

MetS should be considered a multifactorial pathological condition based on IR, closely associated with AO. The leading roles in its pathogenesis are played by disturbances in energy metabolism, mitochondrial dysfunction, chronic subclinical inflammation, and endothelial dysfunction. Particular attention is drawn to adipokines (leptin, adiponectin, resistin), pro-inflammatory cytokines (IL-6, TNF-α), and mechanisms of oxidative stress, which together form a vicious pathological cycle that promotes atherogenesis, myocardial damage, and vascular injury.

Pharmacological treatment of MetS is not limited to correcting a single pathogenic link but requires a comprehensive approach.

Antihypertensive therapy: the best outcomes are achieved with combinations of RAAS blockers (ACE inhibitors, ARBs) with calcium channel blockers; low doses of diuretics are used sparingly (HOPE, ASCOT, ADVANCE).

Glucose-lowering therapy: metformin remains the first-line drug; however, incretin-based agents (GLP-1 receptor agonists) and SGLT2 inhibitors have demonstrated not only efficacy in glycemic control but also reductions in cardiovascular mortality (LEADER, EMPA-REG).

Lipid-lowering therapy: statins remain the foundation; in cases of pronounced hypertriglyceridemia, the addition of fibrates or omega-3 polyunsaturated fatty acids (PUFAs) is appropriate (REDUCE-IT, ACCORD-Lipid).

Combined approaches: the concept of “cardiometabolic protection” involves simultaneous action on all major risk factors. The effectiveness of this approach has been confirmed in large meta-analyses [81].

Lifestyle modification remains an equally important area, capable of reducing the risk of MetS development by 30-50%. The DPS (Finland), PREDIMED (Spain), and Look AHEAD (USA) programs have proven that rational nutrition, regular physical activity and psychosocial support can lead to long-term improvements in prognosis.

For patients with already established syndrome, the key objectives are blood pressure, glycemia, and lipid profile control, improvement of treatment adherence, and active use of digital technologies (telemedicine, mHealth), which is especially relevant in the modern context.

According to population-based studies, MetS increases the risk of all-cause mortality by 40-60%, the risk of T2D by 4-6 times, and the risk of stroke and ischemic heart disease by 2-3 times. However, comprehensive interventions can significantly reduce these risks: combined therapy and high patient adherence lower the risk of complications by 30-50%.

Thus, MetS represents a polyetiological and multifactorial condition with a significant impact on population health and the functioning of the healthcare system. It requires a multidisciplinary, integrative approach that includes early diagnosis, prevention, monitoring and multilevel therapy.

Only a combination of individual interventions (lifestyle modification, pharmacotherapy, psychosocial support) and population-level strategies (educational programs, public health reforms, digital medicine) can substantially reduce the burden of MetS, improve prognosis, and enhance patients’ quality of life.

Practical recommendations are summarized in Table 8.

Level of Intervention Specific Measures Expected Effect

Primary Healthcare Level - Screening: WC, BP, glycemia, lipids

- Use of scales: SF-36, MMAS-8

- Counseling on nutrition and physical activity Early diagnosis, improved adherence, reduced complication rates

Clinical Practice - Implementation of therapy standards (ESC, ADA, IDF)

- Access to modern medications (metformin, GLP-1, SGLT2, statins, PCSK9)

- Telemedicine and mHealth for monitoring Improved risk factor control, reduced mortality and disability

Population Level - Government programs for obesity and T2DM prevention

- Development of infrastructure for physical activity

- Public campaigns on nutrition, smoking and alcohol prevention Reduced prevalence of MS, improved population quality of life

Prospective Directions - Research on genetic and epigenetic factors

- Predictive models using Big Data and AI

- Use of mobile apps and wearable devices

- Evaluation of new drugs (tirzepatide, ANGPTL3 inhibitors) Personalized prevention, improved treatment effectiveness, reduced long-term MS burden

Table 8 - Practical Recommendations for the Diagnosis, Prevention, and Treatment of Metabolic Syndrome

