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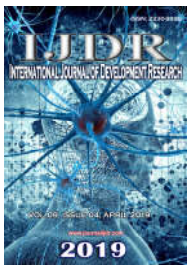

ORIGINAL RESEARCH ARTICLE OPEN ACCESS

METABOLIC SINDROME: PATHOGENESIS, PREVENTION AND TREATMENT

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ABSTRACT

In connection with a change in the lifestyle of a person, energy requirements for fats have decreased due to a decrease in physical exertion.On the contrary, there is a predominance of intellectual and operator types of activity, which are provided by the energy of glucose (the brain uses only glucose as a source of energy).This led to the development of an energy imbalance - a deficiency of one energy source (glucose) against the background of an excess of another (fat). The body is trying to ensure the functioning of the brain due to the supply of glucose with food, but at the same time an excess amount of food is supplied, which contributes to the development of obesity.Brain activity can also be achieved by increasing transport or increasing blood pressure, but this increases the risk of developing hypertension. In the liver, fat oxidation provides energy for the process of gluconeogenesis, and when there is a shortage of substrate or amino acids for gluconeogenesis (for example, during fasting or type 1 diabetes), the need for ATP energy decreases and fat oxidation during the acetyl-CoA phase is blocked.Two molecules of acetyl-CoA are condensed with the formation of acetoacetate, which is then converted into hydroxybutyrate and acetone, i.e. developing ketosis, which is a threat to life.Therefore, the body protects itself from the development of ketosis (adaptive response) through the secretion of the hormone insulin, which prevents the release of fat from the depot to the circulation. However, an increase in insulin also has an adverse effect (in particular, hypoglycemic coma), so the body protects itself against insulin through the development of insulin resistance, which leads to the development of diabetes. In response to insulin, the synthesis of fats increases and their oxidation decreases, leading to the development of dyslipidemia. This deadly quartet (obesity, hypertension, diabetes, and dyslipidemia) has been calledmetabolic syndrome (MS). For the prevention and treatment of MS, it is necessary in the phase of physical and mental activity or in the post-adsorption period to increase the body's supply of glucose energy, which can be achieved through the use of a specialized product for feeding obese individuals (Certificate of Grant of Patent GB 2496119 22 January 2014). This product also improves the interface between lipid oxidation and the process of gluconeogenesis, which prevents the development of ketogenesis. Thus, in addressing the issues of prevention and treatment of MS, it is necessary to use the metabolic approach in conjugating the processes of formation and utilization of ATP energy, which we proposed as a conceptual metabolic model developed taking into account the carbon skeleton transport during the absorptive and postabsorptive periods.

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INTRODUCTION

Unhealthy dietary patterns and a sedentary lifestyle have an important role in human health, especially nowadays, when non-communicable diseases (NCD) such as obesity, cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM) have somewhat unseated communicable diseases practically worldwide, despite the incidence of the former being higher in developed and developing countries (Wang, 2016). The highest prevalence and incidence of NCD is related to cardiovascular, diabetes, obesity, and metabolic syndrome (MetS). MetS– otherwise called syndrome X, insulin resistance syndrome, Reavensyndrome, and "the deadly

