Medicinska istaživanja 2022; 55(1):23-34 | DOI: 10.5937/medi55-38353

OPEN ACCESS

Medical Research | Published by Faculty of Medicine University of Belgrade

REVIEW

Unbalanced diet as a cardiometabolic risk factor

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Summary

A well-balanced diet is an important factor in the promotion and maintenance of good health throughout one's life. The role of a diet as a determinant of chronic non-communicable diseases is well established and it occupies a prominent position in prevention. The burden of chronic diseases is rapidly increasing worldwide. Namely, chronic non-communicable diseases are the leading cause of death worldwide. Preterm mortality in people under 70 accounts for over 40% of the total of 38 million deaths due to chronic non-communicable diseases. Obesity, metabolic syndrome, and diabetes mellitus are also showing worrying trends, not only because they already affect a large part of the population, but also because they have started to occur earlier in life. Thus, the metabolic syndrome is a cluster of more or less related metabolic and cardiovascular derangements including visceral obesity, insulin resistance, dyslipidemia, hypertension and glucose intolerance. This syndrome is characterized by a primary cellular defect in insulin action due to disorders in insulin signal transduction (insulin is unable to adequately achieve its biological effects). Under these conditions, insulin resistance, in combination with hyperinsulinemia causes numerous metabolic and cardiovascular disorders, which are leading causes of morbidity and mortality worldwide. From the pathophysiological point of view, a diet rich in carbohydrates and saturated fats significantly contributes to the development of many chronic diseases (diabetes mellitus type 2, hypertension, accelerated atherosclerosis and its cardiovascular and cerebrovascular complications, nonalcoholic fatty liver disease, polycystic ovary syndrome, and some malignant diseases – breast cancer, etc.). In this review, we provide an overview of recent literature data and practical knowledge related to an unbalanced diet as a cardiometabolic risk factor. Further investigations in the field of molecular prevention may contribute to the development of new biomarkers, or help the setting of strategies for molecular prevention of chronic non-communicable diseases. In other words, they represent the directive for applying nutrigenomics to population sciences.

Keywords: unbalanced diet; obesity; insulin resistance; cardiovascular derangements; nutrigenetics; nutrigenomics

Recived: 24 March 2022
Revised: 15 April 2022
Accepted: 25 May 2022

Check for updates

Funding information:
This paper is funded by project number 175015 of the Ministry of Education, Science and Technological Development of the Republic of Serbia.

Competing interests:
The authors have declared that no competing interests exist

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Cite this article as: Vucevic D, Samardžić[1], Radosavljević M, Radak U, Jorgačević B, Đorđević D, Kovačević S. Unbalanced diet as a cardiometabolic risk factor Medicinska istaživanja 2022; 55(1):23-34 DOI: 10.5937/medi55-38353

INTRODUCTION

Whatsoever was the father of a disease, an ill diet was the mother.

George Herbert

Metabolic syndrome (MS) represents a combined phenomenon of glucose intolerance, arterial hypertension, dyslipidemia, central (abdominal/visceral) obesity type, as well as other metabolic disorders with underlaying insulin resistance (IR). This syndrome is principally characterized by a primary cellular defect of insulin action, i.e. insulin is unable to fulfill its biological role because of inadequate signal transduction. Under such conditions, IR in combination with consequent hyperinsulinemia causes numerous metabolic and cardiovascular (CVD) disorders, which are pandemic-like, and are the leading cause of morbidity and mortality in the world [1–9].

MS is a clinical entity that significantly contributes to the origin and development of a wide range of chronic non-communicable diseases, such as diabetes mellitus (DM) type 2, arterial hypertension, accelerated atherosclerosis with its CVD and cerebrovascular complications, polycystic ovary syndrome and some malignancies (breast cancer, etc.) [1, 8, 10, 11]. This very common set of pathophysiological disorders of metabolic origin, also referred to as syndrome X and IR syndrome, is present in approximately one in four adults [1, 12]. It is also a risk factor for the development of CVD disease, which is why it is called the "deadly quartet" [1].

MS has been the main culprit for the development of CVD in the last decade. People with MS have a 2-fold increased risk of mortality from CVD and are three times more likely to develop myocardial infarction or stroke than healthy people [1]. In addition, these individuals have a much higher risk of developing DM type 2 [1, 3]. Also, all components of MS are independent causes of CVD events, such as stroke, cardiomyopathy, coronary artery disease, myocardial infarction, heart failure, and sudden cardiac death [1]. In addition, MS is a significant risk factor for the emergence and development of non-alcoholic fatty liver disease (NAFLD) [11]. Moreover, NAFLD, as a hepatic manifestation of MS and the most common chronic liver disease, is now one of the independent risk factors for heart (left ventricular dysfunction and hypertrophy, atrial fibrillation, and valvular calcification) and vascular disease, as well as chronic kidney disease. It is also associated with other chronic diseases, such as sleep apnea, malignant diseases (colorectal carcinoma and breast cancer), osteoporosis, psoriasis and endocrinopathies (polycystic ovary syndrome, etc.) [4, 7].

There are several different definitions of MS. In clinical practice, the definitions given by experts from the International Diabetes Federation (IDF), as well as experts from the American Heart Association (AHA) and the National Heart, Lung and Blood Institute (NHLBI) are most commonly used [1, 2]. According to the IDF consensus, MS represents the incidence of population-specific abdominal obesity **(Table 1)**, together with at least two other criteria from the next group (plasma triglyceride /TG/ concentration greater than 1.7 mmol/L or hypertriglyceridemia drug treatment; high density lipoprotein /HDL/ in plasma lower than 1.03 mmol/L in men, and below 1.3 mmol/L in women; arterial blood pressure greater than 130/85 mm Hg or arterial hypertension pharmacological therapy, glycemia above 5.6 mmol/L or previously diagnosed type 2 DM) [1].

AHA and NHLBI experts have accepted the IDF criteria for the clinical diagnosis of MS, where the presence of central obesity was verified by waist circumference greater than 102 cm in men and greater than 88 cm in women [1, 10]. In addition, in order to take into account the overall picture of MS, especially in diabetics and patients with CVD, the IDF consensus emphasizes the need for additional examination of adipose tissue distribution, IR, lipid status and vascular function. Besides, it is necessary to determine the hormonal status (pituitary-adrenal axis), inflammatory process mediators (C-reactive protein /CRP/, inflammatory cytokines, adiponectin, etc.), as well as coagulation factors (fibrinogen, etc.) and fibrinolysis [2].