SELF-ASSESSMENT QUESTIONS

Test Questions

1. What is the maximum blood glucose level in a healthy person?

a. 5.5 mmol/L

b. 6.1 mmol/L

c. 7.8 mmol/L

d. 8.5 mmol/L

e. 9.9 mmol/L

2. What is the fasting blood glucose level in a healthy person?
a. 3.3-7.8 mmol/L
b. 3-5.5 mmol/L
c. 3-6.7 mmol/L
d. 3.4-6.0 mmol/L
e. 3.3-5.8 mmol/L
3. A 30-year-old woman has had type 1 diabetes mellitus for 5-10 years. Over the past 2 years, her vision has significantly worsened, leading to blindness in the left eye. What is the occupational prognosis for this patient?
a. Able to work with adherence to regimen
b. Disability Group I
c. Disability Group II
d. Disability Group III
e. Reduced workload
4. A 63-year-old man complains of thirst, dry mouth, general weakness, fatigue, weight loss, and increased urination. Ill for 6 months. Objectively: overweight, dry skin, scratch marks. Xanthelasmas on eyelids. Heart sounds muffled, rhythm regular. Pulse 98/min, BP 180/100 mmHg. Which of the following investigations is MOST urgent to confirm the diagnosis?
a. Cholesterol
b. Blood glucose
c. Blood alpha-amylase
d. Complete blood count
e. Total protein and fractions
5. A 65-year-old man was found unconscious in the street. Objectively: dry skin, scratch marks, injection traces. Pupils constricted, decreased eyeball tone. Smell of rotten apples. Muscle hypotonia. Kussmaul breathing. Heart: muffled sounds, irregular rhythm. Pulse 102/min, BP 55/30 mmHg. Abdomen painful around the umbilicus. Which preliminary diagnosis is MOST likely?
a. Hypoglycemic coma
b. Ketoacidotic coma
c. Hypothyroid coma
d. Hyperosmolar coma
e. Alcoholic coma
6. A 26-year-old man complains of acute hunger, sweating, tremors, double vision. During examination, he loses consciousness. Objectively: pale moist skin, injection marks. Pupils dilated, marked muscle hypertonia, single clonic seizures. Heart: muffled sounds, irregular rhythm. Pulse 102/min, BP 75/40 mmHg. Insulin replacement therapy: 10 U short + 16 U lente in morning, 10 U short + 8 U lente in evening. Blood glucose: 7.7 mmol/L (8 am), 7.2 mmol/L (12 pm), 3.2 mmol/L (midnight). Urine glucose 0.8%. What is the MOST expected condition?
a. Hypoglycemia
b. Hypovolemia
c. Ketoacidosis
d. Hypokalemia
e. Hypocalcemia
7. A 62-year-old man presents with a trophic ulcer. History: type 2 diabetes mellitus for 2 years, on maninil 1 tab 3 times daily. Objectively: dry skin, no edema. BP 130/70 mmHg, HR 88/min. Local: right foot hyperemic, moderately edematous, ulcer on dorsum 5x6 cm. Peripheral pulses weakened. Blood glucose 14 mmol/L, daily glucosuria 35 g. What is MOST necessary in polyclinic management?
a. Increase sulfonylurea dose
b. Add sulfonylurea + biguanide
c. Refer for inpatient treatment
d. Diet and rational physical activity
e. Switch to biguanides
8. A 19-year-old woman complains of abdominal pain, nausea, vomiting, dry mouth, weakness. History: thirst and polyuria for 10 days. Recently nausea, later vomiting, abdominal pain. Drowsy, answers with difficulty. Dry, pale skin. Acetone smell on breath. Pulse 97/min, BP 100/70 mmHg. Abdomen tender in epigastrium, mild peritoneal signs. Blood: WBC 12.8×10^9/L, glucose 28 mmol/L. Which treatment is pathogenetic?
a. Oxygen therapy
b. Vitamin therapy
c. Regular insulin
d. Oral hypoglycemic drugs
e. Potassium supplements
9. A 49-year-old woman complains of weakness, dizziness, 'flies' before eyes, facial swelling in mornings, dry mouth, thirst (drinks up to 3 L/day), frequent urination (4-5 times at night). Longstanding thirst and dry mouth ignored. Objectively: facial swelling, muffled heart sounds, accentuated II tone over aorta, regular rhythm, pulse 64/min, BP 190/115 mmHg. Left heart border shifted 2 cm outward. Most likely preliminary diagnosis?
a. Type 1 diabetes mellitus
b. Type 2 diabetes mellitus
c. Autoimmune DM
d. Idiopathic DM
e. MODY diabetes
10. A 35-year-old man with type 1 DM and alcohol abuse. Objectively: unconscious, dry skin, soft eyeballs, tongue coated gray. Respiration 34/min. Pulse 110/min. BP 80/45 mmHg. CBC: WBC 10×10^9/L, ESR 22 mm/h. Blood glucose 26.3 mmol/L. Urine: glucose 4.9%. Most likely diagnosis?
a. Hypoglycemic coma
b. Ketoacidotic coma
c. Hyperosmolar coma

