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# METABOLIC SYNDROME: REVIEW

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## Abstracts

The psychosomatic component of the metabolic syndrome, historical aspect of the problem under study, physiological and biochemical mechanisms of pathogenesis are considered in the article. The symptomatic components of the metabolic syndrome and their interrelation are outlined, the ways of diagnosis and therapy and directions of modern research in this field are outlined.

**Key words**: **metabolic syndrome; insulin resistance; hypertonic disease; abdominal obesity.**

## МЕТАБОЛІЧНИЙ СИНДРОМ: ОГЛЯД ПРОБЛЕМИ

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У статті розглянуто психосоматичну складову метаболічного синдрому, історичний аспект досліджуваної проблеми, обгрунтовано фізіологічний та біохімічний механізми патогенезу. Наведено симптоматичні складові метаболічного синдрому та взаємозв'язок між ними, окреслено шляхи діагностики та терапії, а також напрямки сучасних досліджень в даній галузі.

**Ключові слова: метаболічний синдром; інсулін резистентність; гіпертонічна хвороба; абдомінальне ожиріння.**

## МЕТАБОЛИЧЕСКИЙ СИНДРОМ: ОБЗОР ПРОБЛЕМЫ

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В статье рассмотрено психосоматическую составляющую метаболического синдрома, исторический аспект исследуемой проблемы, обоснованно физиологический и биохимический механизмы патогенеза. Приведены симптоматические составляющие метаболического синдрома и взаимосвязь между ними, намечены пути диагностики и терапии, а также направления современных исследований в данной отрасли.

**Ключевые слова: метаболический синдром; инсулинрезистентность; гипертоническая болезнь; абдоминальное ожирение.**

**Relevance.** Importance of combination of mental, somatic and social health of a person was defined by the World Health Organization (WHO) and proved by numerous results of scientific research. The principle of combination of somatic and mental health is essential for all medical specialties. Contemporary scientists pay special attention to psycho emotional aspects of somatic changes, as they are an important element of the notion “life quality”, reflecting affection of a disease on patient’s life expectancy, their living in a social environment, quality of life as well as the ways and methods of the disease treatment. The priority of WHO activity is increasing quality of life. Annually, a huge amount of money and

intellectual resources is spent on providing relevant treatment of diseases and its consequences. Modern developed society requires thorough research of the life quality issue. Among essential ways of life quality increasing are providing with psycho emotional health, support of stress resistance, qualitative and quantitative diet (ratio of basic biochemical food elements according to a person's individual physiological needs, influence of synthetic supplements, preservatives, carcinogens, adaptogens and antioxidants). Some researchers stress the influence of different somatic pathologies on life quality and psychological condition of patients. Metabolic Syndrome (MS), among psycho somatic disorders, caused by psychological traumas, aggression, fear and anxiety, attracts special attention of scientists nowadays [1].

According to the National Center for Health Statistics data, 35% of young and 45% of elderly people from the developed countries suffer from Metabolic Syndrome [2]. MS frequency and occurrence depend on ethnic and age criteria, chosen for identification, accumulation of risk factors, onto-genesis stage, level of genetic predisposition, condition of compensatory systems of an organism and environmental factors [3, 4]. MS is a severe disease, prior for contemporary medicine.

MS issue is especially urgent for Ukraine nowadays while conducting anti-terrorist military activity on the eastern territories: a stress-factor is a leading one for health condition of military men, members of their families and local population.

Psychic symptoms of MS are: constant tiredness, exhaustion, sudden outbreaks of severe hunger, emotional disorders (irritability, attacks of anger, rage and panic fear) [1]. Clinical symptoms of MS include cognitive disorders (hypomnesia and lowering of concentration), disorder of erectile function. Anxious-depressive and hypochondriac conditions are the most frequent [2, 5].

Biological basis for MS is decrease of tissue sensitivity to insulin, but the starting point is the increased activity of sympathoadrenal system [6, 7]. Causative factors of MS are: excessive psychological stress, lowering of physical activity, calorie food and deficiency of biologically active substances. Increase hostility and hidden forms of aggression play a vital role in developing MS [7, 37].

