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The role of the novel adipokines vaspin and omentin in chronic inflammatory diseases

Rola nowych adipokin, waspiny i omentyny w przewlekłych chorobach zapalnych

[1]Joanna Radzik-Zając, [1]Krzysztof Wytrychowski, [2]Andrzej Wiśniewski, [3]Wojciech Barg

[1]Department of Internal Medicine, Pneumology and Allergology, Wroclaw Medical University, Poland
[2]Hirszfeld Institute of Immunology and Experimental Therapy Polish Academy of Sciences, Polish Academy of Sciences, Poland
[3]Department of Human Physiology, Institute of Medical Sciences, Medical College of Rzeszow University

Abstract
Obesity is a disease of epidemic proportions in many countries around the world. White adipose tissue is an active endocrine organ; therefore, its excess results in chronic and systemic inflammation. This inflammation is caused and maintained mostly by adipokines secreted by adipose tissue cells, mainly adipocytes and macrophages.
The relatively newly discovered adipokines comprise vaspin and omentin. Their concentration in the blood, tissues, or bronchial secretion varies depending on the amount of adipose tissue and other accompanying factors, including comorbidities. The aim of this article is to demonstrate the usefulness of omentin and vaspin as biomarkers in inflammatory diseases.
The Medline/PubMed database was used to search for information on obesity, inflammation, omentin, vaspin, and adipose tissue. Data from selected scientific studies, both original and review papers, are presented.
Vaspin has been found to improve insulin sensitivity mainly in white adipose tissue. Omentin has an anti-inflammatory effect and, like vaspin, sensitizes tissues to insulin. The serum concentration and tissue expression of both adipokines are different in different inflammatory diseases.
This review aims to present the biological functions of vaspin and omentin in the body and to indicate the possible use of these adipokines as disease markers in the future.
Key words:
obesity, adipose tissue, inflammation, omentin, vaspin.

Streszczenie
Otyłość jest chorobą o rozmiarach epidemii w wielu krajach na całym świecie. Biała tkanka tłuszczowa jest aktywnym narządem wydzielania wewnętrznego, dlatego jej nadmiar prowadzi do przewlekłego i ogólnoustrojowego stanu zapalnego. Zapalenie to jest powodowane i utrzymywane zwłaszcza przez adipokiny wydzielane przez komórki tkanki tłuszczowej, głównie adipocyty i makrofagi. Stosunkowo nowo odkryte adipokiny to waspina i omentyna. Ich stężenie we krwi, tkankach lub wydzielinie oskrzelowej zmienia się w zależności od ilości tkanki tłuszczowej oraz innych czynników towarzyszących, w tym chorób współistniejących. Celem artykułu jest wykazanie przydatności omentyny i waspiny jako biomarkerów chorób zapalnych.
Wykorzystywano bazę Medline/PubMed w celu wyszukiwania informacji na temat otyłości, zapalenia, omentyny, waspiny i tkanki tłuszczowej. Przedstawiono dane z wybranych opracowań naukowych zarówno prac oryginalnych, jak i prac przeglądowych.
Wykazano, że waspina poprawia wrażliwość na insulinę głównie w białej tkance tłuszczowej. Omentyna działa przeciwzapalnie i podobnie jak waspina uwrażliwia tkanki na insulinę. Stężenie w surowicy i ekspresja tkankowa obu adipokin są różne w różnych chorobach zapalnych.
Niniejsza praca ma na celu nakreślenie biologicznych funkcji waspiny i omentyny w organizmie oraz wskazanie na możliwe wykorzystanie tych adipokin jako markerów chorób w przyszłości.
Key words:
otyłość, tkanka tłuszczowa, zapalenie, omentyna, waspina.

Joanna Radzik-Zając
Department of Internal Medicine,
Pneumology and Allergology,
Wroclaw Medical University,
Wybrzeże L. Pasteura 1, 50-367 Wroclaw, Poland
e-mail: joanna.radzik-zajac@umw.edu.pl

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Introduction

Obesity is a condition in which the body's excessive supply of energy results in an overabundance of body fat. Despite numerous limitations, the basic indicator of obesity assessment is body mass index (BMI, weight in kg/height in m^2) above 30 [1]. Obesity is a growing problem also in children and adolescents. WHO data show that in 2019 a total of 38 million children under the age of 5 years were overweight or obese. In 2016, over 340 million children and adolescents aged 5–19 years were overweight or obese [1].

