

Neurotrophins, VEGF and matrix metalloproteinases: new markers or causative factors of metabolic syndrome components?

Neurotrofiny, VEGF i metaloproteiny macierzowe: nowe markery czy czynniki sprawcze składowe zespołu metabolicznego?

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Abstract

Currently the number of obese people in the world is still growing, as well as people suffering from other metabolic disorders included in the metabolic syndrome. The factors responsible for this are an incorrect diet, low physical activity, as well as a tendency of the population to aging. Therefore, more research aimed at seeking potential factors that could in the future be useful in the prevention or treatment of obesity and related diseases is carried out. In this article we present a few selected biochemical markers, affecting the metabolism of carbohydrates and lipids in a way that is not always clear and obvious.

Key words:

metabolic syndrome, brain-derived neurotrophic factor, glial cell line-derived neurotrophic factor, vascular endothelial growth factors, matrix metalloproteinases

Streszczenie

Obecnie obserwuje się ciągły wzrost liczby osób otyłych i cierpiących na zaburzenia metaboliczne wchodzące w skład zespołu metabolicznego. Za wspomniane zjawisko odpowiedzialny jest nieprawidłowy sposób odżywiania, mała aktywność fizyczna, a także tendencja do starzenia się społeczeństw. W związku z tym prowadzone są liczne badania ukierunkowane na poszukiwanie potencjalnych czynników, które mogłyby w przyszłości być wykorzystane w prewencji lub leczeniu otyłości i chorób z nią związanych. W artykule prezentujemy kilka wybranych markerów biochemicznych mających wpływ na metabolizm węglowodanów oraz lipidów, jednak w sposób nie zawsze jasny i oczywisty.

Słowa kluczowe:

zespół metaboliczny, czynnik neurotroficzny mózgowopochodny – krew, czynniki neurotroficzne glejopochodne – fizjologia, czynniki wzrostu śródbłonna naczyniowego, metaloproteiny macierzowe

Introduction

The metabolic syndrome is a disease that consists of many interrelated metabolic disorders. The components of the metabolic syndrome include insulin resistance, glucose intolerance, dyslipidemia, visceral obesity, and hypertension [1]. Obesity is a major risk factor for other disorders that make up the metabolic syndrome and contributes to the development of many diseases of the cardiovascular system [2]. Currently the number of obese people in the world is increasingly growing, which is caused mostly by physical inactivity as well as incorrect nutrition

[3]. In addition, we observe worldwide aging of population and it is known that the aging process also leads to the deterioration of metabolic processes [4]. Therefore, more research aimed at understanding the pathogenesis of metabolic abnormalities is carried out. Moreover, potential factors that could in the future serve as targets for the prevention and treatment of obesity are sought. In recent years, several factors were described the association of which with obesity and certain components of the metabolic syndrome have been shown. These include leptin that is secreted by white adipose tissue and reduces appetite [5]. Much is also known about adiponectin, the level of which

correlates negatively with BMI [6] and an increase in its plasma concentration is caused by weight reduction [7]. Another adipokine with high expression in abdominal adipose tissue is resistin, the name of which reflects its biological nature that is to limit insulin sensitivity and glucose tolerance [8]. It seems that the adipose tissue is a big endocrine organ that produces many signal substances, not only mentioned here adipokines, but also many other compounds that play a role in metabolic processes. The above-mentioned adipokines have been the subject of many research studies on obesity and insulin resistance, and have been devoted much space in the literature. Nevertheless, in this review we will present less known biochemical markers that are associated with changes in the adipose tissue and seem to affect the metabolism of glucose and lipids, but not always in a clear and obvious way.