Table 1. IDF criteria for visceral obesity in metabolic syndrome

Ethnicity	*Sex*	*Waist circumference (cm)*
Europe	Male	≥ 94
	Female	≥ 80
South Asia	Male	≥ 90
	Female	≥ 80
Japan	Male	≥ 90
	Female	≥ 80
China	Male	≥ 90
	Female	≥ 80
South and Central America	Male	≥ 90
	Female	≥ 80
Sub-Saharan Africa	Male	≥ 94
	Female	≥ 80
Eastern Mediterranean and the Middle East	Male	≥ 94
	Female	≥ 80

Table 2. Classification of body mass according to body mass index (BMI)

Status	*BMI (kg/m²)*	*Disease development risk*
Underweight	< 18.5	Increased
Normal	18.5–24.9	Normal
Overweight	25–29.9	Increased
Obesity class 1	30–34.9	High
Obesity class 2	35–39.9	Very high
Obesity class 3	> 40	Extremely high

MS is based on the interaction of endogenous (genetic) factors and exogenous factors (obesity, physical inactivity, high energy food intake /food rich in carbohydrates and fats/, age, sex, race, positive family history for obesity and/or arterial hypertension and/or DM, difficulty adapting to stressful situations, chronic stress, etc.), which lead to the development of IR and an increase in the amount of visceral adipose tissue [1–25].

According to the disability adjusted life years (DALYs), obesity is among the top ten risk factors for chronic non-communicable diseases, and thus MS [26]. It is often defined as a condition of pathological or excessive accumulation of fat in adipose tissue to a degree that can endanger health, if energy intake is higher than energy consumption over a long period [8, 27]. Obesity can also be defined as the body mass index (BMI) greater than 30 kg/m² [8, 28]. The BMI-based body weight classification is shown in **Table 2**. According to this classification, the BMI between 18.5 kg/m² and 25 kg/m² is considered normal, while a 20% increase in body weight (BMI> 27 kg/m²) poses a health risk [8].

In 2014, the World Health Organization (WHO) published the data stating that 1.9 billion adults were obese. This organization predicts that by 2025, 2.3 billion adults will suffer from obesity [12]. Another devastating point in the WHO data includes the fact that 20 million children in the world under the age of five are overweight [8, 29]. In addition, the average BMI of the adult population in Europe is 26.5 kg/m². This means that 400 million Europeans are overweight, while 130 million Europeans are obese. Besides, the nutritional status of children in Europe is worrying as well, given that 20% of children are overweight and 33% are obese [12, 30].

The prevalence of MS varies significantly depending on the criteria used for its diagnosis, as well as the age, sex, and ethnicity of the patients [1]. In this regard, the prevalence of MS in the United States is 16% in the Afroamerican population, 25% in Caucasian and 36% in the Hispanic population [10]. In contrast, the incidence of MS in teen population of the United States is 9.1% in boys, and 3.7% in girls [31]. However, the prevalence of MS has been shown to increase with age and is 44% in people aged 60–69 [8]. Also, the result of an extensive study conducted in Australia indicates that every fifth inhabitant of this continent suffers from MS [31]. Similarly, every sixth inhabitant of Europe has MS, while in the countries of the European Union every third inhabitant suffers from this syndrome [12].

In Serbia, half of the adult population is overweight, while every fifth adult is obese [12]. In addition, in this geographical region, chronic non-communicable diseases are the leading cause of morbidity and mortality, with the share of CVD in overall mortality being 55.2% [8]. In addition, in the territory of Vojvodina, it was determined that 74.3% of the population of both sexes, aged 45 and older, were overweight and/or obese, while 33.3% of people of this age were obese. In this regard, in Vojvodina, in population of both sexes, aged 45 years and older, the incidence of MS is 16.9%. About 15% of children in this area are obese, with a tendency of MS to develop in every third child [8, 12]. If the number of obese people continues to increase, WHO experts predict that by 2025, 3.27 million adults in Serbia will be overweight, and it is estimated that as many as 249,000 school-age children will be included in the group of obese or overweight [12].

A nutritional explanation for the high prevalence of MS and its consequences in our country and other developing and developed countries is the increase in daily energy intake and energy density of food (high fat content in daily energy intake), as well as insufficient physical activity [1, 25–28, 32, 33]. Thus, in the period from 1964 to 2000, the average daily energy intake of an individual in the world increased from 2358 kcal to 2803 kcal, while fat intake increased from 53 grams to 73 grams [8]. It is important to note that approximately 50% of increased calorie intake is due to the consumption of sugary drinks [34]. It has also been shown that the percentage ratio of fat intake and daily energy intake – fat to energy ratio (FER) is the most important indicator of food energy density. Therefore, the higher the FER, the higher the risk of developing MS and its consequences [6, 17, 25]. It is also estimated that reducing the use of salt in diet from 9 to 12 grams per day, which is the current world average, to the recommended 5 grams per day, could significantly reduce the incidence of hypertension and other metabolic disorders underlying IR [6, 8, 11].

