Metabolic Syndrome –
Modern Overview of the Problem

During the last century the object of discussion between scholars has been the problem of integrated pathology. Published proceedings about this question between 1990–2000 were seldom, and from 2001 until 2010 their amount reached the point of 39 [22]. A condition which is characterized by the presence of several diseases is marked by an appellation “integrated” in academic literature, “multisystemic” or “combined” pathology, “coexisted” or “associated” diseases and conditions [2–4]. Appellations “comorbidity” – for marking simultaneous affection of two organs, body systems or presence of two diseases; and “multimorbidity” – for marking more than 3 diseases at a time, are used more often in literature sources from English-speaking countries [20, 21].

Nowadays the problem of average increasing proportion of the total incidence of humanity with inveterate non-communicable diseases is being actively discussed. Metabolic syndrome (MS) is one of these problems that can cause many diseases and has already reached proportions of non-communicable epidemic, “epidemic of the 21st century.” Around one fourth of population in well developed countries appears to have MS [43]. We can definitely call it “civilization disease”. A huge part in its progression is made by urbanization, life style changes that lead to the lack of exercise, high-calorie food consumption and stress increasing. These factors continue constant increasing of arterial hypertension (AH), dislipidemia, adiposis and diabetes mellitus [1]. Patients with MS have 1.5–3 times higher risk of coronary heart disease (CHD) and apoplectic attack [5]. The average percentage of MS symptoms appear, such as disorders of cholesterol metabolism, glucose and high blood pressure, in the patients over 60 years old is 42–43.5 %.

The death rate of CHD among these patients is 40% higher, of AH – 2.5–3 times higher, of type 2 diabetes – 4 times higher than among general population. Framingham Heart Study during which 5 thousand people from 18 to 74 years old had been carefully examined, gave a chance to identify – the combination of 3 or more components of MS leads to higher risk of CHD by 2.4 times more for males and 5.9 times more for females [6]. Core components of MS like abdominal obesity, hyperlipemia, insulin resistance (IR) are interdependent from the condition of the digestive system [14, 11, 16, 40]. Patients with MS have lower life quality than healthy men, that can be observed on the lower rate of physical and mental activity among both males and females by 1.5–2 times [7]. The survey which took place in Italy found out that the huge part of children (6–14 years old) has a risk factor for cardiometabolic
disorders which is connected with insulin resistance, endothelial damage and non-alcoholic fatty liver disease (NAFLD) usually connected with MS [8]. Women with MS are more likely to have amplifications during their pregnancy (eclampsia, preeclampsia, gestational diabetes, coma) [9]. MS has a negative influence on cardiovascular risk, this connection can be tracked with cardiovascular pathology, atherosclerosis and type 2 diabetes [10]. There are lots of articles about MS comorbidity and sleep apnea syndrome [13], atopy and MS [15], MS and chronic kidney disease (CKD) in modern academic literature [17]. These combinations weight down the course of disease and require more detailed examination, recommendation list elaboration for early detection, treatment and diagnostics of combined pathologies.

The term “metabolic syndrome” is used to call a complex of the diseases and pathology conditions the core of which is clinical and metabolic disorders conditioned by decrease in tissue sensitivity to insulin. That means that MS is determined by the complex of interconnected factors that increase CHD and other cardiovascular diseases and type 2 diabetes level risk [18]. According to the International Diabetes Federation’s definition components of MS are adiposity, insulin resistance, hyperglycemia, dyslipidemia, AH, as well as, breach of hemostasis and markers’ presence of chronic subclinical inflammation [19, 23]. ICD–10 doesn’t include such a disease as “metabolic syndrome”, although it was acknowledged as a separate disease with ID number and code – ICD–9–CM, 277.7 – in the USA.