Brain-derived neurotrophic factor

Brain-derived neurotrophic factor (BDNF) is a member of nerve growth factor family. It was discovered in 1982 as the second neurotrophin [9]. BDNF expression takes place both in the central and peripheral nervous system, as well as in adipose cells, skeletal muscle, or in liver. Neurons in the hypothalamus, as well as in other areas of the central nervous system involved in the regulation of appetite, also produce this neurotrophin [10]. BDNF plays an important role in the modification of synaptic efficacy [11] and takes part in the survival and growth of neurons [12]. BDNF is also considered to be a mediator of brain plasticity and its lower concentration is linked to increased vulnerability for many psychiatric diseases [13].

In addition to the undeniable role that this factor plays in the nervous system, it is also known for its nonneuronal function. At the end of last century, it reported that BDNF takes part in the regulation of body weight and energy expenditure, inducing weight loss and decreasing appetite in rats [14,15]. Until now this endocrinological function of BDNF has been still studied and its metabolic exponents have been repeatedly tested by studies in mice. Hanyu et al. proved that subcutaneous supply of BDNF significantly decreases normal mice's food consumption and improves glucose tolerance [16]. Studies in mice suffering from diabetes led to similar conclusions – Nakagawa et al. revealed this factor reduces food intake and glucose plasma level in obese diabetic mice [17]. Another study proved that although subcutaneous administration of BDNF does not change body weight and white adipose tissue weights in obese diabetic mice, it improves lipid metabolism, which is reflected in a reduction of total cholesterol [18].

Similar activities of BDNF are observed in humans. Lommatzsch et al. demonstrated that concentration of BDNF correlates negatively with weight [19]. Another interesting fact was discovered during research on concentration of BDNF in the elderly. It was then found BDNF plasma level correlates negatively with age [20]. In turn, Chaladakov and partners proved that the plasma level of BDNF is significantly lower in patients with the metabolic syndrome and with the acute coronary syndrome as

compared with the circulating level of control subjects [21,22]. These findings suggest important role of BDNF in human diseases connected with hyperalimentation and aging, pointing to its metabolic potential. What is more, in the pathogenesis of obesity, the metabolic syndrome and atherosclerosis, inflammation play an important role. This fact can suggest BDNF acts not only endocrinological but also immunological function and point to the neuroimmune path of activity of BDNF. If it appears that the lower concentration of BDNF is associated with age, it is not entirely clear whether the decrease of its concentration leads to obesity or obesity lowers the level of BDNF. Chaladakov and partners formulated the hypothesis of metabotropic deficit, which states that the lack of neurotrophins can lead to the development of metabolic diseases [23]. Also Hristova et al. favor neurotropic the hypothesis of the metabolic syndrome [24]. Although this hypothesis seems to be reliable, it requires confirmation in a larger amount of research. The more that the available literature data are not always consistent. Gajewska et al. studying the concentration of BDNF in obese and normal weight patients said that the serum level of BDNF did not differ in subjects, regardless of age, gender, obesity or declared level of physical activity [25]. Similarly, Lee et al. found no differences in plasma concentrations of BDNF in men with the metabolic syndrome in relation to the men's healthy controls [26]. Moreover, as already mentioned, it is unknown what is the primary cause of the metabolic syndrome – we are not sure whether we are dealing with the initial reduction of synthesis of BDNF leading to overeating or excessive consumption of food resulting in a decrease in the production of BDNF. Marosi et al. write that the long-positive energy balance can result in reduced secretion of BDNF in the CNS, what, in turn, may lead to the development of obesity and the metabolic syndrome [10]. Following this line, it seems that the decrease in the serum level of BDNF observed in many studies is only the last link in the pathogenesis of the metabolic syndrome.

There are reports on the impact of physical activity on the concentration of BDNF. Damirchi et al. have studied changes in the concentration of triglycerides, HDL cholesterol, insulin resistance and BDNF in men with the metabolic syndrome performing regular aerobic physical exercise compared to the group of men with the same disease who do not perform physical activity. It has been shown that all of these factors decreased during the training program. What is most interesting, as long as 6 weeks after the end of the exercise, lipid parameters remained lowered, but plasma concentrations of BDNF returned to the baseline [27]. The results highlight the importance of physical exercise in the treatment of the metabolic syndrome, thus preventing related diseases.

