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ADIPOSE TISSUE AS AN ENDOCRINE ORGAN

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Abstract

In recent years, views regarding the function of adipose tissue have undergone a fundamental change. Adipose tissue is no longer regarded as providing only protection against heat loss and storage of triglycerides, but is also considered an endocrinologically active organ which produces numerous biologically active peptides known as adipokines, which have significant influence on metabolic changes in the human body. Many studies have noted a correlation between the secretion of adipokines on one hand and obesity, the development of insulin resistance, atherosclerosis, and the occurrence of inflammatory reactions on the other. Among the hormones produced by adipose tissue are leptin, adiponectin, resistin, and visfatin. This paper reviews the current state of knowledge in the literature on these newly discovered adipokines.

***Key words**: adipose tissue, adipokines, leptin, adiponectin, resistin, visfatin*

Introduction

Adipose tissue may be divided into white adipose tissue (WAT) and brown adipose tissue (BAT). The first of these – the basic lipid store in the human body – is composed of large spherical adipocytes, in which a layer of cytoplasm, along with the nucleus, surrounds a large lipid droplet. Apart from the storage and release of energy as free fatty acids, WAT fulfils an important endocrine function, to which is attributed influence on the regulation of the appetite, on arterial pressure, on the clotting and fibrinolysis systems, and on the development of insulin sensitivity [1]. Brown adipose tissue, on the other hand, is composed of adipocytes with a large number of mitochondria, and with only a small amount of lipid stored in the cytoplasm. Among the main functions of BAT are the regulation of thermogenesis, which constitutes one of the fundamental forms of energy expenditure [1]. In recent years, views on the function fulfilled by adipose tissue have undergone fundamental changes [1]. At the start of the 1940s it had already been hypothesized that the interaction between adipose tissues and other tissues ran in both directions. Apart from that, it was known that the endocrine system is white adipose tissue involved in the regulation of homeostasis through interaction with the endocrine, immunological, and neurological systems [1]. A breakthrough in understanding the role of adipose tissue occurred in 1994, with the discovery of the *Ob(Lep)* gene which encodes leptin, the hormone produced by mature adipocytes [2]. Since that time, adipose tissue has not been regarded as merely protecting against heat loss, storing triglycerides, and releasing fatty acids during energy deficiency, but also as an endocrinologically functioning organ producing numerous biologically active peptides known as adipokines, which both act endocrinologically and paracrinologically within the area of the adipose tissue, and which also influence distant organs and tissues (classic endocrine action).

Among the biologically active peptides produced by the cells of adipose tissue are [1]:

- cytokines and proteins associated with cytokines: leptin, TNF-α (tumor necrosis factor α), IL-6, MCP-1;
- proteins associated with the clotting system, such as the PAIs;
- components of the complement system and proteins associated with them – adiponectin, adipsin, and ASP (acylation stimulating protein);
- proteins of the renin-angiotensin system, such as angiotensinogen;
- lipids and proteins associated with the metabolism and transport of lipids – lipoprotein lipase, cholesterylester transfer protein, apolipoprotein E;
- other hormonally active proteins – resistin, apelin, visfatin;
- enzymes associated with steroid hormone metabolism – P450, 17β-HSD, 11β-HSD1.

In this paper, was described the characteristics of certain cytokines which have a demonstrated association with the appearance of obesity and other civilization diseases.

Leptin

Leptin, the "satiety hormone", was discovered by Zwang et al. in 1994. It is a peptide built from 167 amino acids, and has a molecular mass of 16 kD. It is produced mainly by hypodermic adipocytes [3]. The leptin gene (*OB*) is located on chromosome 7 (7q31.3), and is composed of about 20,000 base pairs, including 3 exons [3]. Receptors for this hormone are also

located in the central nervous system, mainly in the hypothalamus region, in skeletal muscles, in the liver, in the marrow and in the ovaries, where their presence suggests that the hormone may also play a role in the metabolic signaling of the reproductive system [3]. Recently, there has also been data to suggest that leptin receptors are also present in the bones [3, 4]. Leptin synthesis is stimulated by insulin, glucocorticosteroids, TNFα, and estrogen, and inhibited by the activation of β_3-adrenoceptors, androgens, free fatty acids, growth hormone, and agonists that activate peroxisome proliferator receptor γ [3].