History of MS goes back to 1920 when Kylin demonstrated the connection between high blood pressure, glucose blood level and podagra. Later, in 1947 Vague described 2 types of adipopexia: hadron and hyoid, he also mentioned the connection between hadron type of adipopexia and type 2 diabetes, CHD, and podagra. After that, in 1965 Avogaro and Crepaldi described a syndrome which consisted of hypertension, hyperglycemia, and adiposity. In 1968 H. Mehnert and H. Kuhlmann mentioned the interconnection between factors that lead to metabolic disorders in the setting of AH and diabetes, and introduced the concept of “abundance syndrome”. M. Henefeld and W. Leonhardt started naming the syndrome as “ metabolic syndrome ” only after 1980. Later, some scholars mentioned the connection between the course of AH, hyperlipidemia, insulin resistance, and adiposity. Reaven found out “a cluster of risk factors for diabetes and cardiovascular disease” and named them as “syndrome X” in 1988. Kaplan changed the last one for the term “deadly quartet” which included central obesity, impaired glucose tolerance, hypertriglyceridemia, and hypertension in 1989. Haffner renamed it for “IP syndrome” in 1992. Different groups and associations of scholars were trying to elaborate diagnostic criteria for MS. The first attempt was made by the World Health Organization (WHO) in 1998. Later on, the American Association of Clinical Endocrinologists (AACE) suggested some criteria as to the syndrome recognition in 2003. MS includes hyperinsulinemia, hypertension, type 2 diabetes and/or decrease of glucose tolerance [27–29, 32]. According to the records of the Ukrainian Association of Cardiology and Ukrainian Association of Endocrinologists MS is a cluster of 4 cardiometabolic risk factors: 1) adiposity; 2) dyslipidemia; 3) AH; 4) impaired glucose tolerance or diabetes.

In accordance to guidelines for diagnostic and treatment of diabetes, prediabetes and cardiovascular disease made by the European Society of Cardiology (ESC) together with the European Association for the Study of Diabetes (EASD) in 2007, there are 3 variants to identify MS.
**Diagnostic criteria of the MS**

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<td>IR</td>
<td>IGT, IFG, T2DM, or lowered insulin Sensitivity¹ plus any 2 of the following</td>
<td>None, but any 3 of the following 5 features</td>
<td>None</td>
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<tr>
<td>Body weight</td>
<td>Men: waist-to-hip ratio &gt;0.90; women: waist-to-hip ratio &gt;0.85 and/or BMI &gt;30 kg/m²</td>
<td>WC ≥102 cm in men or ≥88 cm in women</td>
<td>Increased WC (population specific) plus any 2 of the following</td>
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<td>Lipids</td>
<td>TGs ≥150 mg/dL and/or HDL-C &lt;35 mg/dL in men or &lt;39 mg/dL in women</td>
<td>TGs ≥150 mg/dL HDL-C &lt;40 mg/dL in men or &lt;50 mg/dL in women</td>
<td>TGs ≥150 mg/dL or on TGs Rx. HDL-C &lt;40 mg/dL in men or &lt;50 mg/dL in women or on HDL-C Rx</td>
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<tr>
<td>Blood pressure</td>
<td>≥140/90 mmHg</td>
<td>≥130/85 mmHg</td>
<td>≥130 mmHg systolic or ≥85 mmHg diastolic or on hypertension Rx</td>
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<tr>
<td>Glucose</td>
<td>IGT, IFG, or T2DM</td>
<td>&gt;110 mg/dL (includes diabetes)</td>
<td>≥100 mg/dL (includes diabetes)²</td>
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<tr>
<td>Other</td>
<td>Microalbuminuria: Urinary excretion rate of &gt;20 mg/min or albumin: creatinine ratio of ≥30 mg/g.</td>
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<td>Other features of insulin resistance³</td>
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¹Insulin sensitivity measured under hyperinsulinemic euglycemic conditions, glucose uptake below lowest quartile for background population under investigation.