Also interesting seems to be a link between the polymorphism of gene for BDNF and obesity [28]. It is known that the polymorphism consisting of amino acid substitution of methionine (Met) for valine (Val) at amino acid position 66 of the BDNF protein is associated with eating disorders such as anorexia and bulimia nervosa [29]. It is also known that the Val66Met polymorphism is associated with the development of mental diseases such as schizophrenia [30] and the bipolar disorder [31].

Therefore Bonaccorso et al. decided to conduct a study to determine whether a variant *Val66Met* is associated with weight gain in patients suffering from the bipolar disorder during their treatment with antipsychotics. It has been shown that individuals with variant *Val66Met* have, inter alia, higher BMI and are also characterized by a higher insulin resistance. This fact allows to recognize the mentioned genotype as a potential factor in the development of obesity and insulin resistance in people with the bipolar disorder during the treatment with antipsychotics [32].

The aforementioned results of several studies suggest that BDNF plays an important role in metabolism. We have a lot of information about the interdependence of this neurotrophin with the components of the metabolic syndrome. Nevertheless, its role has not been fully defined, so it seems that further research in the field of adipobiology has its justification.

Glial cell-line derived neurotrophic factor

10 years after the discovery of BDNF, another neurotrophic factor was described [33]. Glial cell-line derived neurotrophic factor (GDNF) is a member of the family of neurotrophins that has some similarities with transforming growth factor beta (TGF β) and is responsible for survival neurons protecting them from damage [34]. Studies have shown that GDNF plays a neuroprotective role in relation to catecholaminergic and sympathetic neurons that takes part in the regulation of intake and energy expenditure. What is more, GDNF and its receptor expression is very high in the hypothalamus [35], which is responsible for directing activities of the autonomic nervous system and takes part in the regulation of food intake, metabolism of carbohydrates and fats.

Because of a neuroprotective role of GDNF, it was tested for efficacy in the treatment of Parkinson's disease. During the study conducted in parkinsonian monkeys, it was noticed that one of the major side effects of intracerebroventricular injections of recombinant methionine human GDNF was weight loss [36]. Nutt et al. reached the similar conclusions during a randomized, double-blind trial performed on people suffering from Parkinson's disease. The study found that GDNF did not reduce the symptoms of parkinsonism, it recognized, however, that above a certain dose, the administration of GDNF resulted in weight loss in the majority of patients [37].

A lot of relevant information on GDNF was provided by an experiment conducted by Mwangi et al. They tested the capacity of GDNF to prevent obesity in mice, induced by a diet with an increased amount of fat. They used transgenic mice with the overexpression of GDNF in glial cells and wild-type mice as the control group. The study revealed that transgenic mice are protected from obesity caused by a high-fat meal and from hepatic steatosis, too. What is more, they found mice are resistant to a high-fat diet induced glucose intolerance and insulin resistance [38]. These reports suggest GDNF has a protective role against the development of major components of the metabolic syndrome and, similarly to the above-mentioned

BDNF, GDNF signs in suggested metabotropic hypothesis of the metabolic syndrome.

Vascular endothelial growth factors

A growth factor which is more frequently described is the vascular endothelial growth factor (VEGF). VEGF belongs to the family of growth factors that consists of VEGF-A,-B,-C,-D,-E,-F and placenta growth factor (PGF). VEGFs are involved in the formation of new blood vessels from pre-existing vessels. Additionally, VEGF-D,-E play an important role in lymphangiogenesis. It is known that these factors are involved in embryogenesis, wound healing, tumor metastasis or rheumatoid arthritis [39]. However, VEGFs are also recognized to have a metabolic effect.