UNBALANCED DIET AND METABOLIC SYNDROME

Increased total intake of fats, cholesterol and certain fatty acids, as well as excessive energy intake have an adverse effect on lipid metabolism, resulting in the development of obesity and MS [1, 8, 11, 17, 28]. In recent years, investigations have focused on the components of food, which are detected as dietary signals by cellular sensory systems, associated with the expression of genes and proteins and the consequent synthesis of metabolites [17, 35]. From the aspect of chronic diseases development, the influence of cholesterol and fatty acids from food is especially significant for genetic expression [28]. Namely, cholesterol ingested with food leads to inhibition of transcription of the gene for β-hydroxy-β-methyl-glutaryl-coenzyme A reductase (HMG-CoA reductase). In addition, polyunsaturated fatty acids (PUFA) from food suppress the production of lipoprotein synthase in the liver at the level of messenger ribonucleic acid (mRNA). This ability to suppress excess mRNA for lipogenic protein synthesis depends on the degree of unsaturation of fatty acids from food [16]. In this sense, eicosapentaenoic acid (EPA) from fish oil has a stronger effect than arachidonic acid [14]. It is also known that ω-3 fatty acids from food reduce the amount of mRNA for platelet-derived growth factor (PDGF) and interleukin-1β (IL-1β) [13]. In addition, food components affect gene expression through transcription factors, which are also the most important nutritional sensors **(Table 3)** [36]. In total, 48 transcription factors (nuclear hormone receptors) have been identified in the human genome, many of which have the ability to bind to food ingredients and their metabolites **(Table 3)**. Thus, the transcription factor binds to the nucleus receptor - a specific nucleotide sequence (responsive element) in the promoter region of a large number of genes. During ligand binding, the nuclear receptor experiences a conformational change, which results in the coordinated dissociation of the corepressors and the engagement of coactivation proteins in order to carry out the transcription process. In metabolically active organs (liver, intestinal tract, and adipose tissue), these transcription factors act as nutritional sensors, altering the level of transcription of DNA-specific genes in response to nutritional changes [25, 35].

Research conducted thus far indicates the importance of diet in the regulation of the expression and function of the cytochrome P450 gene (CYP). It is a large family of enzymes that catalyze the oxidation of substrate molecules. This enzyme system is responsible for the oxidative biotransformation of a number of exogenous and endogenous substances, including drugs [37]. It has been found that each step in the cycle of CYP enzymatic reactions can also be inhibited by compounds present in food. In addition, the expression of constitutive CYP enzymes is known to be regulated by growth factors and peptide hormones (e.g., growth hormone, etc.) via the Jak-STAT signaling pathway. The protein-1 activator complex (AP1) also participates in the basic regulation of certain CYP genes. Exogenous stress, including the action of prooxidative compounds that may be present in food, has the ability to alter the cell profile of AP1 protein, and thus significantly affect the gene expression of CYP [9, 35, 36]. In addition, food ingredients (fatty acids, etc.) directly or indirectly modulate receptors for steroid hormones that regulate CYP gene expression [17, 23, 25].

Numerous studies have confirmed the effect of the diet rich in saturated fats and/or carbohydrates on the ex-

Table 3. Transcription factors as mediators of nutrient-gene interactions

Food components	Active molecule	Transcription factor
Macronutrients	/	/
Fat	Fatty acids	PPAR, SREBP, LXR, HNF4, ChREBP
Carbohydrates	Glucose	USF, SREBP, ChREBP
Proteins	Aminoacids	C/EBP
Micronutrients	/	/
Vitamins	Vitamin A	RAR, RXR
/	Vitamin D	VDR
/	Vitamin E	PXR
Minerals	Calcium	Calcineurin/NF-AT
/	Iron	IRP1, IRP2
/	Zinc	MTF1
Other food components	/	/
/	Flavonoids	ER, NFκB, AP1
/	Xenobiotics	CAR, PXR

SREBP (protein that binds sterol-regulatory element); LXR (X receptor in the liver); HNF (hepatocyte nuclear factor); ChREBP (protein that binds a carbohydrate responsive element); FXR (farnesoid-X receptor /bile acid receptor/); USF (upstream stimulatory factor); RAR (retinoic acid receptor); RXR (retinoid X receptor); VDR (vitamin D receptor); PXR (pregnane X receptor); NF-AT (activated T cells nuclear factor); IRP (iron regulatory protein); MTF (metal-responsive transcription factor); ER (estrogen receptor); NFκB (nuclear factor κB); AP1 (activator protein 1); CAR (constitutive androstane receptor)

pression of CYP enzymes in the liver [17, 20, 23, 25, 32]. Namely, in experimental models of obesity, induction of CYP2E1 and 4A gene expression and enzyme activity are observed after the application of a diet rich in fat, as well as in the fat-free diet (so-called orotic acid / sucrose model), where carbohydrates increased production of acetyl-coenzyme A (acetyl-CoA) and TG, and they further up-regulated PPARα-responsive CYP4A enzymes [32, 38]. Peroxisome proliferator activated receptor-α (PPARα) is in itself a significant regulator of liver lipid content and is a link connecting nutrition to gene transcription in the liver [35]. In other words, PPARα, found in hepatocytes, regulates TG utilization by controlling genes responsible for lipid transport and oxidation [38]. Similarly, the transcription factor PPARγ, found in adipocytes, plays a role in the control of lipid deposition (regulation of lipogenesis and fat cell differentiation) [35]. CYP enzymes are known to potentially form free radicals during catalysis, which means that their induction by food agents can contribute to the processes of peroxidation of membrane lipids and proteins, especially in hepatocytes [35, 38]. Simultaneous use of inducers and CYP2E1 substrate (ethanol, carbon tetrachloride / CCl4/, etc.) worsens toxic damage caused by excessive production of free radicals. By this mechanism, induction of CYP enzyme expression may exacerbate pre-existing cell damage in obesity, DM, and MS [6, 17, 25]. An association between diet and progression of these diseases has also been established, suggesting that regulation of CYP enzymes by diet may contribute to pathogenetic mechanisms [17, 25].

There is no single dietary regimen for all types of hyperlipoproteinemia, but a combination of multiple dietary measures is commonly used **(Table 4)** [28].

Table 4. Dietetic approach to hyperlipoproteinemias

Total fat intake reduction
Cholesterol intake reduction
Reducing the intake of certain saturated and trans fatty acids
Increased intake of unsaturated fatty acids of cis configuration
Other dietary measures: • reduced intake of concentrated carbohydrates • reduction of total energy intake (hypoenergetic diet) • increased intake of dietary fibers • increased intake of plant origin proteins • increased intake of antioxidants • prohibition or restriction of alcohol intake

Increased total fat intake

Lipids that are ingested through food contain three types of fatty acids (saturated, monounsaturated fatty acids (MUFA) and PUFA). The classification was made based on the number of double bonds between two carbon atoms (C) in a fatty acid molecule. Each of these three types of fatty acids has a different effect on the balance and/or profile of lipoproteins or cholesterol in the blood, as well as on thrombogenic mechanisms [14, 28].