d. Lactic acidosis coma
e. Alcoholic coma
11. A 23-year-old man admitted unconscious. Objectively: dry skin, flushed cheeks. Acetone smell. Noisy Kussmaul breathing. BP 130/90 mmHg, pulse 102/min. Blood glucose 28.4 mmol/L, urine glucose 6%, acetone positive. Preliminary diagnosis?
a. Renal coma
b. Uremic coma
c. Ketoacidotic coma
d. Hyperosmolar coma
e. Lactic acidosis coma
12. Definition of gestational diabetes:
a. Appears during pregnancy and persists postpartum
b. Diabetes with relative insulin deficiency
c. Appears during pregnancy but resolves postpartum
d. Develops on background of type 2 DM
e. Impaired glucose tolerance
17. Fasting blood glucose:
a. 1.1-2.2 mmol/L
b. 3.3-5.5 mmol/L
c. 6.6-8.8 mmol/L
d. 6.7-9.8 mmol/L
e. 7.8-10.0 mmol/L
18. A patient admitted with BP 300/130 mmHg. Crisis with fear, tachycardia, polydipsia. Blood glucose 20 mmol/L. Diagnosis?
a. Conn’s syndrome
b. Pheochromocytoma
c. Cushing’s syndrome
d. Arterial hypertension
e. Secondary hyperaldosteronism
19. A 25-year-old woman complains of excess weight, intermittent thirst. Height 160 cm, weight 70 kg, excess weight +29%. Fasting glucose 5.1 mmol/L. OGTT: fasting 5.5 mmol/L, 2h 7.0 mmol/L. Diagnosis?
a. Obesity grade I
b. Obesity grade II
c. Overweight
d. Type 2 diabetes mellitus
e. Impaired glucose tolerance
20. WHO/ISH (1999) classification: grade II hypertension corresponds to:
a. 140/90-159/99 mmHg
b. 150/90-159/94 mmHg
c. 160/100-179/109 mmHg
d. 135/90-170/100 mmHg
e. 159/99-169/104 mmHg
21. A 47-year-old man hospitalized with headaches, tinnitus, dizziness. History: arterial hypertension, max BP 180/110 mmHg. Objectively: left heart border shifted, muffled heart sounds, II tone accent, BP 160/90 mmHg, tachycardia HR 100/min. ECG: LVH. Preliminary diagnosis?
a. Hypertension stage II, high risk
b. Hypertension stage III, very high risk
c. Hypertension stage III, high risk
d. Hypertension stage II, very high risk
e. Hypertension stage II, moderate risk
22. WHO/ISH (1999) hypertension classification is based on:
a. Hemodynamic vascular changes
b. Hypertensive crises with complications
c. BP level and target organ damage
d. Catecholamine secretion changes
e. Aldosterone secretion changes
23. A 44-year-old woman hospitalized with headaches, low back pain, frequent painful urination. BP 170/100 mmHg. Labs: leukocytosis, ↑ESR. Urine: mild proteinuria, leukocyturia, bacteriuria. Best antihypertensive for renoparenchymal hypertension?
a. Calcium antagonists
b. β-blockers
c. ACE inhibitors
d. Isosorbide dinitrate
e. α-blockers
24. A 57-year-old man hospitalized with headaches, tinnitus, dizziness. History: 5 years of hypertension. BP 160/90 mmHg, HR 100/min. ECG shows hypertension signs. Findings?
a. Right axis deviation, V1 R>S
b. P wave ↑ in II, III, aVF
c. P wave ↑ in I, II, aVL
d. Left axis deviation, tall R in I, aVL, V5-V6
e. ST depression in III, aVF, V1-2