The results of numerous studies have shown that both in men and in women, serum leptin level is positively correlated with the total adipose tissue content expressed in kilograms, in percentage of fat mass, or as body mass index (BMI) [4-8]. The lowest leptin levels are found among people with anorexia and among children with innate lipodystrophy, while the highest levels are found among obese people [9, 10]. However, the results of a study by Ziora et al. [11] indicate a lack of correlation between leptin and BMI in girls with anorexia, which might demonstrate a disturbance in the regulation of leptin secretion associated with low body masses and malnutrition. It has nonetheless been shown that short-term treatments which lead to increases in the energy intake and in body mass also have a positive effect on serum leptin levels [11]. The study of Haas et al. [6] additionally demonstrates the existence of a positive correlation between serum leptin level and the amount of fat mass in anorexic girls. Furthermore, the increase in the level of leptin during treatment contributes to increases in the resting metabolic rate, which may show that leptin has an influence on the resting metabolic rate [6].

Regulation of the appetite and satiety functions by means of interaction with the hunger centre of the hypothalamus is considered to be the main function of leptin [4]. It has been noted that leptin is responsible for transmitting information about the energy status of the organism to the central nervous system, which releases neuropeptides whose function is to maintain the correct body mass [12]. When a positive energy balance is being maintained, accompanied by the excessive accumulation of adipose tissue, leptin synthesis increases; the hormone penetrates the blood-brain barrier and exerts an effect on receptors localized on the hypothalamus, causing the release of mediators leading to anorexic action which inhibits appetite [4]. Attempts to employ this mechanism in the treatment of obesity by using exogenic leptin have unfortunately not shown the expected results. In most people with higher body mass leptin resistance-insensitivity to the anorexic action of the hormone is observed to occur [4, 13]. A negative energy balance contributes to a decrease in serum leptin levels, and the release of neurotransmitters from the hypothalamus stimulates the appetite and decreases the body's energy expenditure [4, 12]. However, despite numerous studies, the role of leptin in the uptake of nutrients and in the development of obesity in humans is not yet fully understood. Nonetheless the data so far clearly indicate that leptin is a link between the size of the adipose tissue reserves and many processes which accompany obesity, including hyperlipidemia and insulin resistance [9].

Serum leptin level is secreted by adipocytes undergoes a twenty-four hour rhythm, with the highest leptin secretion occurring between 22.00 and 03.00, and the lowest level between the afternoon and the later evening which explains why nutrients are not absorbed during the night [9]. It has been noted that the twenty-four-hour rhythm of leptin secretion does not occur in people on high or low energy diets [14]. It is also known that not only the quantity, but also the type of nutrients undergoing absorption, has an effect on the leptin level, as does the speed of intake. Meals with a high carbohydrate content cause an increase in the leptin level as compared to food with high lipid content [14]. Additionally, newer studies show that the level of leptin increases after a meal, if the mean is eaten slowly [14].

Leptin is the hormone that sends information to the brain on the required amount of adipose tissue necessary for the secretion of LH-RH and for the activation and maintenance of the hypothalamus-pituitary-ovary axis [15]. Similarly, leptin is regarded as the link between energy status and reproductive function [15]. Many studies on professional female athletes with low body mass and low proportions of adipose tissue have shown that a low level of leptin in the blood serum may favor the development of disorders in menstrual cycle [15]. Such studies show that very low leptin levels are found among female athletes with amenorrhea, compared with professionals with eumenorrhea [16]. It is also thought that low serum leptin levels among female athletes with amenorrhoea are associated with hypoglycemia as well as with lower levels of insulin, thyroid-stimulating hormone (TSH), cortisol, and other sex hormones [9]. This seems to be true, despite the results of Isidori et al. [5], who demonstrated a positive correlation between serum leptin level, estradiol and luteinizing hormone (LH) levels in women. With men, on the other hand, research found a negative correlation between leptin and testosterone level [5]. Comparing the leptin levels among female athletes and girls suffering from anorexia, it can be stated that at similar percentage of adipose tissue, women practicing professional sports are characterized by low leptin levels, as compared to anorexic girls [6]. These results suggest that decreased leptin levels in athletes might depend not only on percentage of fat mass, but also might be a consequence of regular

physical training. In support of this, there are also data showing that serum leptin levels change in women and men after once-off physical training and also after systematic training [17].