VEGF-A is probably the most widely described member of the family of VEGFs. In literature, there is also a lot of information about its involvement in the metabolism. However, the reports are frequently conflicting. There is information saying that the concentration of VEGF correlates with BMI, that higher levels are observed in overweight and obese patients [40,41], which denies other studies [42] including the experiment conducted by Pasarica's et al. [43].

Pasarica and partners examined the hypothesis suggesting that during the obesity development of blood vessels is insufficient, which, in turn, results in hypoxia adipocyte and can lead to a local inflammation. The results of the experiment confirmed a previously established hypothesis including lower concentration of VEGF in obese patients and proved the reduction of the oxygen partial pressure in adipose tissue leads to the development of an inflammation in humans. Both hypoxia and inflammation are, in turn, they are associated with the insulin sensitivity. It is known that hypoxia causes glucose intolerance [44], and an ongoing low-grade inflammation leads to insulin insensitivity [45] which is associated with the metabolic syndrome.

Following this line Elias et al. conducted an experiment on transgenic mice with the overexpression of VEGF in white and brown adipose tissue. The study showed that transgenic mice presented an increase in the number of medium size adipocytes, whereas in the control group they showed an increase in the number of large adipocytes. Therefore, it appears that the VEGF overexpression protects against the development of obesity. Moreover, the transgenic mice showed an increased thermogenesis activity. Researchers also discovered that transgenic mice were protected from glucose the intolerance and insulin resistance induced by diet and from local hypoxia, too. Furthermore, in their white and brown adipose tissue, increase in the number of macrophages M2 and decrease of M1 was observed [46]. Macrophages M2 are considered to be anti-inflammatory cells, while M1 have pro-inflammatory effects [47]. It seems that the overexpression of VEGF prevents local inflammation that may result in the loss of insulin sensitivity.

Nevertheless, as noted earlier, in the literature there are many conflicting data on the correlation of VEGF with body

weight. A Noteworthy experiment was performed by Wada et al., who have come to different conclusions than the above-mentioned researchers. They found a correlation between plasma levels of VEGF-A and BMI and waist circumference. What is more, the researchers also focused on VEGF-C and its role in metabolism, stating that the concentration of this growth factor correlates with parameters of glucose and lipid metabolism. They recognized that independent determinants of concentration of VEGF-A were age and BMI, whereas independent determinants of VEGF-C were age, triglycerides, non-HDL and HbA1c [48]. This study suggests that VEGF-A is associated with clinical markers of the metabolic syndrome, whereas VEGF-C plays an important role in the shaping of the biochemical components of this disease.

The effect exerted by VEGF-C was also examined during the experiment on rodents. Karaman et al. blocked receptors for VEGF-C and VEGF-D in transgenic mice, thereby improving their insulin sensitivity. Moreover, they revealed VEGFR blockade protects against hepatic steatosis, reduces fat tissue infiltration by macrophages and also changes the ratio of the number of macrophages M2 / M1 present in the adipose tissue in favor of the former [49]. Perhaps VEGF-C plays just as important or even more important role in the development of the metabolic syndrome than VEGF-A. Nevertheless, this statement requires further confirmation, the more that a lot of research on members of the VEGF family often lead to contradictory conclusions.

Matrix metalloproteinases

The last group of biochemical factors presented in the context of obesity and metabolic consequences in this review are metalloproteinases. In contrast to the aforementioned factors, they do not belong to the group of growth factors, but also appear to fall into a group of potential factors that may be associated with the components of the metabolic syndrome. Matrix metalloproteinases (MMPs) are a group of enzymes that degrade extracellular matrix components. While in the tissues there is nothing alarming, the activity of matrix metalloproteinases is low. However, their activity is considerably influenced by an ongoing inflammation and secreted growth factors. The activity of these endopeptidases is also controlled by the tissue inhibitors of metalloproteinases (TIMPs) [50].