The mammal adipose tissue is composed of white adipose tissue (WAT) and brown adipose tissue with distinct functions. In addition to adipocytes, adipose tissue contains a matrix of connective tissues (collagen and reticular fibres), nerve fibres, vascular stroma, lymph nodes, immune cells (leukocytes, macrophages), fibroblasts, and preadipocytes (undifferentiated fat cells) [2]. Brown adipose tissue is responsible for thermogenesis, especially in foetuses and newborn infants. WAT accumulates excess energy in the form of triglycerides; studies also showed that it is an active endocrine organ [2]. The relationship between obesity and inflammation was first noted in 1993 by Hotamisligil *et al*. [3]. They discovered that adipose tissue of obese mice releases tumour necrosis factor α (TNF-α) [3].

White adipose tissue releases a great number of biologically active molecules called adipokines. These molecules include over 50 cytokines, chemokines, hormone-like factors, and other mediators. These mediators are also released by various other tissues and organs that are not functionally related to white adipose tissue [4, 5]. Consequently, obese individuals experience an imbalance between pro-inflammatory adipokines such as leptin, resistin, visfatin, and TNF-α, and anti-inflammatory adipokines like adiponectin, omentin, secreted frizzled-related protein 5 (SFRP5), vaspin, zinc-α2-glycoprotein (ZAG), and interleukin 10 (IL-10) [6]. Obesity, therefore, causes so-called low-level inflammation, resulting from the biologic action of mediators produced by adipose tissue [6, 7].

Two recently discovered adipokines, vaspin and omentin, are hormones produced by adipose tissue, which are involved in regulating processes in inflammation.

Discovery of vaspin

Vaspin belongs to the serpin group of proteins and is a serine protease inhibitor. It was discovered by Hida *et al*. in 2005 [8]. They isolated vaspin cDNA from the visceral adipose tissue (VAT) of Otsuka Long-Evans Tokushima fatty (OLETF) rats, an animal model of metabolic syndrome. The OLETF rat is characterized by type 2 diabetes (DM2), abdominal obesity, insulin resistance, hypertension, and dyslipidaemia [9]. Human vaspin consists of 395 amino acids weighing 45.2 kDa. In humans, the expression of vaspin has been reported in several organs, including subcutaneous fat, skin, stomach, skeletal muscles, pancreas, and liver, with the highest production of vaspin occurring in the liver [10].

Vaspin is one of the most important adipokines in the inflammatory process. Phalitakul *et al*. [11] in their fundamental *in vitro* study investigated the effect of vaspin on TNF-α stimulated vascular smooth muscle cells (SMC). Vaspin was proven to demonstrate anti-inflammatory activities in vascular SMC [11].

Discovery of omentin

An omentin gene was first isolated in intestinal Paneth cells in mice. Komiya *et al*. [12] named the newly discovered gene intelectin because the amino acid sequence was similar to the previously cloned lectin gene from the oocytes of the plane tree (*Xenopus laevis*).

The homolog of omentin-1, with 83% amino acid identity, is omentin-2 (13). Both genes for omentin-1 and omentin-2 are located in the chromosomal region 1q22–q23, the region associated with the occurrence of DM2. The omentin receptor has not yet been identified. Protein sequence analysis revealed that omentin mRNA encodes a 34 kDa peptide of 313 amino acids containing a secretory signal sequence and a fibrinogen-related domain. Northern blot analysis showed that omentin mRNA was expressed predominantly in VAT, but omentin was barely detectable in subcutaneous fat stores in humans and rhesus monkeys [14]. The biological function of omentin is still not fully understood [13].

Omentin mRNA was shown to be expressed abundantly in the human placenta and ovary tissues. Human omentin-1 is highly expressed in the heart, small intestine, colon, renal collecting tubule cells, umbrella cells, mesothelial cells, and alveolar cells, while human omentin-2 is only found in Paneth cells of the small intestine [15].

The anti-inflammatory effect of omentin was first described by Yamawaki *et al*. [16], who demonstrated its preventive effect on TNF-α-induced cyclooxygenase-2 (COX-2) expression in vascular endothelial cells [16], and by Kazama *et al*. [17], who showed that omentin prevents TNF-α-induced vascular cell adhesion molecule (VCAM-1) expression in smooth muscles cells [17].