quartet" is a common clinical disorder characterized when at least three of five of the following factors are present: elevated triglycerides (≥ 150 mg/ dL), reduced high-density lipoprotein cholesterol (HDL-c; <40 mg/ dL in males and <50 mg/dL in females), elevated fasting blood glucose (≥ 100 mg/dL), elevated blood pressure (systolic BP ≥ 130 and/or diastolic BP ≥ 85 mm Hg), and elevated waist circumference (with country-specific definitions) (Kaur, 2014). The presence of these risk factors increases the probability of developing diabetes mellitus and cardiovascular disease, increasing coronary and cardiovascular mortality. MetS is heterogeneous disease (Poulsen, 2010), which is an important cause of high human mortality (Mottillo, 2010). Studies in the last years have reported that MetS affects around 20-30% of the population (Beltrán-Sánchez, 1999). According to the World Health Organization (WHO), in Europe in 2009 - 2010, on average, one in every three children aged six to nine years was overweight or obese, while among children aged 11 and 15 years the prevalence of overweight and obesity was 11 - 33% and 10 - 23%, respectively (WHO, 2018). It is expected that if the current trend continues, there will be 20% or more obese children and adolescents in over 30 countries around the world in 2025 (WHO, 2018). Among the European countries, Poland has one of the highest rates of prevalence of overweight in children and adolescents; 12 - 25% of Polish children and young people are overweight with a tendency toward an increase in the prevalence of both overweight and abdominal obesity (Suder, 2017). It is estimated that around 55% of obese children and 70% of obese adolescents will experience adult obesity (Simmonds, 2016), which increases their risk of obesity-related non-communicable diseases, such as diabetes, cardiovascular disease, various types of cancer, as well as premature mortality (Li, 2016). Therefore, prevention and treatment of childhood obesity is of the utmost importance, given the significant health and social consequences both in the short and long terms (Estrada, 2014). However, the pathogenesis is still not clear. This impedes the development of adequate preventive and therapeutic measures. The main focus development mechanism of MetS is the energy imbalance which caused by a change in the lifestyle of a modern person - the predominance of intellectual and operator activities, which are supplied primarily by glucose, and a decrease in physical activity or a decrease in the use of fat energy. Thus, we see an interesting situation the excess of one energy source (glucose) on the background deficit of another (glucose). In this article we will try to answer the question what is common in the development of the diseases "deadly quartet" and how to deal with them.

The changes used energy sources takes place in a person's life after birth. The first food is the mother's milk; the ratio of macronutrients can be attributed to the high fat (HF) nutrition. When a child goes on natural feeding he receives high carbohydrates (HC) nutrition, but HF principle of nutrition is save between intakes HC nutrition, therefore, the energy supply of life processes is carried out through the use of two food streams: HC or absorptive (exogenous) and HF or posabsorptive (endogenous. The aim of HF nutrition consists of renewal all proteins and cells structures (реабилитации) rehabilitation) and storage of excess energy in the form of glycogen and lipids. The aim of HF nutrition consists of energy support of physical and mental activity. In food hygiene usually takes into account two aspects-adequacy and safety. There are a lot of scientific forums and published many monographs and articles, however, human mortality from non-correct nutrition according to WHO is constantly increasing (Meier, 2019) and in 2016 amounted to 22.4% of the total and 49.2% of cardiovascular diseases. This is due to the fact that all nutrition theories and their visual representation in form of food pyramid assess the body's need for nutrients and energy during the absorption period, while unbalanced which is associated with a change in a person's life style is predominantly post absorptive period. If we imagine the composition of macronutrients in the absorptive and postabsorptive periods in the form of pyramids, leaving the sequence of macronutrients as "food pyramid", the "energy pyramid" (postabsorptive period) will be inverted (Fig.1).

