

Human Metabolic Syndrome as One of the Last Stages of Postembryonic Ontogenesis. Understanding Human Heart Diseases at Old Age

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Abstract

Current definitions of metabolic syndrome give no idea of the origin and metabolic essence of this medical condition. We have provided arguments that from the point of view of the human post-embryonic ontogenesis, MetS may represent metabolic features of the post-reproductive stage of ontogenesis. At this stage, sexual hormones diminish their influence and energy metabolism in men and women becomes based on predominant utilization of fats and proteins. This proposition is confirmed by the facts that the menopause increases incidence of MetS in aging women. Moreover, in younger women, surgical menopause is strongly linked with a higher incidence of MetS [50]. Because the pressure of natural selection on the post-reproductive stage of ontogenesis was weak, the metabolic features at the post-reproductive stage resemble those of our distant ancestors. We suggest that major symptoms of MetS may originate from the mismatch between the genetically predetermined ancient metabolic pattern and the contemporary lifestyle with excessive consumption carbohydrates and insufficient physical activity of elderly people. Inclusion of ontogenesis into the mechanisms of aging and development of MetS might be helpful in finding pharmacological and non-pharmacological methods to slowdown development of these medical conditions.

Keywords: Human Metabolic Syndrome; Postembryonic Ontogenesis; Human Heart Diseases

Introduction

Physicians have long ago noticed that patients with some pathologies have common features of external appearances and biochemical indices of abnormal metabolism. In 1981 Julius, *et al.* [1] found close relations between insulin resistance and abnormalities in lipid metabolism. This publication stimulated research in the related fields, and by the end of 80s the term “Metabolic syndrome” has been accepted as a separate nosological unit. The metabolic syndrome (MetS) refers to several simultaneously existing risk factors, including insulin resistance, obesity, atherogenic dyslipidemia and hypertension. These conditions are interrelated and share underlying mediators, mechanisms and metabolic pathways [2,3]. The practical significance of defining of MetS as a separate nosological entity was quickly appreciated by physicians all over the World because it allows identification of high-risk patients with atherosclerosis, cardio-vascular diseases, hypertension and type 2 diabetes. It was expected that a comprehensive definition for the metabolic syndrome and its key features will facilitate research into its causes and lead to pharmacologic and lifestyle treatment approaches [2]. However, analysis of the tremen-

dous amount of publications regarding MetS revealed that more than 30 years after defining MetS, there is no deep understanding how and why MetS develops. Much of the literature can be roughly divided into supporters and opponents of considering insulin resistance as the primary symptom for the diagnosing MetS [4-10]. These discrepancies were reflected in the criteria for diagnosing MetS provided by several Institutions, which were thoroughly reviewed in [2]. The discussions become heated by publications that ethnic and racial factors may greatly affect the criteria for diagnosis of MetS [11,12].

This brief review is intended to present a new look on the mechanisms of development of MetS and the type of energy metabolism prevailing in patients with MetS that promotes cardiovascular diseases (CVD).

Metabolic syndrome as the last stage of normal human postembryonic ontogenesis.

The most common definitions consider MetS as a clustering of at least three of the five medical conditions: central (visceral) obesity, high blood pressure, high blood sugar, high serum triglycerides, low serum high-density lipoprotein (HDL), and insulin resistance, and differ only in what symptom is the main one [2-10]. However, these definitions are just enumerations of the symptoms and give no clues to understanding the essence of this medical condition. As possible causes of MetS, there were mentioned genetic predisposition [13-15], sedentary life style or low physical activity [16,17], and excessive alcohol use [18]. However, aging is the major factor for development of MetS [19].

Stančakova and Laakso [21] summarized the results of genetic studies on MetS: "Although several candidate genes regulating primarily lipid metabolism, adiposity, or insulin resistance have been found to be associated with multiple MetS-related phenotypes, they provide so far only a limited evidence for common genetic background explaining the clustering of metabolic traits... Growing evidence suggests the importance of epigenetic mechanisms." This conclusion supports our earlier suggestion [Panov, 2018, 2020; Panov, Dikalov, 2019] that the external appearances and metabolic features of MetS reflect the genetic properties of our distant ancestors.