Omentin is produced in VAT, where it reaches concentrations much higher than in subcutaneous adipose tissue or peripheral circulation [14]. Studies have shown that serum omentin levels are inversely related to the degree of obesity [18, 19].

Vaspin and adipose tissue and type 2 diabetes

The serum vaspin concentration in nondiabetic and diabetic patients positively correlates with BMI and impaired glucose tolerance [20].

A study of 196 patients with varying degrees of obesity and fat distribution, different insulin sensitivity, and glucose tolerance showed that vaspin mRNA expression was detectable only in 45 (23%) visceral and 30 (15%) subcutaneous adipose tissue samples. None of the lean subjects (BMI ≤ 25) had a detectable vaspin mRNA expression, while vaspin mRNA expression was increased in overweight and obese subjects.

The latter was particularly in individuals with decreased insulin sensitivity and impaired glucose tolerance. However, there were no differences in the expression of vaspin in visceral and subcutaneous adipose tissue between males and females. Expression of vaspin mRNA was observed significantly more frequently in patients with DM2 than without in those DM2, although it was not detected in all diabetes patients [21].

The study showed that increased vaspin mRNA expression was associated with lower insulin sensitivity in DM2 patients and higher body fat content in obese patients without DM2. It can be assumed that increased expression of vaspin mRNA may be an internal compensatory mechanism of adipose tissue in response to decreased insulin sensitivity or impaired glucose metabolism. These studies confirm the conclusion of previous animal studies with OLETF rats that increased vaspin expression occurs in obesity and insulin resistance [21].

As demonstrated by Li *et al*. [22], serum vaspin levels were low in lean individuals and athletes who had undergone prolonged physical training but increased with weight loss associated with a physical training program. The authors concluded that there was no clear evidence of a causal relationship between vaspin serum concentration and the accumulation of visceral fat or insulin resistance [22]. Other studies have shown that the expansion of adipose tissue is associated with a higher concentration of circulating vaspin in the blood. In a study by Chang *et al*. [23], it was found that serum vaspin levels decreased after moderate weight loss, accompanied by an improvement in parameters related to insulin resistance [6, 23].

In healthy children and adolescents, vaspin serum activity was increased in obese individuals as compared to slim ones. Plasma vaspin concentration positively correlated with BMI-SDS (body mass index standard deviation score), the concentration of triglycerides, fasting insulin, and HOMA-IR index, and negatively correlated with plasma concentrations of adiponectin and the fasting glucose-to-insulin ratio (FGIR) [24].

Omentin and adipose tissue and type 2 diabetes

Omentin-1 is the major isoform circulating in human plasma [13]. The serum omentin concentration is decreased in obese patients along with decreased omentin-1 and omentin-2 expression in visceral adipose tissue [19]. A huge difference in omentin gene expression has been shown between the 2 major fat stores [14]. Omentin expression was found to be higher in human VAT than in subcutaneous fat. Studies have also proven a negative correlation between omentin expression in VAT and BMI, and insulin resistance [18, 25]. Clinical trials demonstrated that serum omentin-1 concentration is significantly decreased in patients with DM2, obesity, and metabolic syndrome as compared to healthy controls [18, 26, 27].The concentration of omentin-1 is negatively correlated with the consumption of saturated fatty acids, BMI, insulin resistance, total cholesterol, glycated haemoglobin ($HgbA_{1c}$), leptin, and systolic blood pressure. In contrast, it is positively correlated with the concentration of adiponectin and high-density lipoproteins, as well as the size of lipoprotein particles with a very high low density (VLDL). Serum omentin-1 levels decreased in diabetes complications such as retinopathy, nephropathy, and neuropathy [13, 18, 26].

Lower serum omentin-1 concentrations were associated with obesity and insulin resistance in children [28]. In contrast, higher vaspin concentrations were found in obese children with metabolic syndrome as compared to healthy controls. In addition, the concentrations of both omentin and vaspin were significantly correlated with high CRP values [29].

The analysis of the studies on omentin and vaspin showed that their concentration in blood, as well as their expression in adipose tissue, are dependent on BMI and insulin sensitivity. Adults, children, and adolescents with normal weight have decreased vaspin serum concentration and increased omentin serum concentration compared to obese people. Obese adults, children, and adolescents have increased vaspin serum concentration and decreased omentin serum concentration compare to normal-weight adults, children, and adolescents. Therefore, vaspin and omentin are presumed to be candidate biomarkers of metabolic disorders.

