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PRACA POGLĄDOWA
REVIEW

Selected adipokines as potential prognostic and diagnostic agents in treatment of metabolic disorders associated with obesity

Wybrane adipokiny jako potencjalne czynniki prognostyczne i diagnostyczne w leczeniu zaburzeń metabolicznych towarzyszących otyłości

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ABSTRACT

Obesity is a chronic disease that constitutes a global problem and a serious challenge to public health. In the course of this disease, excessive accumulation of fat tissue occurs in the body, which not only leads to an increased risk of health complications, but also negatively affects the quality of life. Fat cells – adipocytes – are responsible for the biosynthesis and release of adipokines, among others, leptin, visfatin, chemerin and omentin-1. They are active biological substances, including mediators of inflammation, which may lead to the development of metabolic disorders in the body. The above-mentioned properties of the described adipokines make it possible to potentially use them as diagnostic and therapeutic factors in the course of obesity and its accompanying disorders such as insulin resistance, type 2 diabetes mellitus, and cardiometabolic complications. Despite significant progress in understanding the role played by the discussed adipokines, further research is necessary to precisely describe the mechanisms of action and to determine the precise relationship between their plasma concentrations and state of diseases.

KEYWORDS

obesity, type 2 diabetes mellitus, metabolic disorders, adipokines, leptin, visfatin, chemerin, omentin-1

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STRESZCZENIE

Otyłość to przewlekła choroba, stanowiąca globalny problem i poważne wyzwanie dla zdrowia publicznego. W jej przebiegu dochodzi do nadmiernego nagromadzenia się tkanki tłuszczowej w organizmie, co prowadzi nie tylko do wzrostu ryzyka wystąpienia powikłań zdrowotnych, lecz także negatywnie wpływa na jakość życia. Komórki tłuszczowe – adipocyty – są odpowiedzialne za biosyntezę i uwalnianie adipokin, do których należą m.in. leptyna, wisfatyna, chemeryna oraz omentyna-1. Są to aktywne substancje biologiczne, mogące wykazywać właściwości prozapalne lub przeciwzapalne. Zaburzenie równowagi pomiędzy adipokinami prozapalnymi i adipokinami przeciwzapalnymi może prowadzić do rozwoju zaburzeń metabolicznych. Wspomniane właściwości adipokin sprawiają, że możliwe jest ich potencjalne wykorzystanie jako czynników diagnostycznych oraz terapeutycznych w przebiegu otyłości, a także towarzyszących jej zaburzeń, takich jak insulinooporność, cukrzyca typu 2 czy powikłania kardiometaboliczne. Pomimo znacznego postępu w poznaniu roli, jaką odgrywają omówione adipokiny, konieczne są dalsze badania, których wyniki umożliwią precyzyjne omówienie mechanizmów ich działania oraz określą ścisłe zależności ich stężeń w osoczu od stanu choroby.

SŁOWA KLUCZOWE

otyłość, cukrzyca typu 2, zaburzenia metaboliczne, adipokiny, leptyna, wisfatyna, chemeryna, omentyna-1

Introduction

The ongoing obesity pandemic, which, next to type 2 diabetes mellitus (T2DM) is another noncommunicable epidemic of the 21st century, constitutes a complex health challenge. This disease may develop as a result of the potential coexistence of several different pathological mechanisms. The leading cause of obesity is a disturbed balance between the supply and consumption of energy substrates. This disproportion leads to an increase in the volume and mass of adipose tissue, contributing to changes in its histological structure and deformation of the body figure. The progressive accumulation of triglycerides and triacylglycerols in adipocytes leads to their hypertrophy, and then, after exhausting the ability to increase the size of the mentioned cells, it indirectly contributes to the maturation of preadipocytes, which determines the hyperplasia of fat cells. The described changes in the "energy store of the system", i.e., adipose tissue, are responsible for the intensification of disorders of immune regulatory mechanisms, which is associated with the appearance of chronic – initially local – inflammation. Generalized, progressive inflammation contributes to activation of the biosynthesis and release of pluripotent, regulatory molecules – adipocytokines. The progressive, systemic expansion of immune cells, such as lymphocytes or macrophages (with a changed phenotype – M1), additionally intensifies the "production" and secretion of pro-inflammatory macromolecules, which affect distant tissues, systems and organs, (e.g., the liver, skeletal muscles, nervous and immunological systems) determine the development of disorders within them related to the emerging inflammation [1,2,3]. Owing to the complexity of the above-mentioned processes, adopting a comprehensive approach to understanding the mechanisms of relationships related to the occurrence of obesity, insulin resistance and T2DM is necessary to undertake an effective preventive, diagnostic and therapeutic strategy.