The effects of leptin on the regulation of arterial blood pressure (by influencing the action of the sympathetic nervous system and the expulsion of sodium and water in urine), on hematopoiesis, on angiogenesis, on the healing of wounds, and on the course of inflammatory processes has also been demonstrated [6, 9, 18]. It seems that during acute inflammatory processes, leptin is treated like an acute-phase protein which assists the immunological system. On the other hand, in chronic inflammation, the long-term stimulation of adipose tissue by proinflammatory cytokines inhibits the production of leptin [6].

Recent studies show that leptin can have significant effect on the progression of breast cancer, can accelerate the development of the tumor, and may contribute to metastasis [19]. It has been noted that leptin has this effect only when combined with the leptin receptors located on the hypothalamus, placenta, mammary glands, and on cells of the hematopoietic system, liver, salivary glands, trachea, kidneys, spleen, on the surface of skin cells, blood vessels, lungs, pancreas, testicles, ovaries, bladder, eyes, heart, and pharynx [20]. However, the mechanism of the leptin-receptor system which produces carcinogenic effects requires further research [19].

Adiponectin

Adiponectin was discovered in 1995 by Philipp Scherer's research group and was described as a novel serum protein similar to C1q. It is produced exclusively in adipocytes [21] and is a polypeptide hormone with a molecular mass of 33 kDa, possessing sequences homological to type 8 and type 10 collagens, and to the complement component C1q. There are two types of receptors for adiponectin, encoded by *AdipoR1* and *AdipoR2*, which are located at chromosomal positions 1p36 and 12p13, respectively [12, 22]. The first of these receptors is mainly active in adipocytes and in muscle cells, while the second is active in cells of the liver [23, 24].

The distribution of these receptors might suggest the role of adiponectin in maintaining the body's energy homeostasis, since the liver and the skeletal muscles take part in the storage and use of energy, respectively [9]. Among the factors which influence the synthesis and secretion of this hormone are insulin and PPARγ receptor agonists. TNFα (tumor necrosis factor α) and PPARα receptor agonists, on the other hand, inhibit the hormone [22]. As in the case of leptin, higher adiponectin levels are observed in the hypodermis, in comparison to visceral tissue [9]. Furthermore, a large number of studies have shown that obese children have lower adiponectin levels, compared to their non-obese counterparts [25].

One of the main functions of adiponectin is to increase insulin sensitivity by stimulating the phosphorylation of acetyl-CoA carboxylase and inhibiting hepatic gluconeogenesis (the transformation of non-sugar precursors into glucose) [26]. Additionally, in the skeletal muscles, adiponectin increases the oxidation of fatty acids, the uptake of glucose, and the production of lactates, which also leads to a decrease in insulin resistance [26]. Apart from that, the facilitation of the supply of glucose and insulin to peripheral tissues is also attributed to adiponectin, by relaxing blood vessel muscles, which leads to an increased blood flow [26]. Studies have shown that low adiponectin levels can predict the development of type 2 diabetes, while high levels are said to decrease the risk of it [9]. This correlation is also supported by data concerning the correlation between adiponectin and insulin [27]. It has been found that a much stronger relation exists between decreases in the adiponectin level and the degrees of insulin resistance and hyperinsulinemia, compared to indicators of obesity [28]. This thesis has been demonstrated by Kowalska et al. [29], who suggest that decreased sensitivity to insulin and low adiponectin levels occur among people with normal body mass, but whose parents suffered from type 2 diabetes. On the other hand, the results relating to adiponectin levels and obesity are very ambiguous. A relationship between low adiponectin levels and being overweight or obese has been confirmed on the basis of the increases in level of this hormone after the reduction of body mass and insulin resistance [30]. There are also reports suggesting a lack of increase in cytokine levels after reduction of body mass and improvements in insulin sensitivity [31].