²In 2003, the American Diabetes Association (ADA) changed the criteria for IFG tolerance from >110 mg/dl to >100 mg/dl [10]

³Includes family history of type 2 diabetes mellitus, polycystic ovary syndrome, sedentary lifestyle, advancing age, and ethnic groups susceptible to type 2 diabetes mellitus. BMI: body mass index; HDL-C: High-density lipoprotein cholesterol; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; Rx: receiving treatment; TGs: triglycerides; T2DM: type 2 diabetes mellitus; WC: waist circumference.

Metabolic syndrome is one of the most important problems in public health worldwide [31]. MS expansion varies from 10 % to 84 % and increases with age (10 % among females of 20–29 years old, 20 % in age group from 40 to 49, and 45 % for 60–69 years old) in different countries of the world. There are gender specifications as well; according to the criteria NCEP–ATP III, the expansion among males vary around 8–43 % and 7–56% for females [34]. MS appears to be in 38,5 % of adult population in the USA [30]. According to the information provided by the American Diabetes Association (ADA), there are around 70–80 million people with MS in the USA [33]. In France this syndrome is diagnosed in 21,1 % of population [43], and 27,8 % of Spanish population [25]. Separate criteria of MS that most often appear (according to ATP III definition): high blood pressure (in 85,4 % of examined patients with MS), plasma triglycerides increasing (75,0 %), fasting glucose (70,4 %) (Sael et al, 2006). According to the results of Czech epidemiological study leaded between the population at the age of 25–64 MS appeared to have...
25% of females and 32% of males, older age groups have even higher percentage of spreading [24].

MS is also considered a condition of chronic inflammation.

Pathogenesis of MS [34]:

FFA: free fatty acid, ATII: angiotensin II, PAI-1: plasminogen activator inhibitor-1, RAAS: rennin angiotensin aldosterone system, SNS: sympathetic nervous system.

MS is a chronic disease, which is specified by systematic symptoms. An influence on target organs is conducted with the help of complicated biochemical reactions. While starting waterfall actions this symptom leads to irreversible changes and amplifications that, as a result, increase the risk of mortality.

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<th>Target organs</th>
<th>Systemic effects</th>
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<td>Renal</td>
<td>Microalbuminuria, hypofiltration, hyperfiltration, glomerulomegaly, focal segmental glomerulosclerosis, and chronic kidney disease.</td>
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<tr>
<td>Hepatic</td>
<td>Increased serum transaminase, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), hepatic fibrosis, and cirrhosis</td>
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Clinical identification of patients with MS is a reasonable action as almost all the components can be modified with medicamental and non-medicamental measures of correction. Preventive approaches should include life style changes and treatment – usage of medical drugs for those whose risk factors are not decreasing with the help of preventive methods and life style changes. The treatment is based on solving 5 tasks: body weight stabilization, increasing of physical activity, antihypertensive therapy, lipid-lowering therapy; the usage of antiplatelet agents (acetylsalicylic acid) [1]. Unfortunately, according to statistics Ukrainian population does not pay enough attention to their diet: 10 % of population does not know their body weight; 34 % measure their body weight once a year or rarer; around 25 % eat 1–2 times a day; only 4 % eat 4 times a day; 61.2 % of people have their last meal 1–2 hours before sleep. Only 36 % of population are on a healthy diet. Around 10 % of children in Ukraine have overweight [35]. Most of the Ukrainians consider overweight and adiposity to be only an aesthetic problem, and sedentary lifestyle – usual and non harmful, this makes preventive measures almost inadaptable. Drug therapy is an alternative for these patients is that should be used in all cases of low level preventive measures and life style changes success [36]. As the core of MS is insulin resistance the treatment should be based on this statement [38]. Metformin from biguanide group is the most effective drug in pharmacotherapy for insulin resistance. It is prescribed for the type 2 diabetes treatment but it is also proved to prevent type 2 diabetes in people with overweight and impaired glucose tolerance. Its hypoglycemic effect lies in the inhibition of gluconeogenesis in the liver. Besides that, the medication effects on utilization of glucose peripheral tissues [39]. In British prospective investigation overall mortality between people who were taking metformin was 36 % lower and the risk of myocardial infarction – 39% lower [41]. Metformin reduces the risk of type 2 diabetes by 31 % while comparing to the patients who got non-medical treatment. DPP (Diabetes Prevention Program, 2002) survey claims that metformin therapy at a dose of 850 mg two times a day can prevent type 2 diabetes effectively and safely for the patients with PDB by 31 % especially for those who have a body mass index over 25 kg/mІ and with a high risk of type 2 diabetes [42]. The patients who were taking this drug got less body weight than those who were treated with other intermediaries of hypoglycemic. Metformin is the drug that in its ability to maintain normal glucose level is not inferior to other drugs. It should be noted that metformin has an effect on reducing the risk of cardiovascular complications by influencing insulin resistance. The evidence of this is lowering TG level, low-density lipoprotein (LDL), free fatty acids in plasma and plasma glucose after meal. It is reasonable to believe that treatment with metformin of type 2 diabetes and conditions associated with insulin resistance (adiposity, metabolic syndrome,
prediabetes (IGT)) leads to the formation of favorable pharmacological effects which together with lifestyle modifications are effective ways of IR and hyperglycemia correction. These help to influence positively on the quality and life expectancy of patients as well as the occurrence of life-threatening cardiovascular, micro- and macrovascular complications from type 2 diabetes [44].