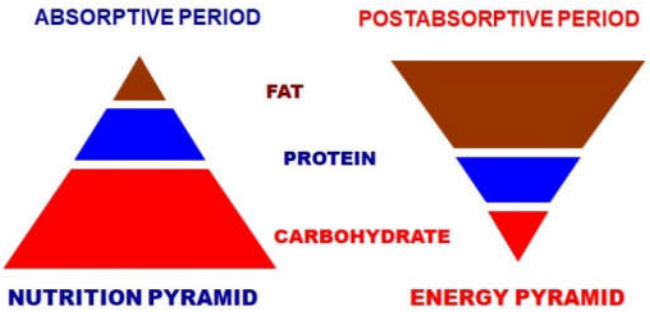

Figure 1. The ratio of macronutrients in the food and energy pyramids

The basic macronutrients in energy pyramids are fats. This was justified by the principle of human existence. Food had to catch up or to produce and was used mostly energy fat. The fats are help to maintain heat production. The use of fats as a source of energy has decreased; they accumulate, which leads to the development of obesity, because now a person is heated by clothes and heaters, buys food in the store. On the contrary, the use of glucose has increased, due to the predominance of intellectual and operator activities, while the endogenous reserves of carbohydrates are minimal. The total blood glucose is about 5 g (based on: blood glucose 100 mg% or 100 mg in 100 ml of blood, and total blood volume of 5 l it will be 5 g), while for the brain activity per day need about 100-150 g (Gruetter, 2011). When the concentration of glucose in the blood is twice lower than the norm, the brain enters low energy and it is turned off (instantaneous loss of consciousness), and after five minutes the die brain cells and death (Finfer, 2012). The stores glycogen in liver will last only for half a day of brain activity (Snitker, 1997), so further provision of the brain in energy in case of prolonged fasting or reduction of the diet is due to glucose endogenous synthesis, but as substrates amino acids or functional proteins are used. At a result insufficient intake of carbohydrates from food, functional proteins are utilized and the development of various metabolic disorders, which are well studied during prolonged fasting (Fig. 2). First of all, there is a loss of muscle proteins ("the most low-value"), which can lead to a violation of the respiratory muscles and the development of pneumonia. Next is the loss of visceral proteins (blood proteins), which are involved in the transport of food compounds, so their loss leads to the development of endogenous food deficiency. At disposing of blood cells (leukocytes, lymphocytes) the immune response is disturbed and the body’s defense against infections is weakened. Further, development disorder of organs and tissues (intestines, liver and heart), violation of adaptation and loss of 70% of nitrogen is the death of organism. Therefore, to reduce for development of functional disorders in clinical

practice often used to inhibition main consumer of glucose (brain), i.e. in some critical cases, simply enter into a coma.

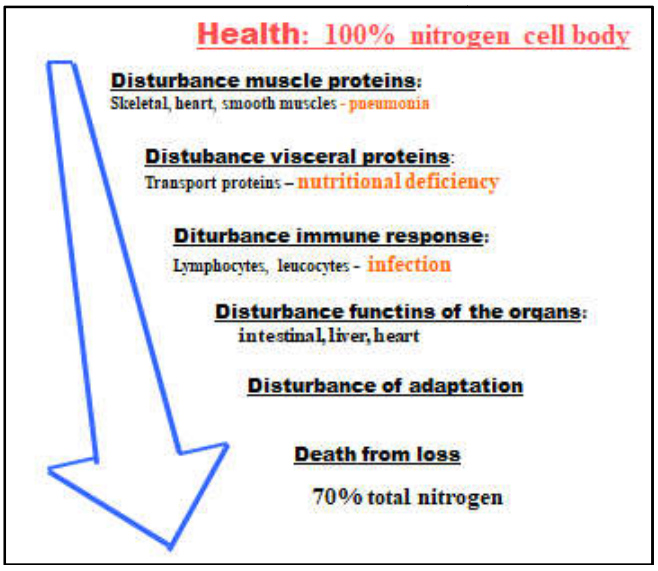

Fig. 2. Development of functional disorders in the dynamics of long-term fasting

Unfortunately, changing the ratio of macronutrients in the" food pyramid" is impossible to change their ratio in the "energy pyramid". This is reason for appear violations in the energy supply of human life (Fig. 3).

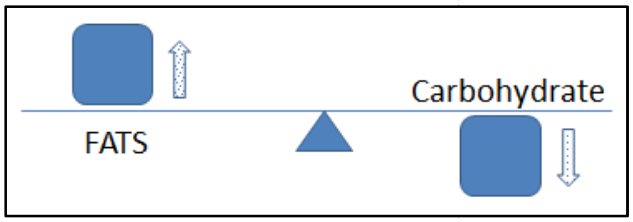

Fig. 3. Changes in human lifestyle which led to the development of energy imbalance

As seen from figure 3, the amount of body fat increases against the background of decrease in the availability of carbohydrates. It seemed that you just need to reduce the amount of fat in the diet, on the one hand, and increase the proportion of carbohydrates, on the other, but there are a lot of difficulties. Even lean meat contains about 30% fat (the fatter meat, is more tasty), and meat with content very low fat often becomes inedible. There are big problems with an increase in the diet of carbohydrates. Excess glucose in the blood is transformed into fat. Therefore, nutritionists must recommend reducing not only fat intake, but also carbohydrates. Let's analyze the consequences of such an energy imbalance (Fig. 4).