Low adiponectin levels are associated with a high risk of cardiovascular disease, diabetes, atherosclerosis, and even with some cancers [32-36]. On the other hand, an increased adiponectin level has been described in cases of renal failure, type 1 diabetes, and anorexia [26, 37, 38]. One of the functions attributed to adiponectin is its preventative properties with respect to atherosclerosis, which come about as a result of its inhibiting the transformation of macrophages into foam cells. Moreover, adiponectin weakens the inflammatory reaction in atherogenesis by inhibiting the adhesion of monocytes to endothelial cells and decreasing the expression of arterial adhesion molecules and E-selectin [39, 40]. It has also been discovered from studies that, among obese people, adiponectin levels are low, directly proportional to the HDL cholesterol fraction, and inversely proportional to the LDL and triglyceride fractions [41]. Furthermore, some authors have indicated that low adiponectin levels may be used to diagnose dyslipidemia, and have also

suggested using adiponectin to treat obese people with low levels of this hormone [42].

Resistin

Resistin (RETN, RSTN, from "resistance to insulin") was discovered in 2001 and described as a cysteine-rich protein hormone with a molecular mass of 12.5 kDa [2]. The gene encoding it is composed of 4 exons and is located on the short leg of chromosome 19, at 19p13.2 [43]. Apart from in adipocytes, resistin has been shown to be expressed widely in mononuclear blood cells, in the spleen, marrow, lungs, placenta, and pancreas [43, 44]. It has been shown to be in close association with resistin and abdominal adipose tissue [45]. For example, Rubin et al. [25] described an approximately 25% higher resistin concentration in those adolescents with a waist circumference above the 90th percentile, compared to adolescents with waist circumference below the 75th percentile.

Much data in the literature indicates the significant role played by resistin in the pathomechanism of obesity, and also of insulin resistance. It has been noted that resistin is a link between obesity, insulin resistance, and type 2 diabetes. Furthermore, it is known that resistin activates gluconeogenesis enzymes and intensifies glycogenesis, the result of which is an increase in hepatic insulin resistance. Furthermore, cytokines are responsible for maintaining glucose level during energy deficiency, and the pathological effect of this phenomenon is associated with the appearance of excessive amount of adipose tissue [2]. It is assumed that resistin has a significant effect on the decrease in obesity caused by a high-fat diet. It has been observed that characteristically higher resistin levels are found in obese people and among those suffering from type 2 diabetes [46]. However, there also exist reports contradicting these results where no correlation has been found [47]. Furthermore, taking into account that the higher secretion of resistin occurs in visceral adipose tissue, it may be assumed that central obesity is associated in a significant way with the increased risk of type 2 diabetes and of some cardiovascular diseases [48]. Furthermore, among healthy people a significant correlation between circulating resistin levels and higher risk of type 2 diabetes has been found, independent of sex, which has been explained by the coexistence of obesity or the presence of inflammation [49].

It has been suggested that resistin is one of the main pro-inflammatory mediators, evidence for which is the increase in the expression of the hormone's gene upon intensification of inflammatory reaction, and the drop in expression which is observed following the application of anti-inflammatory drugs [50]. This hypothesis has been demonstrated by showing the correlation between resistin and CRP protein levels in adults [51]. Taking the above into account, the influence of the anti-inflammatory properties of resistin on the expression of molecules which play a significant role in endothelial dysfunction and the pathogenesis of atherosclerosis has been investigated. According to Verma et al. [52], the resistin level created by monocytes in the peripheral circulation and by macrophages in atherosclerotic plaque is significantly higher, in comparison to the level of resistin produced by endothelial cells (HUVECs) and smooth muscle cells deriving from unaltered vessel walls. Furthermore, in the research of Jung et al. [53], a characteristically higher resistin level among patients with atherosclerosis was observed, compared with healthy individuals.

In the literature there are data showing a correlation between resistin and arterial pressure, and they suggest that a significant increase in the resistin level is found in people with hypertension, as compared to people with normal blood pressure. In a small number of articles there is data concerning the connection of resistin with hypertension during pregnancy. Worthy of note in this respect are the results of Chen et al. [54], who observed higher resistin levels in women in the third trimester, as compared to women in the first and second trimesters, and to non-pregnant women. Furthermore, they emphasized that women in the third trimester suffering from hypertension were characterized by higher resistin levels than women in the same stage of pregnancy with normal blood pressure [54].