Occurrence of certain psychic and somatic features while MS formation is regarded as a particular before-pathological condition, caused by compensatory stresses of adaptive systems of an organism. The degree of adaptive psychosomatic stress of an individual as a cumulative negative dynamics of psycho-pathological phenomena may be taken as the basis

for MS diagnostics which allows prediction of diabetes mellitus type 2, hypertonic disease, coronary heart disease development [1].

**History.** Metabolic Syndrome was introduced into scientific terminology as trisyndrome metabolique by J.P. Camus in 1966 [4]. The name metabolic (polymetabolic) syndrome was introduced in 1967 by P. Avogaro et al., who found frequent combination of hyperlipidemia, diabetes and moderate obesity [2]. H. Mehnert and H. Kuhlmann gave it the name "Wealth Syndrome" in 1968 [4].

It was initially described as a complex of clinical symptoms in 1980 by M. Hanefeld and W. Leonhardt [8]. In 1981 M. Hanefeld and W. Leonhardt suggested the term "metabolic syndrome" to call cases of coincidence of different metabolic disorders [3]. In 1985 S. Eaton and M. Konnor suggested a hypothesis that increased number of the so-called diseases of civilization in the 2nd half of 20 centuries is caused by the fact that genes of people living now, adapted to continuous evolutionary process to nutritional behavior of ancestors, are not capable to provide with health under the conditions of a dramatic change of lifestyle during last 100 years [9]. Prof. G. Reaven, conducting Bantynhovska lecture, based on his own observation and having generalized his research, suggested a hypothesis, according to which resistance to insulin, abdominal obesity, arterial hypertension, atherogenic dyslipidemia and coronary heart disease are symptoms of pathological condition named "syndrome X".

MS has been defined several times and is also known as:

– deadly quartet (J. Kaplan, 1989), as a combination of diabetes mellitus, obesity, arterial hypertension and coronary heart disease [10];

– hormonal MS (P. Bjorntorp, 1991) and syndrome of resistance to insulin (S. Haffner, 1992), which outline the key role of decreased tissue sensitivity to insulin while pathologic progress and the role of increased activity of sympathoadrenaline system for its start;

– deadly sextet (G. Enzi, 1994) – apart from 5 basic features (diabetes mellitus, abdominal obesity, arterial hypertension, atherogenic dyslipidemia and coronary heart disease, it includes the complex of psycho somatic disorders;

– metabolic vascular syndrome (M. Hanefeld, 1997), arterial hypertension, being one of the first clinical symptoms of MS, atherosclerotic vascular affection is a necessary clinical symptom of MS.

The most often used terms are "metabolic syndrome" and "syndrome of resistance to insulin" [9].

**Pathogenesis of metabolic syndrome.** Present day metabolic syndrome is metabolic disorders which are interconnected pathogenetically [10].

A large number of factors, involved in MS occurrence, prevent scientists from defining its pathophysiological mechanisms. According to the data, based on pathogenesis of this pathology, the following disorders are defined:

– resistance to insulin (lowering of insulin dependent utilization of glucose with tissues.
– Hyperinsulinemia (compensatory mechanism).
– Glucose intolerance and hyperglycemia.
– Abdominal obesity.
– Hypertriglyceridemia.
– Low level of cholesterol and high density lipoprotein.
– Arterial hypertension and coronary heart disease.
– Microalbuminuria.
– Hyperuricemia.
– Lowering of fibrinolytic blood activity.
– Hyperleptinemia and resistance to leptin [10, 11].

So, MS is a complex of carbon and lipid metathesis disorders as well as blood pressure and endothelium functions disorders, conditioned by lowering of tissue sensitivity to insulin (resistance to insulin) [12].

MS is spread approximately 10-20% among people over 30 in industrially developed countries. Complex MS is usual for adult males whereas its frequency grows for females during the period of menopause [13].

Metabolic disorders occur at teenage and adolescence long before clinical symptoms of diabetes mellitus type 2, arterial hypertension and atherosclrotic vascular affection. All elements of MS do not occur simultaneously: phenotype of MS occurrence depend on the interaction of genetic and environmental factors [2].