25. A 47-year-old woman hospitalized with headaches, tinnitus, dizziness. History: 3 years HTN, 5 years diabetes. Max BP 170/100 mmHg. Objectively: left heart border shifted, muffled sounds, II tone accent, BP 150/90 mmHg, HR 100/min. ECG: LVH. Preliminary diagnosis?
a. Hypertension stage II, high risk
b. Hypertension stage III, very high risk
c. Hypertension stage III, high risk
d. Hypertension stage II, very high risk
e. Hypertension stage II, moderate risk
26. Most effective hypolipidemic drug for atherosclerosis lipid correction?
a. Nicotinic acid & derivatives
b. Statins
c. Bile acid sequestrants
d. Fibrates
e. Antioxidants
27. This drug raises HDL concentration:
a. Nicotinic acid
b. Fibrates
c. Statins
d. Bile acids
e. β-blockers
28. Which hyperlipidemia types are statins indicated for (lovastatin, fluvastatin, pravastatin)?
a. III
b. II A & B
c. IV
d. V
e. Hypo-α-cholesterolemia
29. This drug raises HDL concentration:
a. Nicotinic acid
b. Fibrates
c. Statins
d. Bile acids
e. β-blockers
30. WHO/ISH (1999): grade I hypertension corresponds to:
a. 140/90-159/99 mmHg
b. 150/90-159/94 mmHg
c. 160/95-179/104 mmHg
d. 135/90-170/100 mmHg
e. 159/99-169/104 mmHg
31. A 68-year-old woman with CAD. Dispensary exam: cholesterol 7.8 mmol/L. Most effective hypolipidemic drug for lipid correction in atherosclerosis?
a. Cardiket
b. Nifedipine
c. Aldactone
d. Fosinopril
e. Simvastatin
32. A 60-year-old man at preventive exam: persistent systolic hypertension, morning occipital headache, palpitations, systolic epigastricmurmur. Preliminary diagnosis?
a. Aortic coarctation
b. Renal artery aneurysm
c. Abdominal atherosclerosis
d. Renal artery hypoplasia
e. Aortic hypoplasia
33. A 63-year-old woman complains of chest pain with exertion (walking >500 m), relieved by nitroglycerin. History: arterial hypertension. Preliminary diagnosis?
a. Cardiomyopathy
b. Rheumatic carditis
c. Endocarditis
d. Angina pectoris
e. Myocarditis

Situational Task 1
Patient M., 46 years old, was admitted to the hospital on referral from a district outpatient primary-care physician. He complains of headaches, “floaters” before the eyes, persistent thirst, frequent urination, low back pain that worsens with movement, and marked weakness. From the history: over the past six months he has noticed changes in appearance-his face has become rounded, the extremities have become thinner, the abdomen has increased in volume; he is troubled by dry skin and hair loss on the scalp. He consulted a neurologist because of low back pain. Lately he has noted increases in blood pressure up to 220/110 mmHg and is taking enalapril 5 mg twice daily. Objectively: condition satisfactory; height 161 cm; weight 95 kg; BMI = 36.7 kg/m2. The patient appears significantly older than his years; there is redistribution of subcutaneous fat, with excessive deposition at the level of the seventh cervical vertebra, in the supraclavicular areas, on the chest and abdomen. The skin is dry, “mottled/marbled,” thinned. On the abdomen there are wide purple-red striae. In the lungs, vesicular breath sounds are heard; no rales. Respiratory rate 17 per minute. The cardiac borders are displaced to the