Visfatin

Visfatin is a newly discovered adipokine composed of 491 amino acids, encoded by genes located on chromosome 7, between 7q21.1 and 7q31.33. It is produced and secreted mainly by visceral adipose tissue, which is why data on its function in the human body is still limited [55]. It was initially identified as PBEF (from "pre-B-cell colony enhancing factor"), as it was first noted as a growth factor stimulating the differentiation of pre-B cell colonies, and is synthesized by cells of the marrow, liver, and skeletal muscles [56]. Insulin induces increases in the visfatin level, as do insulin-like growth factor (IGF), IL-7, IL-6, and TNFα [55], as well as activated lymphocytes, monocytes, and neutrophiles [56]. On the other hand, free testosterone inhibits the secretion of visfatin, both in hypodermic and in visceral adipose tissues [55].

The nature of the correlation between visfatin levels and body mass or body composition is ambiguous. Some authors suggest that there is a positive correlation between visfatin levels, the percentage of body fat mass, and BMI [57]. Ingelsson et al. [58], however, denies this hypothesis. Such a correlation was also not noted in malnourished girls with anorexia [10]. In the research of Semik-Grabarczyk et al. [57], a higher visfatin level was observed in obese women with insulin resistance, in comparison to obese women without in-

sulin resistance. These results found further confirmation in the research of Chen et al. [59]. Furthermore, a positive correlation has also been shown between visfatin levels and insulin resistance in obese women with normal glucose levels [57, 60]. Furthermore, in Formeska-Iciek's [61] study, there was shown to be a lack of correlation between visfatin levels, insulin resistance, and the adipose tissue mass, despite the existence of positive correlation with waist circumference. It has been shown that visfatin results in an increase in glucose uptake by 3T3-L1 adipocytes and L6 monocytes, and also inhibits the release of glucose by hepatocytes [62]. Furthermore, visfatin facilitates adipogenesis, and also binds to and activates insulin receptors, causing an effect which imitates the action of insulin both *in vitro* and *in vivo* [62]. Intravenous injection of visfatin induces a decrease in the glucose levels, although it has no influence on the insulin level, as shown by the hypoglycemic effect of visfatin [63].

Taking into account the fact that visfatin is secreted by the kidneys, it has been suggested that kidney insufficiency might have an effect on visfatin level increases. However, some researchers have demonstrated lower visfatin levels among patients on hemodialysis, as compared to healthy people [64], while Erten et al. [65] did not observe any significant difference between healthy and sick individuals in this case.

Furthermore, on the basis of the studies of Aller et al. [66] and Romanowska et al. [67], in which adults and children with non-alcoholic fatty liver disease were studied, and in which higher visfatin levels were found among those individuals with more intense inflammatory processes, it can be surmised that visfatin is characterized by proinflammatory properties. This assumption has also found support in other experimental studies which demonstrated visfatin's close connection with another proinflammatory cytokine, IL-6 [68]. In other research, a correlation has additionally been demonstrated between visfatin levels and the value of diastolic arterial pressure, which may suggest that this cytokine acts to modulate arterial blood pressure [61].

Summary

Alarming rises in the frequency of obesity, type 2 diabetes, atherosclerosis, and certain tumors has fuelled the ongoing expansion of knowledge of therapeutic methods. The discovery of adipokines led immediately to the realization that adipose tissue constitutes an important element of the endocrine system, and that the hormones secreted by it figure prominently in the etiology and treatment of the above-mentioned disorders. In this article we have drawn attention to the characteristic features of cytokines and their relation with obesity and the regulation of appetite and satiety. The correlation between these hormones and the occurrence of type 2 diabetes, insulin resistance, and atherosclerosis is also of exceptional importance. The relationship between the hormones produced by adipose tissues and the etiology and development of certain tumors is also worthy of attention and requires further research. Also significant are the anti-inflammatory properties which characterize the adipokines. More detailed knowledge of the structure and metabolism of adipose tissue is a particularly significant and promising direction of research, as it may facilitate the development of effective and safe methods of prevention and cure.

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A – Study Design
B – Data Collection
C – Statistical Analysis
D – Data Interpretation
E – Manuscript Preparation
F – Literature Search
G – Funds Collection