Numerous epidemiological data indicate an association between total fat intake (mainly saturated fatty acids) and coronary heart disease mortality [1, 6, 8, 10, 11, 25, 26, 28]. The results of some studies have shown that the replacement of saturated fatty acids with unsaturated forms of these lipid molecules is more effective in reducing blood cholesterol levels than reducing the total fat intake [8, 15, 17, 20, 39]. In addition, it has been found that low total fat intake can cause a decrease in HDL, as well as a reduction in the intake of essential fatty acids and vitamin E [26]. Also, scientific research has shown a connection between high fat intake and thrombosis tendency, i.e., a positive correlation was observed between high postprandial TG levels and an increase in coagulation factor VIIa concentration, which increases the risk of coronary heart disease [3, 28]. In addition, high intake of lipids as the most energy-rich nutrients can lead to a positive energy balance, excessive weight, obesity and MS [1, 28]. Therefore, it is recommended to replace one part of fat with carbohydrates that have a lower energy value [17]. A higher degree of replacement would lead to a reduction in HDL particle levels, bearing in mind that all fatty acids increase the level of HDL lipoprotein fraction to a greater or lesser extent, stimulating the secretion of apolipoprotein AI (apo AI), with saturated fatty acids effect of MUFA being greater than PUFA [16, 23]. In this regard, studies in one region of Finland (North Karelia) showed that reduced energy intake and reduced total fat intake, with changes in the ratio between saturated and polyunsaturated fats, after six weeks lead to a decrease in total cholesterol by 24%, and TG by 26%. It is important to mention that reducing the daily energy content of fat from 40% to 30% leads to a reduction in cholesterol levels by 0.5 mmol/L, while normalization of body weight of a moderately obese person is accompanied by a decrease in cholesterol by about 0.8 mmol/L [8]. Therefore, it is recommended that total fat intake should be less than 30% of total daily energy intake, i.e., less than 75 g/day (85 g/day in high-intake countries). It is also recommended to avoid frying, baking and breading when preparing meals, as well as to use skimmed or semi-skimmed dairy products and lean meat in the diet, and to avoid cured processed meat products and fatty pastries containing the so-called "hidden fats" [8, 27].

Increased cholesterol intake

Cholesterol is the most abundant lipid in the body. It is present in free (nonesterified) form and esterified form. Plasma contains about 75% of cholesterol in esterified form, most often with polyunsaturated linoleic fatty acid. Free cholesterol is found mostly in tissues. About 2/3 of cholesterol is synthesized in the body (approximately 900 mg per day), and the rest is ingested through food [11, 28].

Blood cholesterol levels are affected by an increased intake of cholesterol itself, some long chain saturated fatty acids and *trans* isomers of unsaturated fatty acids. Excessive energy intake also affects the concentration of cholesterol in the blood [7, 28].

The average daily intake of cholesterol in many countries, especially in the developed world, is 450–500 mg. On the other hand, when it comes to this lipid, it has been proven that the physiological daily needs of an adult are 150–300 mg. According to the recommendations given by the AHA, in the first stages of a diet, which refers to milder cases of lipid metabolism disorders, the daily intake of cholesterol is limited below 300 mg, and in the second degree (severe forms of lipid metabolism abnormalities) below 200 mg. It has been proven that for every 100 mg of increased cholesterol in the diet per day, the concentration of cholesterol in the blood increases by 0.21–0.26 mmol/L [8, 28].

Particularly rich sources of cholesterol are egg yolks (one chicken egg yolk contains about 280 mg of cholesterol), all offals (mostly brain, liver, kidneys, and heart), fish eggs, caviar, butter, whole milk and its products (cheese, sour cream, ice cream, etc.), mayonnaise, fatty meats, fatty meat products and animal fat. Generally speaking, meat does not contain large amounts of cholesterol, but it is an everyday part of the diet of our population, and therefore significantly contributes to increasing cholesterol intake through food [8].

When it comes to limiting cholesterol intake, it should be emphasized that its biggest source in the diet is egg yolks, since eggs are a very common ingredient in food, although some other foods contain a significantly higher percentage of cholesterol (for example, brain and other offal, fish caviar, lobster meat, etc.) [40].

Vegetarian studies also support the role of fats of milk origin and the importance of eggs as a source of cholesterol. Thus, vegetarians who base their diet on milk, dairy products and eggs (lacto-vegetarians) have the same or even higher values of total cholesterol, LDL particles and TG than people who eat a standard mixed diet. In contrast, strict vegetarians, who not consume milk, dairy products and eggs, have very low blood lipids [8].

It has been found that increased intake of dietary (exogenous) cholesterol leads to an increase in serum cholesterol to a much lesser extent than some saturated fatty acids. Since foods rich in cholesterol contain a significant amount of saturated fatty acids, a strategy based on reducing the intake of these fatty acids will also reduce cholesterol intake **(Table 5)** [20, 23]. In this regard, the recommended reduction of calorie intake depends on age, sex, and levels of physical activity [8]. It is also known that exercise and moderate alcohol consumption increase HDL values, while obesity and tobacco smoking reduce them [11]. In addition, chronic activation of the immune system, caused by overeating, can be observed before the clinical manifestations of obesity [3].

Saturated fatty acids

There is strong evidence for a link between saturated fatty acid intake and levels of not only total serum cholesterol, but also LDL and HDL lipoprotein fractions. This is especially true of palmitic, myristic and lauric acid, while stearic acid, which also has a long chain, does not manifest this effect [23]. Numerous studies, including the so called The Seven Countries Study, which included Serbia, found that populations that consumed large amounts of saturated fatty acids had relatively high blood cholesterol levels [8]. In contrast, low saturated fatty acid intake is accompanied by low concentrations of total cholesterol [28].

Saturated fatty acids are found in fats of animal origin (fatty meats and fatty meat products/sausages, salami, paté, bacon, various luncheon meats, hot dogs, etc./, whole milk and dairy products), as well as in some vegetable oils (coconut and palm oil), solid margarines and various toppings. The highest amounts of saturated fatty acids are present primarily in pork, beef and lamb red meat. However, poultry and other types of meat can have significant amounts of saturated fatty acids, so when preparing a meal, it is necessary to remove all visible fat impurities from the meat [8, 20].