- To improve the body's provision in glucose increases appetite, and this contributes to the development of the first criterion MetS–obesity.
- To improve the provision brain in glucose can be by increasing its transport or increase blood pressure, which contributes to the development of the second criterion MetS – hypertension.
- Excess fat in the blood leads not only to the development of lipidemia, but also poses a serious threat to the processes of life.
  a) Lipids can lead to fat embolism of capillaries and disorders circulatory.
  b) When lipids are increased in the liver, their lipolysis increases to acetyl-CoA. Oxidation of acetyl-CoA in liver promotes the formation of ATP, which is used to maintain the energy-dependent process of gluconeogenesis, but deficiency of the substrate (amino acids), the rate of gluconeogenesis reduced and decreases ATP energy. This leads to an increase in the coefficient ATP/ADP, this helps to inhibit the oxidation of acetyl-CoA and stimulates the condensation of two molecules of acetyl-CoA in acetoacetate and then oxybutyrate and acetone or stimulated ketogenesis, which is a threat to life. To reduce the amount of fat oxidation, it is necessary to reduce their entry into the circulation or keep fats in the depot, which is done by increasing insulin secretion, which causes the development of hyperinsulinemia (HI) in obese individuals (Erion, 2017).

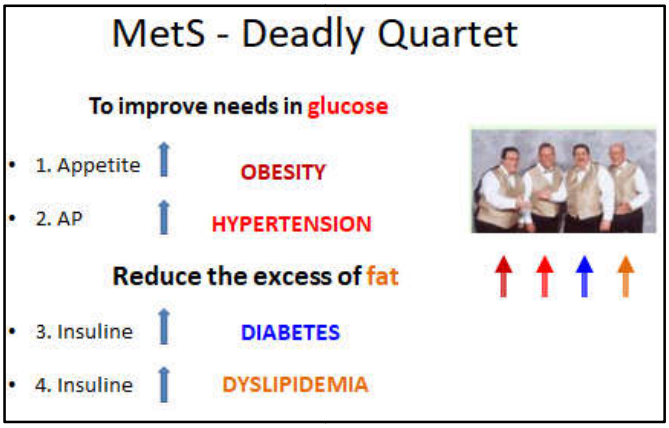

Figure 4. Energy imbalance – the cause development main symptoms of MetS or «the deadly quartet»

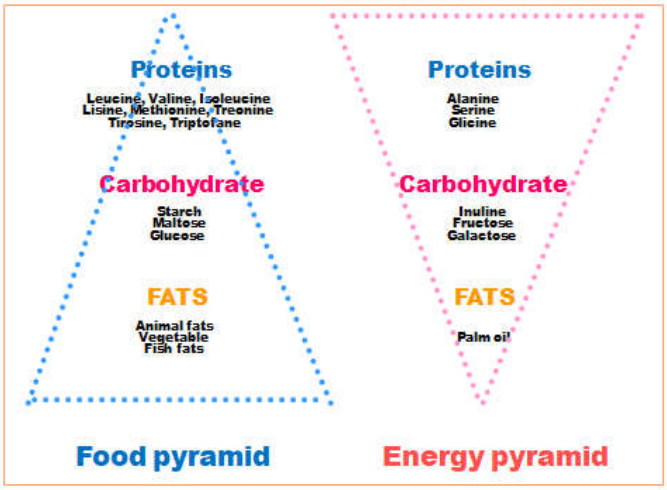

Figure 5. Nutritional compounds for maintenance activity of food and energy pyramids