left. Heart sounds are muffled and regular. Heart rate 88 per minute. Blood pressure 190/100 mmHg. The abdomen is soft, non-tender, enlarged due to subcutaneous adipose tissue. The liver and spleen are not enlarged. The kidneys are not palpable. Costovertebral angle tenderness is negative on both sides. On palpation the thyroid gland is not enlarged; it is elastic and non-tender; no nodular formations are palpable.
Results. Complete blood count: erythrocytes 5.3 × 109/L, hemoglobin 135 g/L, leukocytes 10.2 × 109/L, band neutrophils 10%, segmented neutrophils 73%, lymphocytes 12%, monocytes 4%, eosinophils 1%, ESR 3 mm/h. Blood biochemistry: glucose 11.2 mmol/L, K+ 3.1 mmol/L, Na+ 140 mmol/L, cholesterol 5.7 mmol/L, Ca 3.6 mmol/L, ALT 34 U, AST 33 U, total protein 67 g/L. Urinalysis: reaction alkaline, specific gravity 1.025, glucose ++, protein 0.03, leukocytes 1-2 per HPF, epithelium 2-3 per field. ECG: sinus rhythm, heart rate 84 per minute. Horizontal electrical axis. Left ventricular hypertrophy. Dystrophic changes of the LV myocardium. Radiograph of the thoracic and lumbar spine: osteoporosis of the vertebral bones. Adrenal ultrasound: the right adrenal gland is markedly increased in volume.
Questions: 1) Suggest the most likely diagnosis.
2) Justify your diagnosis.
3) Formulate and justify a plan for additional evaluation of the patient.
4) Formulate and justify a treatment plan.
5) Assess the prognosis for the patient and choose a follow-up strategy.
Situational Task 2
Patient N., 30 years old, presented to the polyclinic with complaints of general weakness, dry mouth, polyuria, visual deterioration, numbness and paresthesias in the lower extremities, and frequent hypoglycemic episodes (at night and during the day). He has had diabetes mellitus since the age of 15; the disease initially manifested with ketoacidosis. Current therapy: Humulin NPH-20 units in the morning and 18 units in the evening-and Humulin Regular-18 units per day. He leads an active lifestyle and is trained in self-monitoring techniques. Objectively: general condition satisfactory. Male body habitus and pattern of hair distribution. BMI 19 kg/m2. Skin is dry and clear. Angular fissures (angular cheilitis) at the corners of the mouth. No peripheral edema. Thyroid gland not enlarged. Lungs: vesicular breath sounds, no rales. Heart: tones rhythmic; pulse 82 beats per minute. Blood pressure 120/80 mmHg. Abdomen soft, non-tender. Liver and spleen not enlarged. Skin of the shins and feet is dry; areas of hyperkeratosis on the feet; dorsalis pedis arterial pulsation is adequate.
Results: fasting plasma glucose 10.4 mmol/L; 2 hours after a meal 14.5 mmol/L. Urinalysis: specific gravity 1.014; protein-traces; leukocytes 1-2 per high-power field. Ophthalmologist: fundus shows single microaneurysms, hard exudates, and macular edema. Podiatrist: decreased vibratory and tactile sensation.
Questions: 1) Formulate the preliminary diagnosis.
2) Justify your diagnosis.
3) Develop and justify a plan for additional evaluation.
4) State and justify the target glycated hemoglobin (HbA1c) level for this patient.
5) Propose and justify adjustments to glucose-lowering therapy.
Situational Task 3