The fact that a large intake of saturated fatty acids is realized in environments where there is an extensive network of fast-food restaurants (hamburgers and similar

Table 5. WHO recommendations for dietary reduction of high serum cholesterol concentration

Nutrients	Recommendations
Total fats	15–30%
Saturated fatty acids (% energy intake)	< 7%; trans< 1% energy intake
PUFA	6–10% energy intake (5–8% ω-6; 1–2% ω-3)
MUFA	10–15% energy intake
Cholesterol	The lowest possible intake
Sodium	< 1700 mg
Fish (n–3)	1–2 servings per week (200–500 mg EPA per serving)
Fruit and vegetables	400–500 g daily

products) is often overlooked, which is the case in Serbia as well. Also, another very important source of saturated fatty acids are whole milk and its products. Therefore, it is necessary to exclude cow milk of 3.2–4% milk fat, sheep milk (which contains twice the amount of fatty substances compared to cow milk), whole cheeses, sour cream, butter, ice cream, etc. These products need to be replaced with semi-skimmed or skimmed milk (from 2.2% fat in milder forms of hyperlipoproteinemia, or 0.2–1.6% fat in more severe forms of these disorders) and products made from such milk [8].

In order to avoid excessive intake of saturated fatty acids, one should pay attention to foods that contain the so-called "hidden fats" (various types of fatty pastries, croissants, donuts, fatty pies, cakes, fatty crackers, etc.). Since eggs are often added to such products, they thus become a very rich source of cholesterol [40].

Taking into consideration the aforementioned facts, it is recommended that the share of saturated fatty acids in the total daily energy intake be up to 7% (Table 5), i.e., less than 25 g/day [8].

Unsaturated fatty acids

The term unsaturated fatty acids nowadays refers to unsaturated fatty acids of *cis* configuration, while *trans* isomers are separated into a separate group [7]. As previously pointed out, the intake of unsaturated fatty acids of *cis* configuration should be increased, especially MUFAs [16, 23].

MUFAs are known to lower total serum cholesterol and LDL particles [6, 15]. The main MUFA in the diet is oleic acid, which is most present in olive oil (72%), followed by canola oil (54%) and peanuts (49%) [15]. In addition, the presence of this acid in the so called high oleic type sunflower is also of importance. Larger amounts of MUFAs are also found in hazelnuts, almonds, walnuts and dried pumpkin seeds. To a lesser extent, MUFAs are present in meat and meat products [8]. In this regard, the diet in the Mediterranean countries (the so-called Mediterranean diet) results in lower incidence of atherosclerosis and its complications, because, among other things, it is based on high intake of oleic acid through olive oil [15].

Of particular interest from the dietary point of view are the ω-6 (n-6) and ω-3 (n-3) families of PUFA (the number indicates the position of the double bond in the C atom chain). ω-6 PUFAs, of which linoleic acid is the most abundant, are of plant origin (sunflower and soybean oil, corn oil, etc.) and moderately lower total cholesterol, LDL particles, and to some extent HDL particles [16]. ω-3 PUFAs are found in fatty fish, fish oil, some vegetable oils (flaxseed oil, etc.), nuts, and leafy green vegetables [39]. α-linolenic acid and its two metabolites (EPA and docosahexaenoic acid /DHA/) are the most important ω-3 PUFA [14]. They are formed in the chloroplasts of plants and phytoplankton and are therefore present especially in the oil and meat of marine fish that feed on phytoplankton. It has been established that these fatty acids predominantly lower the level of TG, as well as reduce the level of cholesterol only if there is a marked increase in TG at the same time. Conversely, when there is only an increase in cholesterol, these PUFAs can even lead to a further increase in cholesterol content, which is their side effect [13, 39]. On the other hand, the beneficial effect of ω-3 PUFA is largely achieved by reducing platelet aggregation in the blood vessel wall, improving endothelial function, moderate reduction in blood pressure, etc. [14, 39].

Some PUFAs are essential (linoleic and α-linolenic acid), so it is necessary to take them daily [8]. However, it should be borne in mind that excessive intake of PUFA can cause some side effects (accelerated development of osteoporosis, increased production of gallstones, etc.) [8, 39].

The modern diet is most often characterized by a lack of ω-3 PUFA and a combined excess of saturated fatty acids, ω-6 PUFA and *trans* isomers of unsaturated fatty acids [11]. The reasons for this diet are the use of large amounts of vegetable oils, margarine and food of animal origin, and insufficient intake of leafy green vegetables and seafood (sources ω-3 PUFA) [13, 15]. In such circumstances, excess ω-6 PUFA is susceptible to the formation of lipid peroxides whose action is atherogenic and carcinogenic. In addition, there is an imbalance of ω-6 and ω-3 PUFA in food, which is as high as 25–30:1 [39]. Thus, for example, in the case of intake of a large amount of ω-6 linolenic acid, the production of EPA and DHA from ω-3 α-linolenic acid is difficult. The type of eicosanoides that will be synthesized in the body also depends on the relationship between ω-6 and ω-3 PUFA in food, because these acids are their precursors. If the diet is dominated by ω-6 in relation to ω-3 PUFA, the immune response will be weaker, the inflammatory reaction stronger, vasoconstriction and increase in blood pressure will also be evident, which is a predisposition for the development of atherosclerosis, thrombosis, hypertension, cardiac arrhythmias, etc. Therefore, it is recommended that the ratio between ω-6 and ω-3 PUFA need to be 2 or lower [8, 13, 14]. It is also suggested to consume fish in the amount of 200–500 grams 1–2 times a week **(Table 5)**, primarily saltwater fish rich in ω-3 EPA and DHA (tuna, cod and anchovy), as well as cold northern sea fish (salmon and herring) [8, 41]. Pike and perch have the most favorable fatty acid composition of all freshwater fish [8].

Trans isomers of unsaturated fatty acids

All unsaturated fatty acids have a *cis* or *trans* geometric isomeric shape. When we talk about MUFA and PUFA in general, it is common to think exclusively of their *cis* form, while *trans* forms are singled out in a special group. The geometric isomerism of unsaturated fatty acids depends on the orientation of the radical around the double bond. If the radicals are on the same side of the double bond, it is

a *cis* shape, and if the radicals are on opposite sides, it is a *trans* configuration [7]. Spatial configuration is extremely important, since *trans* isomers have harmful effects on the body (accelerate the process of atherogenesis, adversely affect the growth and development of infants and young children /disrupt the metabolism of essential fatty acids/, slow down the mechanisms of hemostasis, lead to IR and thus facilitating the development of MS and type 2 DM) [7, 11, 28]. There is a large number of fatty acids of the *trans* configuration, and the most common in the diet are *trans* monoenes (primarily elaidinic acid, and in smaller quantities vacenic acid). It is important to note that the metabolism of *trans* forms of unsaturated fatty acids in the human body is more similar to the metabolism of saturated fatty acids compared to the metabolism of unsaturated fatty acids of *cis* configuration [7].