MS acquired epidemic nature for ethnic groups in economically developed countries where people keep traditional lifestyle: autoimmune and allergic diseases, diabetes mellitus, obesity, kidney and gallstone diseases, arterial hypertension do not occur. New approach to etiopathogenesis of contemporary diseases changing from organ, tissue and cellular to sub-cellular and molecular levels. As the result of activity of various stress factors and agents (physical, chemical, biological, social, psychogenic and complex), which exceed compensatory capabilities of an organism, accelerated exhaustion of adaptive nutrients supply

(functional ingredients) occur [7]. Under progressing deficiency of macro and micro nutrients and their metabolites, there occur dis balance of activity of basic regulatory mechanisms of homeostasis support that leads to physiological, metabolic and behavioral disorders. In order to get rid of them, an organism mobilizes immune and neurohumoral systems of homeostasis saving. Increased synthesis and transportation of various transmitters, hormones, mediators of immune and proxidant antioxidant reactions into biological liquid redirect organism's supply to provision of the most important livelihoods systems. In case risk factors, stress sources have been removed, and additional nutrients are provided, an organism regenerated its livelihoods completely. Having no supply of functional endogenous ingredients, vital for the synthesis and relevant mediator's activity, as well as metabolic reactions, continuous deficiency of macro and micro nutrients in food and micro ecological dis balance of digestive tract, functional dis-adaptation of relevant functional systems provoke occurrence of irreversible process of pathological conditions and diseases. When negative factors, leading to MS occurrence are active, it leads to a complete exhaust of compensatory adaptive supply of an organism and basic clinical complications of MS (obesity, hyperglycemia, resistance to insulin, hyperinsulinemia, arterial hypertension, dyslipidemia, oxidant and inflammatory stresses and endothelopathy. In case of dis-balanced dieting and dysbiosis, functional disorders turn into stable metabolic, hemo-dynamic and organ damages (continuous increased activation of sympathetic nervous and hormonal systems, vegetative dis-balance; organic dysfunction of endothelium, constant lowering of synthesis of stress sensitive factors and increase of neuron-mediators formation, stable arterial hypertension, increased number of free lipid acids in blood serum, dyslipidemia with negative lipid profile, increase of proliferation of the cells of smooth muscles of blood vessels and heart which lead to the formation of atherosclerotic plaques etc.). As the result, certain diseases or their complex occur, associated with a variety of symptoms as well as complications leading to disabilities or death [14].

The most common elements of MS pathogenesis are resistance to insulin, coronary heart disease, hypertension and obesity, which are interrelated.

*Interrelation of resistance to insulin and coronary heart disease.* Based on the results of epidemiologic research, conducted on Paris, Helsinki and Buss Elton (Austria) [15], it was found out that people suffered from basal and postprandial hyperinsulinemia long before coronary heart disease occurrence and development. The fact proved hyperinsulinemia and coronary heart disease interrelation. 11 983 people were involved into 12 years' trial. Insulinemia as a cause of coronary heart disease was proved by numerous further clinical trials conducted among patients suffering from diabetes mellitus. The fact has been explained

by a specific influence of insulin and tissue resistance on synthesis and lipid transportation. Besides, insulin, called atherogenic hormone, can fasten atherosclerotic plaques formation on tissue level [14]. According to research data, insulin concentration in plasma influences basic components of atherosclerotic plaques: lipid, collagen, macrophages and proliferating vascular smooth muscles cells. There occur proliferation of cells, increase of synthesis of endogenous cholesterol and triglycerides. Stimulating impact of insulin on lipid synthesis is conditioned by its activity concerning lipogenic enzymes; glucose phosphate dehydrogenase and hydroxyacetylate dehydrogenase [8, 11, 16]. It is proved that insulin enhances collagen synthesis, one of basic elements of atherosclerotic damage. Stimulating proliferation and cells growth, insulin causes formation of other growth factors, such as insulin-like growth factor. Additionally, progressive atherosclerosis and coronary heart disease are caused by coagulogical disorders, particularly hyperfibrogenemia and increased activity of inhibitor of tissue activator plasminogen type 1 [17].