Mechanisms underlying insulin resistance

Insulin resistance (IR) is a pathogenetically complex disorder characterized by an abnormal cellular response of target tissues to the action of insulin in relation to target tissues (for the action of the mentioned anabolic hormone), such as adipose tissue, muscle tissue or the liver. The result is a reduced tissue sensitivity to the action of this hormone, a reduced tissue response to the presence of glucose in the bloodstream, and a reduced glucose uptake into the cells. The above-mentioned abnormalities contribute to the disturbance of systemic glucose homeostasis. In response to impaired glucose uptake from peripheral blood, the secretion of insulin secreted by pancreatic β-cells increases [4]. The result of this is a further progression of carbohydrate metabolism disorders along with the accompanying development of impairment of the body's lipid metabolism, ultimately contributing to the "exhaustion" of the secretory capacity of pancreatic β-cells in addition to an increasing reduction in tissue response to insulin. IR is a key feature of T2DM [5]. An illustrative mechanism of the development of IR is shown in Figure 1.

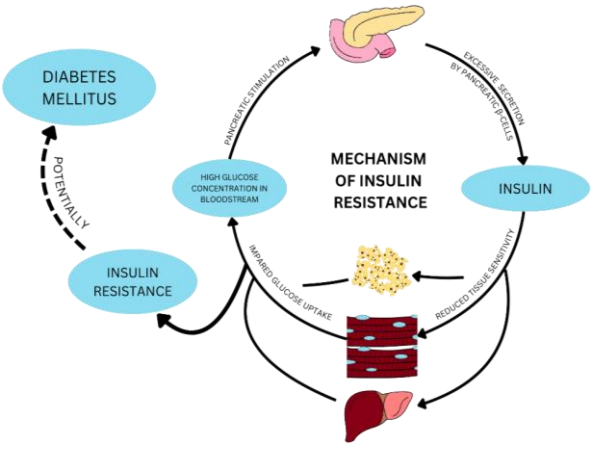

Fig. 1. Mechanism of insulin resistance (based on [4,5]).

The pathogenesis of IR development is not fully known. Factors that increase the risk of IR are the same as those leading to obesity. They include environmental factors such as high-calorie meals, a sedentary lifestyle and insufficient physical activity. Moreover, the phenomenon of IR is also caused by genetic factors, physiological aging processes, and disorders in the intestinal microbiome, which depend on diet and lifestyle. Factors occurring at the cellular level are also of great importance in the development of IR, such as inflammation, oxidative stress, disturbed cell regeneration processes, chronic inflammation (related to obesity). The increased amount of adipose tissue correlates with the severity of adipocyte apoptosis as a consequence of a reduced oxygen supply. As a result, there is increased secretion of pro-inflammatory adipocytokines, reactive oxygen species (ROS) and free fatty acids, the source of which are adipocytes. These mediators have a direct impact on both cellular organelles (mitochondria, endoplasmic reticulum, lysosomes) and entire tissues (muscle, adipose tissue) [5,6].
Another described mechanism of IR formation is direct disruption of the insulin signaling pathway. Because of its complex and extensive signaling mechanism, this hormone is particularly sensitive to disruptions in its functioning. On its basis, two molecular mechanisms of IR development can be distinguished [5].

Target cell receptor disorders

Insulin can interact with membrane receptors (IRS), proteins (IRS1, IRS2) and protein-tyrosine phosphatase 1B, which then transmit the signal further in the form of cascades. The reduced expression of IRS membrane receptors and the activity of related kinases have been observed in obese individuals. A decrease in IRS1 phosphorylation was observed in skeletal muscle cells. In the liver, a reduced occurrence of the insulin receptor (INSR) is responsible for the lack of inhibition of gluconeogenesis and glycolysis by insulin [6].

Secondary signal disorders

Protein kinase B (AKT), one of the keys signaling molecules in the insulin cascade, apart from acting within the stem cell, is also secreted into the lumen of blood vessels, which exerts a significant influence on distal tissues through its specific receptors. One of the most important receptors for AKT is GLUT4 (glucose transporter type 4). This protein is responsible for the transport of glucose in muscle tissue and white adipose tissue. Disturbances in AKT phosphorylation due to obesity-related factors significantly reduce the sensitivity of GLUT4 to AKT, which ultimately leads to a reduced glucose uptake and an increased risk of IR [7,8].