Aging and MetS have been commonly regarded as the result of accumulation of different kinds of damages caused by oxidative stress and/or improper life style [16-18,22,23]. However, aging is also the process of growing older or changing over time [24]. All human beings after birth undergo changes during postembryonic ontogenesis. Each stage is controlled by different hormones and genes, and MetS is usually observed when an individual enters one of the last stages of ontogenesis, namely the post-reproductive stage, which usually happens at the age of 50 - 55. The sharp changes in appearance and metabolism are particularly evident in women, when they enter the menopause, which increases the risk of MetS by 60% [25]. It is important, that the emergence of MetS in the post-menopause period does not depend on the body mass index (BMI) and physical activity [26], but may depend in women on the dynamics of estrogen decline with age [27]. Interestingly, studies on sex hormone replacement in animals have shown that males receiving testosterone showed MetS deterioration, while females with estrogen replacement showed improvement in their MetS symptoms such as decreased hypertension [28]. This agrees with our suggestion that transition to the post-reproductive stage of normal ontogenesis, which is accompanied by changes in the hormone status, is the major natural cause of MetS.

Due to the fact that for hundreds thousands years the life span of our predecessors was very short, there was no natural selection pressure on the genes governing organism in the post-reproductive stage of ontogenesis. For this reason, people after entering the post-reproductive stage are under control of genes received from our distant ancestors. What was the kind of life of our ancestors? They often starved, were poorly protected from cold and other external conditions, they did not consumed pasta, sugar and had no domestic animals. They had to work hard to hunt or find food, which depending on environmental conditions, could be very different in different geographical locations. As a result, currently existing various mitochondrial DNA haplotypes reflect different ways of metabolic adaptation of ancient populations to different conditions and affect manifestation of the MetS symptoms. From the presented point of view, manifestation of obesity or insulin resistance as the leading symptoms in MetS may depend on the patient's mtDNA background, and can explain variations in prevalence of the MetS-associated diseases observed between populations with different mtDNA haplotypes [29-31].

MetS as a reflection of a new type of energy metabolism in the post-reproductive stage of human ontogenesis

In men, the metabolic transition from reproductive stage to the post-reproductive stage of ontogenesis may begin earlier than 50 years and is not as sharp as in women. Initially, development of some MetS symptoms in men, such as visceral obesity, dyslipidemia and others, may look like primarily associated with the excessive consumption of food, alcohol and sedentary life style, which is true, but this is not all. The much sharper development of the MetS symptoms in women gives much more specific information about the metabolic features of the post-reproductive stage of ontogenesis.

Before the menopause, women are relatively protected against CVD as compared with men. The reasons for this sex difference are not completely understood, but hepatic fatty acid metabolism may play a role [32]. Studies of fatty acids metabolism in young men and women have shown that in comparison with men, young women partition fatty acids towards ketone body production rather than VLDL-TAG, which may contribute to their more advantageous metabolic profile, as compared with young men [32]. However, the postmenopausal status had a pronounced effect on the characteristics of small VLDL particles, which were considerably enriched in triglycerides [33]. People living in the Northern countries at age after 50 often develop visceral obesity with bulky body and other signs resembling their distant ancestors, which are similar to characteristics of the contemporary indigenous populations of the North. Thus, we can conclude that men and women at the age after 50 - 55 switch to the type of metabolism similar to our distant ancestors when fats and proteins were the main source of energy. From this point of view, symptoms of MetS reflect this transition. Some of MetS associated pathologies, like dyslipidemia and T2D, may arise from the inconsistencies between the “new” metabolism adapted to fasting, food rich in fats and proteins and active life, and the “old habits” of excessive food consumption rich in carbohydrates and sedentary life style. Naturally, in different parts of the World variations of MetS are expected to be associated with variation in mtDNA haplotypes.