Omentin in asthma and acute respiratory distress syndrome

A study by Pemberton *et al*. [30] proved that single nucleotide polymorphism in the human omentin gene was associated with an increased risk of asthma [30]. In addition, human omentin was found to be involved in the allergen-induced production of IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) in asthma and atopic dermatitis. It was shown that the expression of omentin was significantly increased in the airways of asthmatics and the skin of patients with atopic dermatitis (AD) as compared to healthy subjects [31]. Omentin-1 concentration in the sputum of patients with asthma exacerbation was significantly higher than in patients with stable asthma and in healthy subjects. It was noted that higher concentrations of omentin-1 in the bronchial mucus were associated with increased sputum eosinophils (> 2%). This is indirect evidence that omentin-1 may be upregulated by IL-13 in the airway epithelium. Upregulation of omentin-1 is a feature of 'T helper type 2-high' ('Th2-high') asthma. Indeed, high levels of omentin-1 are found in bronchial mucus during exacerbations in patients with this asthma endotype [32].

Omentin was demonstrated to have a protective effect against the development of acute respiratory distress syndrome (ARDS) caused by lipopolysaccharide (LPS), reduce the inflammatory response, and strengthen the pulmonary endothelial barrier. It was demonstrated that decreased circulating omentin levels negatively correlated with inflammatory parameters like white blood cell count or procalcitonin [33].

Vaspin in inflammatory bowel diseases

Serum vaspin levels were examined in patients with ulcerative colitis (UC), in patients with Crohn's disease (CD), and in healthy volunteers. They were found to be higher in the UC pa-

tients as compared to CD and controls. Moreover, it was shown that serum vaspin concentrations increased with induction of UC remission. These observations indicated that vaspin may be a useful biomarker of UC activity [34].

Omentin in inflammatory bowel diseases

A cross-sectional study showed that serum omentin-1 levels were reduced in patients with CD and UC as compared to healthy controls. Moreover, serum omentin-1 levels were correlated with CD and UC activity. Consequently, it was suggested that decreased serum omentin-1 levels were associated with the presence and activity of IBD [35].

Due to the known anti-inflammatory properties of omentin and vaspin as well as fluctuations of serum concentrations and tissue expression of those adipokines, it can be assumed that omentin and vaspin are candidate biomarkers of IBD activity.

Vaspin and omentin in other inflammatory diseases

Alterations in serum vaspin concentration were observed in diseases associated with chronic inflammation, such as atherosclerosis, obesity, or rheumatoid diseases. Vaspin activity was increased in rheumatoid arthritis (RA), and this was not related to the homeostasis model assessment for insulin resistance (HOMA-IR) index or the carotid intima-media thickness (IMT) index. In contrast, in active Behcet's disease, vaspin concentrations were decreased. The results of these studies suggest that distinct chronic inflammatory processes have different effects on vaspin serum concentrations [36].

Omentin plasma concentrations were elevated in patients with systemic lupus erythematosus and psoriatic arthritis but not in patients with systemic lupus erythematosus and psoriasis without arthritis [13]. Omentin and vaspin concentrations in the synovial fluid varied depending on the site of local inflammation in patients with RA and osteoarthritis (OA). Patients with RA showed lower levels of omentin and higher levels of vaspin in the synovial fluid as compared to patients with OA [37].

Cantarini *et al*. [38] were the first to investigate vaspin and omentin concentrations in patients with juvenile idiopathic arthritis (JIA). They found that serum omentin concentrations were significantly higher in JIA patients as compared to healthy children. They demonstrated that serum omentin concentrations were positively correlated with the intensification of the inflammatory process and the number of joints involved. In contrast, serum vaspin concentrations did not show statistically significant differences between children with JIA with and without active arthritis [38].

The serum vaspin concentrations and the serum and synovial fluid omentin concentrations fluctuate depending on the presence or severity of systemic or local inflammation. Therefore, these adipokines can become markers of advancement in particular diseases, but this requires further research.

Summary

The adipokines, most importantly vaspin and omentin, act as hormones and cause an imbalance between pro-inflammatory and anti-inflammatory factors. Although the anti-inflammatory effects of omentin and vaspin have been convincingly proven, the exact mechanism of their action is not yet fully understood. Further research is needed for a better understanding of the biological effects of vaspin and omentin and their possible use as biomarkers in the diagnosis and staging of various inflammatory diseases.

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