Type 2 diabetes mellitus

T2DM is associated with a gradual decline in the ability of pancreatic β-cells to secrete insulin, which is accompanied by IR, and results in decreased tissue sensitivity to insulin. Initially, there is often a relative insulin deficiency and abnormalities in the secretion of this hormone depending on the glucose concentration. These functional abnormalities occur to varying degrees well before the clinical onset of diabetes, either independently or as part of the metabolic syndrome [9,10]. The risk factors for the development of T2DM include genetic predispositions, obesity, a lack of physical activity, an unhealthy diet or smoking. In addition, it should be mentioned that taking certain medications such as antipsychotics, diuretics, immunosuppressants, or beta-blockers, may also contribute to the occurrence of glucose metabolic disorders in the body [11]. Symptoms that may indicate T2DM include polyuria, excessive thirst, or fatigue. In some cases, the disease may initially be asymptomatic. Untreated or improperly controlled T2DM may lead to serious complications, e.g. nephropathy, retinopathy, neuropathy or diabetic foot syndrome caused by the frequent state of hyperglycemia. This is why prevention, early diagnosis and effective pharmacotherapy are so important to minimize the impact of the disease on the body. It should be mentioned that modifying various aspects of lifestyle by introducing healthy habits (including increasing physical activity, maintaining a healthy body weight, quitting smoking, or performing regular check-ups) can help both in the prevention and effective treatment of the disease in question [9].

Adipocytokines (adipokines) – characteristics

Adipokines are proteins produced by fat cells (adipocytes) that perform various functions in the body. In T2DM, adipokines are divided into pro--inflammatory (e.g. leptin, resistin, visfatin, chemerin and dipeptidyl peptidase 4) and anti-inflammatory (e.g. adiponectin, omentin-1, cardiotrophin-1). An imbalance between pro- and anti-inflammatory adipokines lays the basis of IR, T2DM and damage to blood vessels, which may result in, among others, cardiovascular disorders [12]. In this study, we will analyze the potential therapeutic and prognostic perspectives of selected adipokines: leptin, visfatin, chemerin and omentin-1 in the treatment of metabolic disorders associated with obesity, while paying attention to, among others, aspects of cardiovascular diseases [13].

Leptin

Detection of the obesity gene in 1994 became significant evidence for the statement that adipose tissue performs important regulatory functions in the body. The product of this gene is leptin, which is a protein with multidirectional effects – neurohormonal, metabolic, immunomodulatory. This adipokine plays an important role in controlling energy homeostasis by inhibiting the orexigenic appetite-stimulating system (neuropeptide Y-NPY and Agouti protein – AgRP) and stimulating the anorexigenic appetite-suppressing system. As a result of these activities, there is a feeling of satiety, decreased appetite and food consumption, stimulation of thermogenesis and increased energy consumption by the body [13]. Obesity is often accompanied by disruption of the proper functioning of the described mechanism owing to the development of tissue resistance to leptin caused by hyperleptinemia. There are many potential mechanisms leading to leptin resistance in obesity, including: negative regulation of signaling of the long isoform of the leptin receptor – ObRb in the hypothalamus, increased signaling of pro-inflammatory cytokines in the brain, and reduced transport of leptin across the blood-brain barrier [14]. The regulation of leptin biosynthesis and secretion is a complex process, dependent on many endocrine, neuroendocrine and paracrine signals. Changes in the leptin concentration in the blood are influenced by factors such as: fasting, food intake, the total fat tissue content and its type (leptin secretion is greater in subcutaneous fat tissue than in visceral fat tissue), some hormones secreted by the pancreas such as insulin, glucagon, or amylin, and it is also assumed that they are also released by other glands, e.g. the thyroid [15]. Many studies have linked hyperleptinemia with the occurrence of IR and T2DM [12,16,17,18]; some also indicate a relationship between an increased leptin concentration in the blood and the occurrence of complications in T2DM including cardiac diseases [19,20,21]. Leptin and insulin have co-regulatory effects in maintaining blood glucose homeostasis and energy metabolism. Leptin inhibits insulin secretion, which in turn stimulates the synthesis and secretion of the above-mentioned adipokine [22]. An illustration of the insulin-leptin negative feedback mechanism is shown in Figure 2.