Insulin leads to the development of hypoglycemic coma and impaired metabolic processes, so the body begins to protect itself from HI through the development of insulin resistance (IR) or develops the third criterion MetS–type 2 diabetes. In this regard, IR should be considered as an adaptive reaction of the body, and not pathological, as is usually. HI activates

lipogenesis and inhibits lipolysis, which leads to the development of atherogenicdyslipidemia, i.e. this is the reason for the development of the fourth criterion MetS. In this regard, the main way of prevention and treatment of MetS are measures aimed at correcting the energy imbalance. In this regard, you should again refer to Figure 1. Food and energy pyramids differ not only in the ratio of macronutrients, but also in food compounds for their functioning (Fig. 5). If in the food pyramid the main nutrient is carbohydrates, then in the energy pyramid – fats. In addition to the ratio of macronutrients, these pyramids differ in the composition of food compounds necessary to ensure the activity of their metabolic processes. Thus, for the food pyramid, saturated fats are required as basic, polyunsaturated plant and fish fats for constructing cell membranes and synthesizing biologically active compounds; Anabolic amino acids (leucine, valine, isoleucine), irreplaceable (lysine, methionine, threonine) and mediator (tyrosine, phenylalanine) are required as proteins; as carbohydrates – starch polysaccharide, maltose disaccharide and glucose monosaccharide. In the energy pyramid, saturated short-chain (4 - 10 carbon atoms) triglycerides, such as palm oil, are suitable as fats; as proteins –gluconeogenic amino acids (alanine, serine, glycine); as carbohydrates – polysaccharide inulin, monosaccharides fructose and galactose. In other words, all food compounds should be divided into two groups: some are required for the food pyramid, but have a negative impact on the functioning of the energy pyramid. For example, glucose promotes the secretion of the hormone insulin and the activation of metabolic pathways that promote protein synthesis and repair and renew cellular structures (rehabilitation) and store excess energy, but at the same time inhibit energy generation processes. In other words, at the same time the working capacity decreases – “well-fed animal is not a hunter”.

When we work, we use the energy deposited in the body. This is the so-called endogenous nutrition. Nowadays the life style of a person has changed significantly. This is due to decline in physical labor and a predominance of intellectual and operator activities, which led to a reduction in fat consumption and increased need for glucose. This led to the development of a deficit of the one energy source (glucose), against an excess of the other – fats. An energy imbalance has been developed that contributes to the increase of metabolic pathologies – diabetes, obesity and cardiovascular diseases. It is necessary to adjust the energy imbalance by developing a specialized product for the work phase or the post-absorptive period. Based on such principles, we have developed a specialized product for feeding obese patients, to which English patent GB 2496119 of January 22, 2014 was received. This product does not induce the secretion of insulin, so working capacity doesn’t decrease; it contributes to the maintenance of glucose homeostasis, reducing fat deposit and prevents the development of functional disorders using technologies to reduce body weight.
On the other hand, food energy pyramid connections have a negative influence on the processes of rehabilitation. In the literature, a large amount of information about the negative effect of fructose monosaccharide (Mancini, 2015) and palm oil (Asghar, 2017), has accumulated. Many of these aspects have been repeatedly discussed in the scientific literature regarding sugar and its component of fructose as toxic compounds promoting the development of chronic non-infectious diseases. Fructose is not used as an energy source in humans, but in the liver it is converted into glucose and in this form is used as an energy source. During HC diet, insulin secretion occurs, which is an information signal about the excess intake of glucose from food. Therefore, during insulinemia, gluconeogenesis is blocked in the liver and fructose from the food passes through the liver unchanged, which increases fructose level in blood (fructosemia) and lead to the development of its toxic effects. However when fructose enters the post-absorptive period, it totally turns into glucose and has not its toxic effects. Moreover, in the absorptive period fructose promotes activation of lipogenesis and obesity, but in the post-adsorption period it promotes fat oxidation and activation of energy use processes (6 ATP molecules are consumed to synthesize glucose from fructose) and lipid oxidation and a decrease in body mass index are noted. The same dependence is noted for palm oil. Palm oil is not required for rehabilitation processes and entering the absorption period it contributes to the development of lipidemia, but when it enters the post-absorptive period it enhances gluconeogenesis, improves glucose homeostasis and activates utilization and promotes weight loss. Therefore, the phasic nature of the intake of food compounds is an important aspect of maintaining health and developing preventive and curative measures against weight gain. You should also consider another model development of Met S (Fig. 6), which we have already discussed when assessing approaches to the problem of obesity [20], but this model considers the pathogenesis of the development ofMetS somewhat differently and will allow the development of integrated approaches in the development of technologies for the prevention and treatment of Met S.