The level of mortality because of cardiovascular amplifications between patients with metabolic syndrome is still high despite the presence of a great amount of information and results of medical research in this problem. This reveals about the necessity for further investigation about metabolic modifications and their influence on different homeostasis components; and searching for key answers for the questions that deal with early detection and prevention of metabolic syndrome in these patients [46]. Thus, we can make a conclusion, that with the increasing number of patients with overweight and adiposity it is very important in every day medical practice to detect the patients with MS and evaluate amplification. The rationale of this topic highlights the necessity for further study of pathogenetic and clinical features of MS for early diagnosis and prevention algorithm development and ways of rational treatment as these can have a positive influence on quality and lifetime.

The rationale of this article is very topical as there are many discussions about metformin. Now, it is approved for metabolic syndrome treatment but a great amount of search shows the necessity of metformin usage for the patients with impaired glucose tolerance [12]. It helps to slow down some risk factors of MS and waterfall reaction that can lead to different amplifications. Metformin is recommended as a first-line drug for patients with overweight and type 2 diabetes. Class of recommendation – IIa, level of evidence – B. Diabetes’ development impaired glucose tolerance can be postponed with the help of prescription for some of pharmacological drugs (metformin, acarbose and glitazones). Class of recommendation – 1, level of evidence – A [1]. Since many drugs have many side effects, metformin continues to be the only one for the patients with overweight and impaired glucose tolerance.

СПИСОК ЛІТЕРАТУРИ


7. Мітченко О.І. Лікування метаболічного синдрому, цукрового діабету, предіабету і серцево-судинних захворювань : рекомендації Асоціації кардіологів України та Асоціації ендокринологів України / О.І. Мітченко, В.В. Карпачов // Серцево-судинні захворювання : рекомендації з діагностики,
Метаболічний синдром: сучасний огляд проблеми

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Метаболічний синдром — один з найбільш складних питань медицини в XXI ст. Представлено сучасні дані діагностики та заходи з його корекції та профілактики. Ефективність успішного лікування хворих із МС прямо пропорційно зв'язана зі зміною способу життя, що має на меті зниження маси тіла. Хоча не у всіх немедикаментозне лікування дає позитивні зміни. Тоді препаратом вибору є метформін, завдяки якому купіруються основні прояви МС. Сьогодні немає єдиного визнаного методу лікування МС. Із огляду на це, розроблення нових методів лікування і нагляду, вибору оптимальних препаратів для лікування МС є актуальною проблемою медицини.

Ключові слова: метаболічний синдром, фактори ризику, діагностика, лікування, профілактика, метформін.