Patient V., 45 years old, was admitted to the hospital on referral from a district primary-care physician. She complains of headaches, “floaters” before the eyes, persistent thirst, frequent urination, low back pain, profound weakness, and changes in appearance. From the history: over the last 5 years, after cessation of menses, her appearance has changed markedly-facial redness and rounding, thinning of the extremities, increased abdominal girth; the skin has become dry; scalp hair has thinned; a moustache has appeared. She was followed by a neurologist for 3 years because of low back pain, which was interpreted as osteochondrosis. For 2 years she has been followed by a primary-care physician for arterial hypertension (maximum BP 170/100 mmHg). Objectively: height 175 cm, weight 110 kg, BMI 35.9 kg/m2. The patient appears significantly older than her years; there is redistribution of subcutaneous fat with excessive deposition at the level of the seventh cervical vertebra, in the supraclavicular areas, on the chest and abdomen. The skin is dry, “mottled/marbled,” thinned, with numerous hemorrhages; hyperpigmentation is present on the elbows, abdomen, and in the axillae. On the thighs there are wide purple-red striae. Lungs: vesicular breath sounds, no rales. Respiratory rate 17 per minute. The cardiac borders are displaced to the left. Heart sounds are muffled and regular. Heart rate 92 per minute. Blood pressure 190/100 mmHg. The abdomen is soft, non-tender, enlarged due to subcutaneous adipose tissue. The liver is at the costal margin, non-tender.
Laboratory studies. Complete blood count: erythrocytes 5.3 × 10ą2/L, hemoglobin 135 g/L, leukocytes 10.2 × 109/L, band neutrophils 10%, segmented neutrophils 76%, lymphocytes 12%, monocytes 2%, eosinophils 0%, ESR 3 mm/h. Blood biochemistry: glucose 7.7 mmol/L, K+ 2.5 mmol/L, Na+ 170 mmol/L, cholesterol 5.7 mmol/L, Ca 3.6 mmol/L, ALT 34 U, AST 42 U, total protein 57 g/L. Urinalysis: reaction alkaline, specific gravity 1.025, glucose ++, protein 0.25 g/L, leukocytes ++. ECG: sinus rhythm, heart rate 84 per minute. Horizontal electrical axis. Left ventricular hypertrophy. Dystrophic changes of the LV myocardium. Radiographic examination of the skull and spine revealed marked osteoporosis of the dorsum sellae and of the vertebral bones. MRI shows diffuse enlargement of both adrenal glands.
Questions: 1) Suggest the most likely diagnosis.
2) Justify your diagnosis.
3) Formulate and justify a plan for additional evaluation.
4) Formulate and justify a treatment plan.
5) Assess the prognosis for the patient and choose a follow-up strategy.
Situational Task 4
At a district primary-care physician’s appointment, a 48-year-old male patient. Type 2 diabetes mellitus was detected incidentally during a routine medical check-up one week ago. He is not receiving any pharmacological therapy. From the history: no myocardial infarction, no stroke. He presented to the primary-care physician for treatment initiation.
On examination: height - 170 cm, weight - 106 kg. Body mass index (BMI) - 37.5 kg/m2. Waist circumference - 120 cm. Skin moderately moist, subcutaneous fat deposition predominantly in the abdominal area. Lungs: vesicular breath sounds. Pulse - 76 beats per minute. Heart sounds rhythmic, muffled. Blood pressure - 160/90 mmHg. Liver not enlarged. No edema.
Self-monitoring glucometer results: fasting glucose - 7.8 mmol/L, 2 hours postprandial glucose - 10 mmol/L. HbA1c - 7.5%.
Blood biochemistry: total protein - 75 g/L, albumin - 46 g/L, total bilirubin - 13.1 μmol/L, creatinine - 80 μmol/L, ALT - 65 U, AST - 53 U. Glomerular filtration rate (GFR) - 91 mL/min.
Questions:
1. Formulate the main clinical diagnosis of diabetes mellitus according to current standards.
2. Justify the choice of the individual target glycated hemoglobin level in this patient. Determine the target glycemic parameters for this patient.