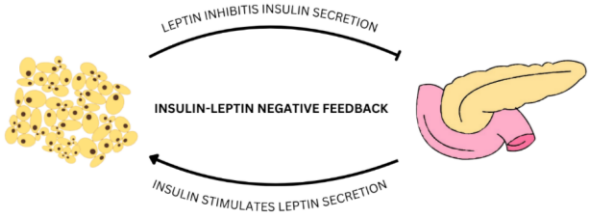

Fig. 2. Insulin-leptin negative feedback (based on [12,16,17,18,22]).

Leptin plays a significant role in the pathogenesis of cardiovascular diseases such as hypertension, atherosclerosis, ischemic heart disease, stroke, myocardial infarction, by participating in processes such as inflammation and oxidative stress, leading to, among others, dysfunction of the endothelium of blood vessels, as well as structural changes in the heart and arteries and instability of atherosclerotic plaque [19]. Moreover, leptin exhibits the potential to determine the likelihood of micro- and macrovascular complications in addition to other cardiac diseases as an independent diagnostic factor. This property can be used in monitoring the health of patients with T2DM [23,24]. Another prognostic application of leptin is the usage of the leptin-to-adiponectin ratio as a biomarker indicating the development of atherosclerosis as it correlates with the amount of intima-media thickness of the common carotid artery. A study was conducted that showed increased leptin expression with decreased adiponectin levels in patients with coronary artery disease [25,26]. In some countries, leptin is employed in the treatment of lipodystrophy with coexisting IR. Lipodystrophy is a rare genetic disease characterized by a deficit or improper development of adipose tissue. Patients with lipodystrophy often suffer from metabolic disorders, including tissue resistance to insulin, excessive fat accumulation in internal organs, and an increased risk of cardiovascular diseases. The use of leptin may help regulate metabolism, improve insulin sensitivity as well as maintain normal blood glucose levels in these patients. Further research is being conducted on the use of leptin alone or in combination with other medicinal substances in the treatment of obesity or other diseases in which its action could help maintain normal glycemic values [17,27,28].

Visfatin

Visfatin (pre-B-cell colony enhancing factor – PBEF-1)/(nicotinamide phosphoribosyltransferase – NAMPT)/(Visfatin/NAMPT) – the presented names are used interchangeably in scientific studies and are expressions of various functions that this protein performs in the body. As a result of research, it was discovered that the mentioned molecule exists in intracellular (iNAMPT) and extracellular (eNAMPT) forms. Initially, it was described as a cytokine stimulating the secretion of pre-B lymphocytes through its stimulating synergistic effect on interleukin 7 (IL-7) and the stem cell factor (SCF), and named the pre-B-1 colony stimulating factor. It was also discovered that the studied protein is an enzyme – nicotinamide phosphoribosyltransferase, taking part in the nicotinamide (NA) pathway, acting by catalyzing the process of converting NA into nicotinamide mononucleotide (NMN), which plays a key role in the biosynthesis of nicotinamide adenine

dinucleotide – NAD+. Research in 2005 showed further properties of this cytokine; it was discovered that it is secreted by visceral adipose tissue, as a result of which it was named "visfatin". Additionally, it has been proven to exhibit insulinomimetic properties, which, according to the descriptions of further experiments, consist in binding and activating insulin receptors, but the connection occurs at a different point of receptor attachment than when activated by insulin. It is now known that, apart from adipocytes, visfatin is also expressed in many other cells, including the liver, heart, muscles, kidneys and bone marrow [29,30]. Research on the properties of visfatin has shown its involvement in disorders that often co-occur with IR, e.g., T2DM, gestational diabetes mellitus (GDM) or polycystic ovary syndrome (PCOS). The relationship of visfatin with the development and progression of cardiovascular complications was also considered, such as atherosclerosis or heart failure. An experiment conducted on mouse models demonstrated that the administration of visfatin resulted in a rise in the concentration of interleukin 6 (IL-6), the action of which may contribute to the destabilization of atherosclerotic plaque [31]. Zheng et al. [32] observed that among patients with T2DM, the serum visfatin levels were elevated in those with atherosclerotic plaques, especially in those with carotid atherosclerotic plaques. A study conducted by Uslu et al. [33] in patients with T2DM showed a positive correlation of the visfatin concentration with the concentration of an indicator of endothelial dysfunction – homocysteine. The importance of visfatin in metabolic and cardiovascular diseases remains unclear resulting from conflicting research results [34]. The significant discrepancy in the meta--analyses may be due to insufficient understanding of the mechanisms and interdependencies that the described adipokine plays in the pathophysiology of diseases such as obesity or T2DM. Additionally, poor understanding of its action may be a consequence of the fact that visfatin is a relatively recently discovered adipokine and requires further research to draw more accurate conclusions about its importance in metabolic diseases and whether it could act as a marker and prognostic factor for these diseases.