*Interrelation of resistance to insulin and hypertension.* According to clinical trial results, MS with obesity is closely connected with frequent arterial hypertension development, which is common among 10-15% of adults [18]. Clinical trials data prove direct dependence of arterial hypertension and MS levels. Insulin provides with various effects, capable to increase arterial hypertension, in case of stable and long lasting hyperinsulinemia [14]. Slightly increased level of insulin in blood leads to lowering of renal excretion of sodium and water and increasing of arterial hypertension. Hyperinsulinemia provokes disorders of transmembrane ion transportation which causes increasing of intracellular concentration of sodium and calcium. Increasing of insulin level in blood leads to activation of sympathetic nervous system, increases production of catecholamine's which condition synthesis suppression and glucose accumulation in liver, lowers glucose absorption my muscle tissue [12, 15]. Under MS conditions, arterial hypertension may be increased by stimulation of vascular wall of smooth muscles hypertrophy which totally leads to general peripheral vascular resistance.

So, mechanisms of arterial hypertension are:

1) activation of sympathoadrenal systems;

2) increase of renal re-absorbtion of Na and water (especially in case of obesity and diabetes mellitus);

3) stimulation of cell growth factors (myocardium, vascular wall);

4) transmembrane ion exchange mechanisms disorders (Na+/H+; Na+/K+-ATPhase; Ca2+ - ATPhase transmembrane pumps) [19].

*Interrelation of resistance to insulin and obesity.* Clinical trials data prove decrease of insulin receptors in case of obesity, which leads to resistance to insulin and hyperinsulinemia, a lipotropic agent. These factors enhance accumulation of lipid tissue especially in upper part of the trunk and abdomen [11, 20]. MS is also frequently developed because of abdominal obesity. Free lipid acids travel through vena porta to a liver and then into the system of blood circulation. In the liver they activate processes of gluconeogenesis which leads to the increased production of glucose by the liver and development of hyperglycemia on an empty stomach. Having being transported into the system of blood circulation, free lipid acids provoke disorders of insulin receptors functioning and increase resistance to insulin (lipotoxic effect) [21].

Extra free lipid acids, substrates of triglycerides synthesis, cause increased production of lipoproteins of a very low density. The level of lipoproteins of high density decreases. Moreover, structure of lipoproteins of low density change by producing lots of small lipoproteins of low density with a high level of atherogenicity. So, hyperinsulinemia: a). supports appetite; b). lowers lipolysis level; c). increases lipoproteins of low density production; d). decreases lipoproteins of high density synthesis [19].

**MS Diagnostics.** Examination of patients before clinical symptoms occurrence include:

- identification of hereditary factors of obesity, diabetes mellitus, coronary heart disease and arterial hypertension;
- social anamnesis (lifestyle, dieting);
- anthropometric measurements (height, weight, index of body weight, waist circumference, hip circumference);
- blood pressure monitoring;
- electrocardiogramma;
- identification of biochemical data: triglycerides levels, general cholesterol level, cholesterol level of lipoproteins of high density, cholesterol level of lipoproteins of low density, apoliproprotein B in plasma;
- identification of glucose in blood on an empty stomach, insulin in blood on an empty stomach, according to the symptoms – glucose tolerance test.

The most accurate indicators, which may be used during the exmination:

- waist circumference as a marker of abdominal visceral obesity;
- triglycerides level as an indicator correlating occurrence of small parts of lipoproteins of low density;

- level of atherogenic lipoproteins indicator level ( if not available – atherogenesis calculation (correlation of cholesterol level of lipoproteins of high density and cholesterol level of lipoproteins of low density));
- insulin level on an empty stomach as resistance to insulin indicator [22];

In case late MS symptoms, like glucose tolerance disorders or diabetes mellitus type 2, MS is diagnosed according to presence of three out of the following MS features:

- waist circumference/hip circumference for males - more than 0,9; for females – more than 0,85;
- blood pressure – more than 160/90 mm;
- triglycerides level – more than 1,7 m/l;
- microalbuminuria – more the 20 mg per day;
- cholesterol level of lipoproteins of high density for males – more than 0,9 m/l and for females – more than 1,0 m/l [23].