3. Define the scope of additional examinations according to the standard of medical care for type 2 diabetes mellitus.
4. Determine the treatment strategy for this patient.
5. Define the glycemic control indicators that should be used to evaluate the effectiveness of antihyperglycemic therapy during follow-up.

Situational Task 5

Patient M., 44 years old, presented at the district primary-care physician's appointment complaining of rapid fatigability, memory decline, drowsiness, chilliness, constipation, weight gain, hearing loss, and hoarseness of voice. From the history, these complaints appeared 6 years ago without obvious cause and developed gradually. During this time, his weight increased from 76 to 118 kg.

Past history includes recurrent tonsillitis.

On examination: general condition satisfactory, height - 165 cm. Skin clean, dry, especially on the elbows, cold to the touch. Face puffy and pale. Hands edematous. Dense edema on the lower extremities. Distribution of subcutaneous fat is uniform. The thyroid isthmus and both lobes palpable, right lobe larger; the gland is firm, painless. Lung auscultation: vesicular breath sounds, no rales. Respiratory rate - 16 per minute. Borders of relative cardiac dullness: left - 1.5 cm lateral to the midclavicular line; right - 1.5 cm lateral to the right sternal border. Heart sounds markedly weakened. Pulse - 53 per minute, rhythmic. Blood pressure - 90/70 mmHg. Tongue moist, with teeth marks. Abdomen enlarged due to fat and bloating. Palpation painless. Liver not enlarged. Stool regular.

Laboratory findings: TSH - 14 mIU/L (normal 0.4-4 mIU/L), free T4 - 5.6 pmol/L (normal 10-25 pmol/L), anti-TPO - 364 IU/mL (normal ≤30 IU/mL). Complete blood count: erythrocytes - 3.5×10ą2/L, leukocytes - 5.8×109/L, hemoglobin - 96 g/L. Blood cholesterol - 8.8 mmol/L. Urinalysis normal. Electrocardiography: low-voltage QRS, bradycardia, flattened T wave.

Questions:

1. Suggest the most likely diagnosis.
2. Justify your diagnosis.
3. Develop and justify a diagnostic plan required to confirm the diagnosis.
4. Prescribe treatment according to medical care standards.
5. After 3 months of pathogenetic therapy, TSH is 7.2 mIU/L. What is your further management strategy

Situational Task 6

Mr. A., 48 years old, a mechanic, presented to the district primary-care physician with complaints of diffuse headaches. Arterial hypertension was identified: blood pressure seated-150/95 mmHg; supine-165/100 mmHg. Fundus examination revealed arterial narrowing, dilation and tortuosity of venules, arteriovenous crossings (Salus-Gunn II), microaneurysms, and isolated punctate peripheral hemorrhages. Fasting blood glucose-10.1 mmol/L; random glucose during the day-15.0 mmol/L. From the history: headaches have troubled him for about a year; he has not undergone evaluation.

Objectively: general condition satisfactory. Skin is normal in color and clean. No edema or striae. Mucous membranes clean. Waist circumference-103 cm, hip circumference-88 cm, weight-107 kg, height-172 cm. Resting respiratory rate-18 per minute. On percussion of the lungs: clear pulmonary percussion note. On auscultation: vesicular breath sounds over all lung fields. Blood pressure-175/90 mmHg; heart rate-100 per minute. The left cardiac border is displaced 1 cm to the left; the upper and right borders are normal. Heart tones rhythmic, muffled. Tongue coated with a white film, moist. The abdomen is enlarged due to the adipose layer. The liver protrudes 3 cm below the costal margin; the edge is rounded. Costovertebral angle tenderness is negative on both sides. Urination is not frequent and is painless. Bowel movements occur daily. Diuresis has not been measured. On examination of the lower extremities: skin of usual color and moisture, clean. Temperature sensation is absent on the feet and in the distal third of the lower legs; tactile and pain sensations are preserved.