Chemerin

Chemerin is a protein secreted in large amounts by the adipocytes of white adipose tissue, but it is also expressed in the liver, intestines, kidneys and lungs. Its receptor CMKLR1 (also known as ChemR23) is expressed mainly in adipocytes and immune cells. The described adipokine is encoded by the retinoic acid receptor 2 (Rarres2) gene [35]. Many studies have been carried out examining the potential importance of chemerin in the regulation of glucose concentration, as well as its impact on the development and course of, among others, T2DM, IR, GDM, as well as cardiovascular diseases. In the course of the above--mentioned studies, the relationship between chemerin and the mentioned diseases was most often assessed by looking for a correlation between the concentration of this adipokine and various parameters related to obesity, inflammation or glycemic control, such as fasting glucose, fasting insulin, HOMA-IR, hsCRP and BMI [35,36,37]. Zhou et al. [38] conducted a meta-analysis which showed that circulating chemerin levels were significantly increased in women with GDM compared to healthy pregnant women. The results of another study indicate that the chemerin concentration in obese patients with T2DM is closely related to the occurrence of IR. Nonetheless, during its course it was not clearly established whether the increased concentration of chemerin is the result of a compensatory response to IR or serves as a causative factor in IR. Additionally, it has been shown that the chemerin concentration is closely related to oxidative stress and inflammation. Therefore, the described adipokine may be an inflammatory mediator playing an important role in the initiation and development of type 2 diabetes associated with obesity [39]. In a study conducted on 87 patients with T2DM and 85 healthy controls, the chemerin concentration in T2DM patients showed a progressive rise with increasing BMI, reaching highly significant values in obese and severely obese patients, respectively [40]. Another study that measured the blood chemerin concentrations in obese patients with type 2 diabetes treated with a long-acting insulin analogue or a mixed insulin analogue showed no significant change in the chemerin concentrations after treatment, suggesting that it may not be a specific indicator for monitoring diabetes progression or the efficacy of pharmacotherapy [41]. A study was conducted to analyze the effect of moderate walking exercise on the chemerin concentration in patients with T2DM. In active the T2DM patients, the chemerin concentrations were significantly lower than in the inactive T2DM patients. The results showed that in the active T2DM patients, the chemerin concentration was significantly lower than in the inactive T2DM patients [42]. It is worth mentioning, however, that there are publications in the scientific literature questioning the value of chemerin as a diagnostic factor. Bobbert et al. [43] in a study conducted on a group of 440 patients, observed a correlation between the risk of T2DM and the concentration of chemerin in plasma. Additionally, the correlation between the chemerin concentration and the risk of IR was analyzed. In both cases, although some correlations were found, they were not considered statistically significant. There are studies describing

the role of chemerin in the development and progression of cardiovascular diseases. This is related to the influence of this adipokine on glucose and lipid metabolism, which leads to the accumulation of lipids in the endothelium and the initiation of inflammation, which in turn contributes to the development of atherosclerosis. Due to the existence of contradictory studies, it is not possible to clearly state what is the cause of the relationships between chemerin concentrations in metabolic disorders and cardiovascular diseases observed in the studies and what their nature is. Do IR and T2DM lead to an increase in the chemerin concentration, or on the contrary, does a high chemerin concentration contribute to abnormalities in glucose homeostasis? Further research is needed to understand the mechanism of action and the role of this adipokine in the etiology of metabolic diseases [44,45].

Omentin-1

The discovery of omentin expression in human adipose tissue took place in 2005. Omentin is mainly synthesized in visceral fat tissue, where its concentration is approximately 20 times higher than in subcutaneous fat tissue. The omentin gene, located on chromosome 1q22-q23, consists of 8 exons and 7 introns. There are two isoforms of omentin – omentin-1 and omentin-2, whose amino acid sequences are 83% homologous. The omentin gene is expressed mainly in visceral adipose tissue stromal cells, fibroblasts, macrophages, endothelial cells, mammary adipose tissue and epicardium [46]. In recent years, researchers have focused on the analysis of omentin (in particular omentin-1) as a potential marker in metabolic diseases, including T2DM, cardiovascular diseases, as well as the role this adipokine plays in overweight and obesity. The main roles of omentin-1 in the body are anti-inflammatory effects and blood glucose control. The proposed mechanism of action of this adipokine is to increase tissue sensitivity to insulin via the para- and endocrine pathway. This is the result of ameliorating the insulin signaling pathway through the activation of AKT kinase. The conducted research allows us to conclude that omentin-1 does not exhibit an insulinomimetic effect on its own, but only enhances the cellular response to the presence of insulin in the blood [47,48]. An illustration of the mechanism of action of omentin-1 is shown in Figure 3.