The origin of *trans* isomers in the diet of modern man is dual. Much smaller quantities are of natural origin and are found in butter and dairy products, some fats of animal origin and in ruminant meat. It was found that these isomers were present in cow milk in the amount of 2–6%. They are also present in the milk of other animal species. Beef tallow is also an important source of these fatty acids [7, 8]. The largest amounts of *trans* isomers of fatty acids are found in fats obtained by partial hydrogenation of vegetable and fish oils [11]. During the conversion of liquid oils into solid fats, one part of unsaturated fatty acids is converted into saturated fatty acids (complete hydrogenation), and the other is converted from *cis* to *trans* form (partial hydrogenation). Namely, *trans* isomers are formed when hydrogen atoms are added to liquid oils. It should be mentioned that these adverse effects are further exacerbated during the oil refining process, which leads to the conclusion that natural and cold pressed oils, according to today's understanding, have the most favorable composition from a dietary point of view [7, 11].

It is known that the highest content of *trans* isomers is found in many types of margarine, margarine-based products, various dressings and coatings, and most importantly, in vegetable fats and fish oils of solid consistency, and such lipid substances are most often used in fast food [8, 11]. To illustrate, for example, one donut contains 3.2 grams, a large portion of French fries 6.8 grams, and a bag of popcorn over 10 grams of *trans* isomers of fatty acids. It is also known that 100 grams of low-calorie margarine obtained by partial hydrogenation process contains about 12 grams of *trans* fatty acids. It is important to point out that the amounts of *trans* fatty acids in industrially hydrogenated fat can reach as much as 60% of the total fatty acid content, unlike natural products where the content of these fatty acids is far lower (maximum 6%) [7, 8, 11]. It should be emphasized that there are significant differences in the action of *trans* fatty acids of natural origin, compared to *trans* isomers that are industrially produced by partial hydrogenation [8]. In this regard, it was found that industrially produced trans *fatty* acids were extremely atherogenic, because they affected, on one hand, the increase in total cholesterol, LDL particles, and Lp(a), and on the other hand led to lower HDL particles [7, 11]. These isomers also lead to an increase in the concentration of TG in the blood [28]. The adverse effect of *trans* fatty acid isomers on lipid status has been shown to be greater than the effect of long chain saturated fatty acids. These isomers lead to a damage to LDL receptors on cell membranes, thus reducing their activity **(Figure 1)** [11].