It is known that MMPs take part in many processes, such as angiogenesis, bone resorption, or wound healing [51]. Some reports suggest that MMPs, especially MMP-2, play an important role in the metabolism of adipose tissue taking part in the modulation of adipogenesis and reconstruction of extracellular matrix [52]. MMPs have been also extensively studied in connection with their role in the pathogenesis of atherosclerosis and cardiovascular disease. MMP-9 is attributed to a particularly important role when it comes to the instability of atherosclerotic plaques [53]. Both of this metalloproteinases, MMP-2 and MMP-9, have significantly greater expression in the atherosclerotic vascular wall compared to a healthy blood vessel wall [54].

The two above-mentioned metalloproteinases were tested for their connection with the insulin resistance. Miksztowicz et.al found that the activity of MMP-2 and MMP-9 was reduced in adipose tissue of rats that were drinking water with sucrose compared with the control group. There were, however, no differences in the plasma concentration of endoproteinases. Besides, researchers found that adipocytes in the study group had larger sizes and that the blood vessel density was lower than the in the control group [55]. These latter results are corresponding with results observed in experiment conducted by Pasarica et al. that we mentioned above. Maybe a lower expression of MMPs hinders the expansion of adipose tissue and deepens the effect of pending local inflammation. However, some reports from the experiments performed on rodents contradict the results obtained by Miksztowicz et al. [56]. Moreover, many studies in humans, evaluating the concentration of MMP-2 and MMP-9 have shown that their plasma levels are increased in patients with the metabolic syndrome with and without diabetes mellitus [57].

What is worth noting are the results of the study which evaluated simultaneously plasma concentration MMP-2, MMP-9 and VEGF. Erman et al. showed MMP-2, MMP-9 and VEGF levels were significantly higher in patients with the metabolic syndrome compared to a healthy control group [58]. These results seems to be totally inconsistent with the previously quoted findings in a rat model of obesity performed by Miksztowicz. The authors argue that the concentration of MMPs is not affected by individual components of the metabolic syndrome, while changes in their concentrations are caused by generally understood metabolic dysregulation. Certainly further studies are needed to support or deny current findings.

So far, the potential links between metabolic markers and all components of the metabolic syndrome were showed, with the exception of hypertension. However, there are reports that investigated the relationship between blood pressure and level of metalloproteinases. Yasmin et al. found that MMP-2 and MMP-9 were elevated in patients with isolated systolic hypertension as compared to the control group. Moreover, they found that MMP-9 may be an independent predictor of aortic stiffness, even in young healthy people with compensated blood pressure [59]. Similar conclusions were made by Belo et.al examining the concentration of MMP-2 in obese children and adolescents. They found a positive correlation between serum MMP-2 and blood pressure, not only in obese children and adolescents, but also in the control group [60]. Elevated levels of MMP-2 were also observed during animal tests [61]. It seems that MMPs contribute to the development of many diseases of the cardiovascular system, including hypertension.

Summary

It appears that factors mentioned above can serve as potential markers of the dysmetabolic state. The key question remains whether these factors are indicators of the current

disturbed metabolic state or whether they are the cause of these disorders. Perhaps further research will contribute to these factors serving not only for the diagnosis of metabolic diseases but will also be used in the treatment of diseases. Such capabilities could potentially be associated with VEGF, the increased expression of which leads to an increase in thermogenesis and consequently weight loss, or GDNF, whose supply may be helpful in the treatment of obesity. Similarly, efforts to increase the concentration of BDNF seem to be helpful in the prevention and treatment of obesity and diseases associated with it. Maybe it will also be possible to identify people who benefit from the use of metalloproteinase

inhibitors. But the fact is that the development of adipose tissue is complicated and multifaceted, so despite many studies, knowledge about changes in adipose tissue is incomplete. Still little is known about the mechanisms of interaction between cytokines and growth factors involved in the development of adipose tissue and induction of insulin resistance. A better understanding of what affects their expressions, will certainly contribute to an adoption of a more detailed targets of potential actions in the future. Until now, a healthy lifestyle is the best way to prevent and treat obesity, and thus, related diseases.

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