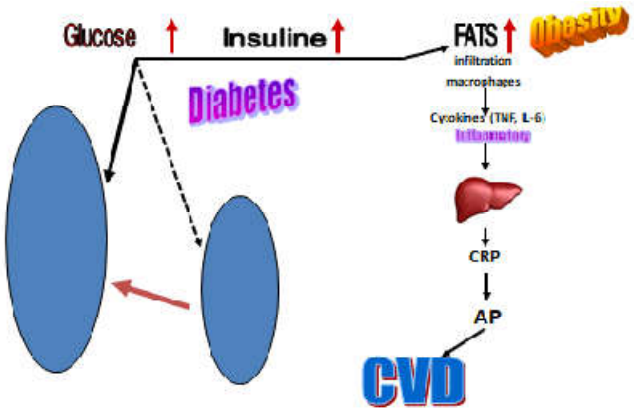

Fig. 6. The model of the relationship between muscle loss and the development of MetS

Reducing the size of muscle mass leads to a decreasein the amount of glucose utilization and there is anincrease in the amount of glucose in the blood(glycaemia). In response to hyperglycemia, increasedinsulin secretion and increased the concentration of thehormone in the blood (insulinemia), i.e. the mainmanifestations of diabetes mellitus developed. Theseinclude glycaemia, insulinemia, and reduced glucoseconsumption by muscles. Under the influence ofinsulin the carbon skeleton of glucose is released intofats, which leads to the development of lipidemia, increasing lipid deposition in adipocytes and thedevelopment of obesity. Rapid growth of adipose tissue leads to a worseningof its blood supply and development of hypoxia,macrophage infiltration and secretion of inflammatorycytokines, so diabetes and obesity are related to chroniclow-grade inflammation (Heilbronn, 2008) Inflammatory cytokines enterthe liver and promote the secretion of the CRP (Garrido, 2015), whichpromotes increased blood pressure and marked thedevelopment of cardiovascular diseases.

Consequently, there is a decrease in the utilization ofglucose and the development of non-communicablediseases (diabetes, obesity, cardiovascular) insarcopenia, so it is necessary to carry out measures toincrease muscle mass in order to interrupt this chain.

First of all, it is an adequate substrate support for the process of protein synthesis. In this regard, it is necessary to use high-grade proteins with a high content of anabolic amino acids, in particular whey protein (Hector, 2015).

Secondly, use technology to activate protein synthesis:

(a) Anabolic resistance exercise (Smeuninx, 2017).
(b) Proteins and amino acids with a high of muscle protein synthesis activity (Cholewa, 2017)
(c) Vitamins and microelements having a positive effect on protein synthesis (Ceglia, 2009).
(d) Can use anabolic sex hormones testosterone and estrogens;
(e) Technologies to restore the function of the insulin receptor (Fougerat, 2018).
(f) Reduce inflammation (Skulas-Ray, 2015).
(g) Use nutraceuticals to reduce absorption and increase glucose utilization (Shan, 2016)

Accordingly, it should completely change the ideology of the fight against obesity, taking as a basis the principles of maintaining glucose homeostasis and technology to combat sarcopenia. Strange as it may seem, these technologies have long been tested in in vitro, in vivo and human studies, only in this review we tried to give them a theoretical basis.

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