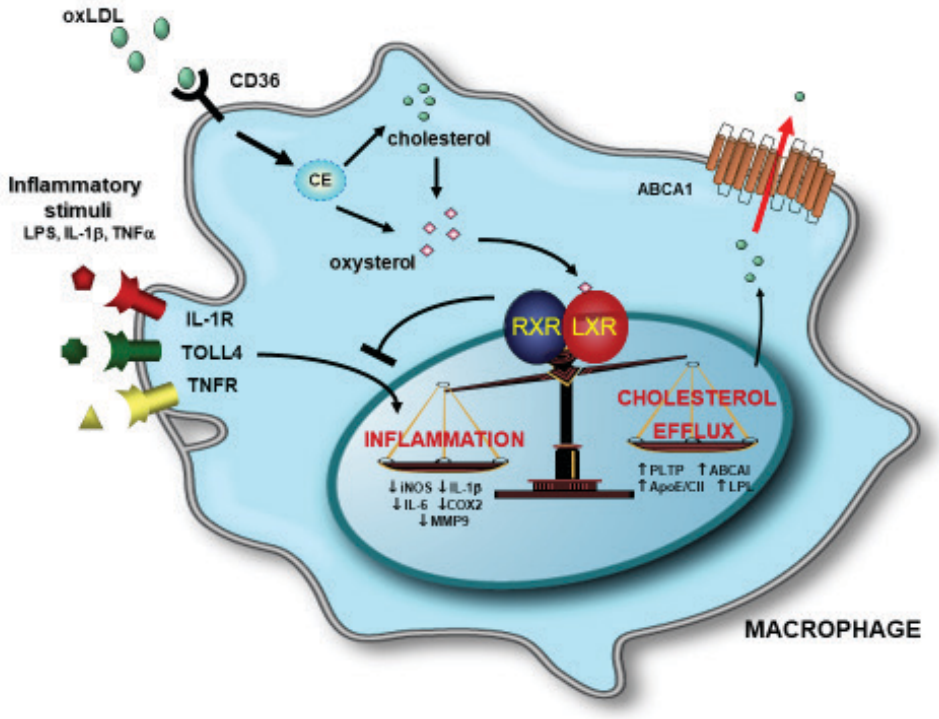

Figure 1. A macrophage response to inflammatory stimuli

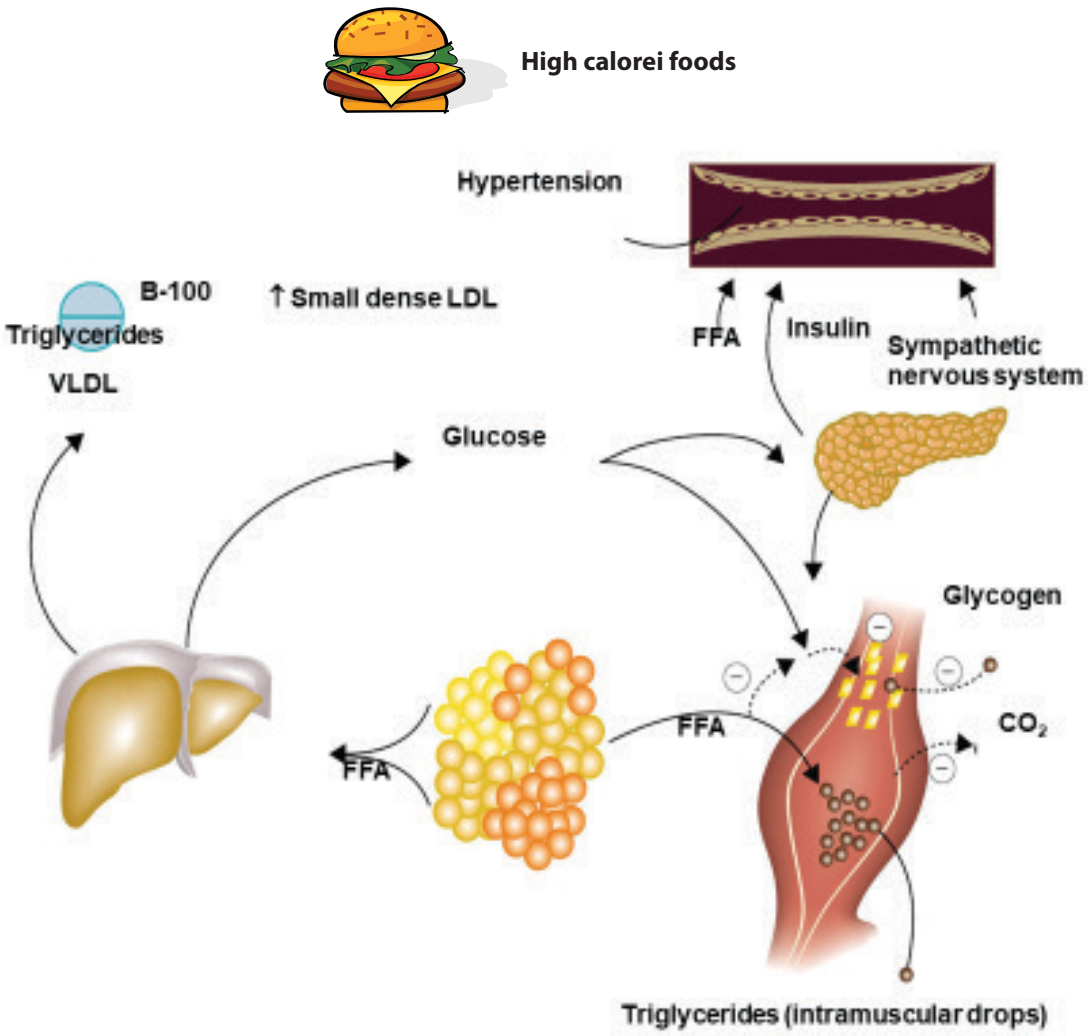

Figure 2. Insulin resistance and metabolic syndrome - FFA, free fatty acids

In addition, industrially produced *trans* isomers increase the activity of the protein responsible for cholesterol ester transport (CETP), which has been found to play an important role in lipoprotein particle metabolism (redistributes cholesterol esters from HDL to VLDL and LDL fraction) [7]. It has also been noticed that a gram of industrially produced *trans* isomers of fatty acids, compared to consuming the same amount of saturated fatty acids, is ten times more harmful concerning the development of heart and blood vessel diseases. A positive correlation was also registered between the alimentary intake of industrially produced *trans* fatty acids and the relative risk of developing MS and type 2 DM **(Figure 2)** [7, 8, 11].

Today, the question arises as to what amount of *trans* isomers of industrial origin is acceptable in a well-balanced diet. According to AHA recommendations, their intake should be limited to a maximum of 1% of daily energy intake (Table 5) [11]. However, according to numerous studies, their intake in the daily diet is far higher, and ranges to the extreme 50 grams. In Serbia, the exact data on the alimentary intake of *trans* isomers of industrial origin are not known, but it is quite certain that the intake of these harmful substances is significantly higher than the stated allowable amount [8, 12].

With all the harmful effects of industrially produced *trans* isomers of fatty acids in mind, residents in many countries, especially in Scandinavia and most Western European countries, have significantly reduced their intake. Moreover, in Denmark, for example, these fatty acid isomers are completely out of use, primarily due to new technological processes in the food industry ("soft" type of margarine, etc.) [8]. Until the content of *trans* isomers of unsaturated fatty acids of industrial origin in margarines in our country is reduced from the existing 12.13% to a negligible level, it is necessary to well inform the population about the principles of proper nutrition. In addition, detailed declarations on the content of certain types of fatty acids in food products, and not only information on the total fat content in their composition, from a health point of view will significantly facilitate the selection of the most favorable foods and food products [8, 12].

The research results on eating habits of the Serbian population indicate the need to raise the awareness level and knowledge quality related to proper nutrition, since only every tenth adult inhabitant of Serbia eats adequately. In addition, it was found that only 15.5% of adults in Serbia consume two servings of fruit every day, while only 12.2% regularly consume three or more servings of vegetables every day [8].

NUTRIGENETICS AND NUTRIGENOMICS

Nutrigenomics deals with the study of the influence of diet on metabolic pathways and homeokinesis, i.e., their regulation in the early stages of diet-related diseases, as well as the degree to which a person with the appropriate genotype is susceptible to these diseases. It is the science of the effect of nutrients on gene expression, which opens the possibility of identifying genes that affect the risk of diet-related diseases. In this sense, in this new scientific field on the example of MS, as multifactorial and polygenic diseases, the so called "genomic-based" phenotypic biomarkers are actively sought, which would be valid and enable detection of diseases in the preclinical phase and effective implementation of dietary strategies in prevention [35-37, 42]. The complementarity of the two approaches is emphasized was less than 1%. - diet, which is important for the earliest stages of the disease and preservation of homeokinesis, and drugs, which are necessary for the treatment of later stages of the disease [42].

Nutrigenetics tries to answer why food and diets have different effects on each individual. The study of the role of genetic variation in explaining individual diversity in response to diet is the basis for studying susceptibility to diet-related diseases. Historically, diet has influenced gene expression, enabling the formation of phenotypic characteristics that have been able to successfully respond to stimuli from the external environment and allow more efficient exploitation of food resources. Such adaptation has been crucial for human growth and development [36, 42].