Abdominal ultrasound was performed: no free fluid. Liver: right lobe-183 mm (reference 130-150), left lobe-90 mm (reference 50-60); contours smooth; structure diffusely heterogeneous, with increased echogenicity. Intrahepatic bile ducts are not dilated. Gallbladder of normal shape, 68 × 28 mm; wall-2 mm; content anechoic. Common bile duct-6 mm (reference 4-6 mm). Pancreas of normal size, smooth, well-defined contours; structure diffusely heterogeneous, with increased echogenicity. Spleen-48 cm2 (up to 50), unchanged.

Questions: 1) Suggest the most likely diagnosis.
2) Justify your diagnosis.
3) Develop and justify a plan for additional evaluation.
4) Develop and justify a treatment plan.
5) Assess the prognosis for the patient and choose a follow-up strategy

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Glossary

Term	Decoding	Role in the Pathogenesis of MS
AMP	Adenosine monophosphate	Stimulator of energy status reduction, activates AMPK.
AMPK	5'-Adenosine monophosphate-activated protein kinase	'Energy sensor', stimulates catabolism and increases insulin sensitivity.
Acetyl-CoA	Acetyl-Coenzyme A	Key metabolite, participates in the Krebs cycle and fatty acid synthesis.
ATP	Adenosine triphosphate	Universal cellular energy molecule.
DAMP	Damage-associated molecular patterns	Trigger inflammatory responses via TLR.
eNOS	Endothelial nitric oxide synthase	Synthesizes NO; decreased activity causes endothelial dysfunction.
FXR	Farnesoid X receptor	Regulates bile acid, lipid, and glucose metabolism.
GLUT4	Glucose transporter type 4	Ensures glucose transport into muscles and adipose tissue under insulin action.
GLP-1	Glucagon-like peptide-1	Incretin hormone; stimulates insulin secretion, lowers appetite.
HbA1c	Glycated hemoglobin	Reflects average glucose levels over 2-3 months; marker for diabetes control.
IAPP	Islet amyloid polypeptide	Forms amyloid deposits in the pancreas, damaging β-cells.
IL-1β	Interleukin-1 beta	Pro-inflammatory cytokine, activates lymphocytes and damages β-cells.
IL-6	Interleukin-6	Involved in chronic inflammation; its dysregulation may play a role in MS.
IL-18	Interleukin-18	Enhances inflammation, associated with progression of IR.
SGLT2 inhibitors	Sodium-glucose transporter 2 inhibitors	Glucose-lowering drugs, excrete glucose via urine.
IRS-1	Insulin receptor substrate-1	Key protein in insulin signaling; its dysfunction leads to IR.
MCP-1	Monocyte chemoattractant protein-1	Chemokine attracting monocytes; stimulates inflammation.
Mfn1/2	Mitochondrial fusion proteins (Mitofusin 1/2)	Regulate mitochondrial fusion; deficiency causes dysfunction.
NADH	Nicotinamide adenine dinucleotide (reduced form)	Electron carrier, essential for oxidative phosphorylation and ATP synthesis.
NF-κB	Nuclear factor kappa B	Transcription factor, regulates expression of inflammatory genes.
NLRP3 inflammasome	NOD-like receptor protein 3 inflammasome	Protein complex; activates caspase-1, IL-1β, IL-18.
PI3K/Akt pathway	Phosphoinositide 3-kinase/Akt signaling pathway	Key insulin signaling pathway; regulates glucose uptake.
RBP-4	Retinol-binding protein 4	Adipokine associated with insulin resistance.
ROS	Reactive oxygen species	Cause oxidative stress and cell damage.
TGR5	G-protein bile acid receptor 1	Bile acid receptor, regulates energy metabolism and GLP-1 secretion.

TLR	Toll-like receptors	Innate immunity receptors, activate inflammation.
TNF-α	Tumor necrosis factor-alpha	Key pro-inflammatory cytokine, increases IR.
Treg cells	Regulatory T-lymphocytes	Control inflammation, maintain immune tolerance.
11β-HSD1	11β-hydroxysteroid dehydrogenase type 1	Activates cortisol in tissues, enhances IR and obesity effects.