Major features of energy metabolism in the heart after transition to the post-reproductive stage of ontogenesis

It is known that hearts of young animals no less than 90% of required energy derive from β -oxidation of fatty acids [34]. Recently, we have shown that mitochondria from heart and brain oxidize fatty acids only in the presence of the so called supporting metabolites, which are metabolites from catabolism of carbohydrates (pyruvate), amino acids (glutamate), or intermediary metabolites of the tricarboxylic acids cycle (succinate) [35,36]. For a number of reasons, fatty acids metabolism at the mitochondrial level was not studied well. However, we can suggest that in young animals and humans, the sex-dependent differences in fatty acids metabolism may be caused by differences in the origin of supporting metabolites: in females they originate predominantly from glucose (pyruvate), in males from catabolism of proteins (glutamate) [32]. After ontogenetic transition to the post-reproductive stage, both men and women oxidize fatty acids supported by metabolites derived from catabolism of proteins. This is an interesting and important subject for futures studies.

As we have shown earlier, oxidation of fatty acids by heart mitochondria in the presence of supporting substrates results in several-fold increase in production of reactive oxygen species [37,38]. There is a growing evidence that in patients with MetS mitochondrial dysfunction may lead to obesity and insulin resistance [39,40]. We have presented arguments that the major radical that causes mitochondrial dysfunction is the protonated form of superoxide radical, namely perhydroxyl radical (HO_2^*) [37,38,41]. The major damaging effect of HO_2^* consists in activation of the isoprostane lipid peroxidation (IPLP) [41], which produces a racemic mixture of hundreds of biologically active and toxic products that cause numerous and different lesions to mitochondria gradually causing wear and tear of mitochondrial and cellular functions [38,42]. We have suggested that actually only after transition of the general metabolism to the post-reproductive state and development of MetS the rate of aging may accelerate manifold [37,38,42].

The ways of protection from accelerated aging and development of the MetS associated pathologies

As it happened many times in the history of Medicine, sometimes physicians use intuitively methods of treatment of diseases without exactly knowing the causes and mechanisms of a disease. As regards MetS, physicians long time ago recommend increased physical activ-

ity and restrictions in food consumption for the prophylaxis of type 2 diabetes and cardiovascular diseases. Now we know that the major mechanism of these positive impacts consists in slowing down the rate of oxidative stress and thus slowing down aging.

Reactive oxygen species are constantly produced by mammalian mitochondria at potentially 11 different sites, and the rate of ROS (superoxide radical + H₂O₂) production depends on substrates oxidized by mitochondria [43, 44]. Six sites of superoxide production are controlled by the redox isopotential pool of NADH/NAD⁺, about -280 mV, and five sites operate at the redox potential of the ubiquinol/ubiquinone (QH₂/Q) isopotential pool, about +20mV [44]. The most active production of ROS occurs during oxidation of fatty acids [39,46-49]. The rates of ROS production vary strongly between organs and tissues [37,44]. Skeletal muscles, heart and brain function in a wide range of workloads. At rest, heart consumes much more oxygen than any other organ and under heavy physical loads oxygen consumption by heart mitochondria may increase 10-fold [47]. Therefore, in heart mitochondria oxidation of fatty acids in the presence of supporting substrates is the only substrate mixture that can provide enough ATP even at the highest workload. If the heart's workload diminishes, the overcharged mitochondria may transfer electrons from the reduced coenzyme QH₂ by reversing electron transport on complex II (succinate dehydrogenase) towards the mitochondrial complex I and complex III and thus increase the rate of ROS production [46,48]. Physical activity diminishes mitochondrial energization and production of ROS, whereas food restriction diminishes supply of supporting substrates thus diminishing ROS production at lower physical activity.

It should also be mentioned, that brain and heart possess an indigenous mechanism for restricting ROS production when mitochondria are at rest. This is the intrinsic inhibition of succinate dehydrogenase (complex II) by endogenous oxaloacetate or malate [49]. However, these metabolic regulations of mitochondrial activity and ROS production have to be further investigated in the future for development of pharmacological methods of slowing down aging and development of MetS.

Conclusion

The hypothesis that Mets represents a natural stage of aging, namely the post-reproductive stage of the human ontogenesis, provides a new approach to understanding mechanisms of aging and development of several diseases typical for aged people. The gender differences in energy metabolism between men and women may be, probably, explained by different hormonal effects on provision of supporting metabolites for beta oxidation of fatty acids, which are the main source of energy in human's heart. This hypothesis can explain the gender differences in the rates of aging and development of the Mets symptoms in men and women.

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