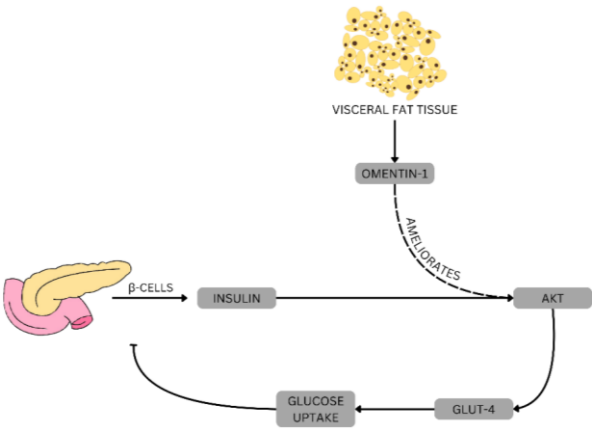

Fig. 3. Omentin-1 – mechanism of action (based on [12,16,17,18,22]).

The results of the meta-analysis from 2019 conducted on 42 research studies revealed a strong, negative correlation between the concentration of omentin-1 in plasma and T2DM as well as GDM. At the same time, Pan et al. [49] found no correlation between the omentin-1 concentration and type 1 diabetes. The studies included in the meta-analysis came from various countries, e.g., Egypt, China, Poland, Australia, Canada, Germany, India, Japan and Iran. The correlation between the severity of T2DM and the concentration of omentin-1 in plasma was also examined. Latif et al. [50] in their study on 250 patients discovered that with the progression of the disease and the occurrence of complications related to the course of T2DM, a decrease in the concentration of the analyzed adipokine in plasma was observed compared to patients without identified complications. This fact may be a reason to use omentin-1 not only as a diagnostic marker, but also as a factor monitoring the course of the disease, the effectiveness of pharmacotherapy and increasing the effectiveness of prognostic activities. One of the most common complications associated with T2DM is peripheral artery disease (PAD), which significantly increases the risk of major adverse cardiovascular events (MACE). Biscetti et al. [51] examined the relationship of omentin-1 levels with the incidence of PAD. Their results indicated a significant correlation between low concentrations of omentin-1 and the number of occurring MACE. This is another reason to consider the omentin-1 concentration as an important monitoring factor. A similar conclusion was reached by Askin et al. [52] in their review, who, comparing the concentration of omentin-1 and the risk of coronary heart disease, found that also in this disease,

omentin-1 may be an independent prognostic factor for the course of the disease.

Conclusions

Obesity and its accompanying metabolic disorders constitute a serious health challenge around the world, which requires new and individualized solutions to reduce the incidence of disease through, among others, appropriate prevention and effective treatment. The adipokines leptin, visfatin, chemerin and omentin-1 play a key role in the functioning of the body. They influence, among others, inflammation processes, glucose homeostasis and hormonal balance. Owing to these properties, it is possible to potentially use them as therapeutic and diagnostic factors in the course of obesity and its accompanying metabolic disorders such as IR or T2DM, as well as the resulting complications, including cardiovascular ones. Therefore, it is very important to search for new and more accurate biomarkers, thanks to which it would be possible to precisely assess the probability of the occurrence of the mentioned diseases, as well as monitor the treatment of already diagnosed diseases. A thorough analysis of biological markers could also allow control of the effectiveness of improving the patient's health after introducing physical activity and an appropriate diet into their life as elements of therapy. Despite significant progress in understanding the role played by the described adipokines, further research is necessary to describe the mechanism of their action and to determine the precise relationship between their concentrations in the body and the state of the disease.

Author's contribution

Study design – K. Stocerz, A. Sokal, M. Kuczera, M. Kadela-Tomanek, K. Orlińska, P. Olczyk

Data collection – K. Stocerz, A. Sokal, M. Kuczera

Manuscript preparation – K. Stocerz, A. Sokal, M. Kuczera, M. Kadela-Tomanek, K. Orlińska, P. Olczyk

Literature research – K. Stocerz, A. Sokal, M. Kuczera

Final approval of the version to be published – M. Kadela-Tomanek, K. Orlińska, P. Olczyk

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