**MS Therapy.** While treating MS patients, special attention should be paid to the possible influence on tissue resistance on insulin and hyperinsulinemia as well as general mechanisms for the pathology. It has been proved theoretically that improvement of tissue sensitivity to insulin and lowering of chronic hyperinsulinemia, at least for patients without arterial hypertension symptoms, atherosclerosis or diabetes mellitus, can influence positive on metabolic disorders. The issue has been discussed at various special forums: on resistance to insulin (Hamburg, 1992) (Insulin sensitivity: cardioprotection vs. metabolic disorders, 1992), Symposium at 6$^{th}$ European conference on hypertension (Milan, 1993). The conclusions are (Parathyroid Hypertensive Factor: A New Circulating Substance in Essential Hypertension, 1994):

1. Modern scientists define MS as a complex of disorders which lead to the development and progress of essential hypertension, coronary heart disease and diabetes mellitus.
2. Patients resistant to insulin, regardless of clinical symptoms, should take preventive measures or treatment.
3. Taking into account the necessity of using antihypertensive, antianginal and other cardiovascular medicined for patient's resistant to insulin, the ones which improve sensitivity to insulin and carbon tolerance are preferable [8, 20].

Polisyndromy of MS requires complex therapy treatment consisting of:

1). Measures aiming at loosing extra weight:

- low calorie diet;

- increase of physical activity;
- taking medicine for loosing extra body weight and incresing sensitivity of tissues to insulin.

2). Therapy of basic MS symptoms:

- antihypertensive drugs;
- hypolipidemic drugs
- oral hypoglycemic drugs in case of diabetes mellitus type 2 [24].

Metformin is a well-known agent, influencing several chains of MS [6].

One of effective ways of decreasing inflammatory process and resistance to insulin is including dietary supplements rich in polyphenols (bioflavonoids), such as grapes [25-27]. Bioflavonoids are low molecular weight compounds, providing with antioxidant effects. Their chemical structure helps to lower oxidative stress using a couple of mechanisms. Bioflavonoids regenerate a large amount of simple phenolic acids, capable to suppress the activity of free radicals and strengthen the effects of other antioxidants. According to numerous researches, bioflavonoids of grapes in forms of different extracts, suppress oxidative stress very effectively [28-30].

Polyphenols decrease chronic inflammatory process by the modification of inflammation and lowering of free radical's levels by using certain mechanisms. The first one includes using of antioxidant polyphenols, genes and proteins [31, 32]. The second aims at lowering the intensity of stress signals of endoplasmatic reticulum. Polyphenols are capable to block inflammatory cytokines, endotoxin-mediated kinases and transcriptive factors, which are related to the development of metabolic disorders, to suppress inflammation and strengthen the activity of metabolic disorders by stimulating histone-deacetylase activity, as well as chronic inflammatory activity [33, 34].

Further research proved high effectiveness and safety of nonsteroidal anti-inflammatory agent Indomethacin for patients suffering from atherosclerosis [35, 36].

So, polyphenols may be considered as nutraceuticals in complex therapy of diabetes mellitus type 2 in case of body extra weight and combined with relevant physical activity and modificated dieting.

**Strategies of contemporary research.** MS issue has been under international clinical research at present times. According to the clinical trial data of 2005, proper dieting and physical activity provide with better effect than Metformin therapy with reduction of MS manifestations [11]. 3-year trial, completed in 2006, proved positive effect of lifestyle change (increased physical activity and improved dieting) on diabetes mellitus type 2 and

overweighed elderly patients [12]. International clinical trial, aiming at identification of influence of modified lifestyle Cooperative Lifestyle Intervention Program (CLIP), was held in 2005-2010 [17].

While conducting international clinical trial Partnership Programs to reduce cardiovascular diseases risk (2004-2009), scientists were identifying influence of complex interrelations of behavior, social and economic status, culture and ethnicity for working age people on MS formation as a risk factor of cardiovascular diseases. The aim of the trial was to define certain psycho-sociological factors as predictors of overweight and MS, analyze new biomarkers of human pathobiology, assess innobative dynamic medical strategies for MS patients [8]. So, the issue of MS diagnostics is vital for contemporary world medicine and needs further study.

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