Today, the so called "omics" sciences (transcriptomics, proteomics, metabolomics, etc.) are being intensively developed, which enable the determination of interactions between nutrients and other bioactive components of food and genes, and such relationships are important for more successful treatment and personalized nutrition [42, 43]. In this regard, epigenetic mechanisms underlying phenotype modification, whose modulation is possible through nutrients, are considered. In recent years, there has been a growing interest in epigenetic mechanisms whose dysregulation may be important for the development of disease in the human population [42].

According to the so-called fetal hypothesis about the origin of the disease, there are clear relations between maternal nutrition, fetal epigenetic programming and the appearance of the disease in adulthood. This emphasizes that the diet in the earliest periods of life "programs" unwanted outcomes in adulthood. Such effects of early nutritional exposure to the risk of developing adult obesity, hypertension, and IR have been shown in various animal models [42, 44].

In research in the field of nutrigenomics, two strategies are generally applied. The first provides detailed data at the molecular level on the interactions between nutrients and genomes, while the second focuses on human nutrition [42]. The first approach identifies transcription factors that serve as nutritional sensors and target genes **(Table 3)**, reveals signaling pathways and characterizes major nutritional signals, measures gene expression and metabolic consequences of specific micronutrients and macronutrients, and identifies genotypes that are risk factors for diet-related diseases such as DM, hypertension and atherosclerosis and quantifies their impact. Another approach involves the application of nutritional biology in the detection of biomarkers of early metabolic dysregulation and susceptibility to dietary influences [42, 45].

Incorporating genomics into nutritional practice offers the potential for personalized nutrition and prevention assistance by targeting nutrient-responsive molecular mechanisms that respond to nutrients [42]. The best example of this is phenylketonuria, in which proper nutrition minimizes the consequences of the disease [42, 46]. In these patients, the implementation of dietary treatment begins in the first days of life, and the essence is in the lifelong use of special preparations that do not contain phenylalanine [42]. In addition, research in the field of molecular prevention is expected to lead to the discovery of new biomarkers, more accurate measurement of disease susceptibility (personalized risk assessment), as well as new knowledge about the effects of interactions related to gene-environment and especially food-genes [42, 47]. In that way, the application of genomics in the population sciences would be useful both for the improvement of health status and for the prevention and treatment of diseases [42, 48].

CONCLUSION

Despite the continuous mastery of biomedical knowledge and techniques, scientists are still far from fully understanding the etiopathogenesis of chronic non-communicable diseases. In this regard, it is necessary to fight against these diseases and their consequences in a more efficient way. For that purpose, given the tendency of increasing prevalence of MS in the coming decades, it is necessary to take preventive measures to combat risk factors that may be affected (inadequate diet rich in carbohydrates and saturated fatty acids, obesity, smoking, sedentary lifestyle and physical inactivity). In addition to lifestyle changes, the use of a low-calorie diet and increased physical activity, patients with MS also need the use of appropriate drug therapy for certain components of the syndrome. We remain hopeful that further research in the field of molecular prevention will be able to contribute to the discovery of new biomarkers, help create strategies for molecular prevention and control of chronic non-communicable diseases and be a guideline for the application of nutrigenomics in population sciences.

ACKNOWLEDGEMENTS

This paper is funded by project number 175015 of the Ministry of Education, Science and Technological Development of the Republic of Serbia.

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NEPRAVILNA ISHRANA KAO KARDIOMETABOLIČKI FAKTOR RIZIKA

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Sažetak

Izbalansirana ishrana je važan faktor promocije i održavanja dobrog zdravlja u toku čitavog života. Njen značaj kao determinante hroničnih nezaraznih bolesti dobro je poznat i ima važnu ulogu u prevenciji. Opterećenost hroničnim nezaraznim bolestima rapidno se povećava širom sveta. Naime, hronične nezarazne bolesti su vodeći uzrok umiranja na globalnom nivou. Od 38 miliona smrtnih ishoda u svetu zbog hroničnih nezaraznih bolesti, više od 40% čini prevremeni mortalitet koji se odnosi na osobe mlađe od 70 godina. Gojaznost, metabolički sindrom i dijabetes melitus takođe pokazuju zabrinjavajuće trendove, ne samo zbog naglašenog ispoljavanja kod velikog dela stanovništva, već i zbog sve češćeg prisustva u ranijim godinama života. Tako, metabolički sindrom predstavlja udruženu pojavu intolerancije glukoze, arterijske hipertenzije, dislipidemije, centralnog (abdominalnog /visceralnog/) tipa gojaznosti, kao i postojanje drugih metaboličkih poremećaja u čijoj se osnovi nalazi insulinska rezistencija. Ovaj sindrom prevashodno odlikuje primarni ćelijski defekt dejstva insulina, to jest insulin usled defekta u signalnoj transdukciji nije u mogućnosti da ostvari svoje biološke efekte. U takvim uslovima, insulinska rezistencija u kombinaciji sa posledičnom hiperinsulinemijom izaziva brojne metaboličke i kardiovaskularne poremećaje, koji imaju pandemijski karakter i predstavljaju vodeći uzrok morbiditeta i mortaliteta u svetu. U patofiziološkom smislu, ishrana bogata ugljenim hidratima i zasićenim masnim kiselinama značajno doprinosi nastanku i razvoju širokog spektra hroničnih nezaraznih bolesti, kao što su dijabetes melitus tip 2, hipertenzija, ubrzana ateroskleroza sa svojim kardiovaskularnim i cerebrovaskularnim komplikacijama, nealkoholna masna bolest jetre, sindrom policističnih ovarijuma i pojedine maligne bolesti (karcinom dojke i dr.). U okviru ovog preglednog članka dat je prikaz najnovijih literaturnih podataka i praktičnih saznanja o nepravilnoj ishrani kao kardiometaboličkom faktoru rizika. Buduća istraživanja u oblasti molekularne prevencije mogu da doprinesu otkrivanju novih biomarkera, pomognu u stvaranju strategija za molekularnu prevenciju hroničnih nezaraznih bolesti i budu smernica za aplikaciju nutrigenomike u populacionim naukama.

Ključne reči: nepravilna ishrana, gojaznost, insulinska rezistencija, kardiovaskularni poremećaji, nutrigenetika, nutrigenomika

Primljen: 24.03.2022. I **Revizija:** 15.04.2022. I **Objavljen:** 25.05. 2022

Medicinska istaživanja 2022; 55(1):23-34