Review paper

The roles of vaspin, chemerin, and omentin in the determination of metabolic syndrome

Rola waspiny, chemeryny i omentyny w determinowaniu zespołu metabolicznego

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Abstract

Metabolic syndrome (MetS) is defined as multiple risk factors including abdominal obesity, dyslipidaemia, abnormal glycaemia, and elevated blood pressure. The incidence of MetS and pathophysiological mechanisms underlying its development are still not fully understood. It is thought that the occurrence of MetS arises from the complex relationship between genetic and environmental factors. The aim of the study was to overview and summarise current knowledge regarding genetic determinants of MetS. Also analysed were the relationship between polymorphisms of the genes encoding selected adipokines (vaspin, chemerin, omentin) and the risk of MetS, as well as other metabolic disorders. The precise determination of MetS genotype is difficult because metabolic syndrome occurrence is a combination of multiple risk factors. A thorough understanding of pathomechanisms of MetS, involving selected adipokines, may in the future allow the use of these adipokines as potential biomarkers of metabolic disorder risk.

Streszczenie

Zespół metaboliczny (MetS) definiowany jest jako nagromadzenie czynników ryzyka, takich jak otyłość brzuszna, dyslipidemia, nieprawidłowa glikemia i podwyższone ciśnienie tętnicze. Przyczyny występowania MetS oraz mechanizmy patofizjologiczne leżące u podłoża jego rozwoju nadal nie zostały do końca poznane. Uważa się, że zespół ten wynika ze złożonej zależności pomiędzy czynnikami genetycznymi i środowiskowymi. Celem pracy był przegląd dotychczasowych badań nad genetycznymi uwarunkowaniami MetS oraz analiza powiązań między polimorfizmami genów kodujących wybrane adipokiny (waspinę, chemerynę, omentynę) a ryzykiem występowania MetS i innych chorób metabolicznych. Określenie genotypu charakterystycznego dla MetS jest trudne ze względu na współwystępowanie wielu czynników ryzyka. Zrozumienie patomechanizmu powstawania MetS, w tym udziału wybranych adipokin, może w przyszłości pozwolić na opracowanie biomarkerów chorób metabolicznych.

Background

In general, metabolic syndrome (MetS) is defined as a collection of multiple risk factors including abdominal obesity, dyslipidaemia, abnormal glycaemia, and elevated blood pressure [1]. Metabolic syndrome is also associated with an increased risk of type 2 diabetes, cardiovascular morbidity, and mortality [2–7]. Furthermore, there is an association between MetS and increased total cancer mortality [8, 9]. The incidence of metabolic syndrome and the pathophysiological mechanisms underlying its development are still not fully understood. It is believed that the occurrence of MetS arises from the complex relationship between genetic and environmental factors.

The aim of the study was to give an overview and summarise the current knowledge regarding genetic

determinants of metabolic syndrome. The relationship between polymorphisms of the genes encoding selected adipokines (vaspin, chemerin and omentin) and the risk of MetS, as well as other metabolic disorders, was also analysed.

Heritability as a metabolic syndrome risk factor

Based on the results of a family study conducted in 2015, it was concluded that daughters whose mothers had MetS had a higher risk of an occurrence of this syndrome than children whose fathers were suffering from MetS [10]. On the other hand, in Teheran the population with the highest risk of an occurrence of MetS components was observed among families whose fathers and offspring had abdominal obesity, dyslipidaemia, abnormal glycaemia, or elevated blood pressure [11].

According to reports [10, 12, 13], in 24–32% of cases, MetS is inherited. It was also found that the percentage of heritability varies and is dependent on the number of MetS components.

Bellia *et al.* demonstrated that among MetS subtypes, a cluster of three components (central obesity, hypertriglyceridaemia, and a low level of HDL) had the highest heritability at 31% [13].

Results of MetS component analysis, based on the Northern Manhattan Family Study, obtained two independent factors: factor 1 – lipids/glucose/obesity, and factor 2 – blood pressure, of which heritability accounts for 44% and 20%, respectively [12]. Panizzon *et al.* demonstrated that in a group of siblings in Vietnam, two main MetS factors can be selected. It was shown that insulin resistance (glucose, insulin), lipids (HDL, triglycerides – TG), and adiposity (body mass index – BMI, waist circumference) share genetic influences, which accounts for factor 1. They also detected genetic influences that were mutual for both adiposity and blood pressure (factor 2), but not with lipids or insulin resistance [14].

Multiple studies confirm that adiposity is the sole component of MetS that is genetically related to all the others. Long-term observation indicates that a large waist circumference precedes the appearance of other MetS components. The researchers suggest that genetic predisposition to adiposity may steer overlapping pathophysiologies in MetS components [15].

However, the precise determination of the MetS genotype is difficult because metabolic syndrome occurrence is a combination of multiple risk factors. In recent years, research on the most likely genetic variants of MetS have been conducted using molecular biology and statistical methods like multiple candidate gene association studies, linkage studies, and genome-wide association studies (GWAS), all with ambiguous results. For example, based on the results of GWAS, conducted by Zabaneh and Balding, it can be established that there are no common genetic mechanisms explaining MetS occurrence [16].

Nevertheless, there are many studies confirming that several candidate gene polymorphisms are associated with a risk of MetS occurrence. All data on this are shown in Table 1 [17–31].

In 2011 Avery *et al.* identified three new pleiotropic loci associated with multiple metabolic trait domains: APOC1, BRAP, and PLCG1 [22]. In the same year Kraja *et al.* demonstrated that five single nucleotide polymorphisms (SNPs) were associated with MetS and are located within three locations: LPL, CETP, and APOA5 cluster (including BUD13, ZNF259, and APOA5); all of these selected genes play an important role in lipid metabolism [20]. In 2012 Kristiansson *et al.* identified only one gene, namely SNP (rs964184) of ZPR1, which is significantly associated with MetS. Other identified mutations were located in or near a lipid-related genetic loci APOA1/C3/A4/A5, APOB, LPL, and CETP. However, the association was significant only with the TG/HDL/WC factor, but none was associated with two or more individual uncorrelated MetS components [18]. Other studies show that two SNPs, rs17782312 in MC4R (involved in weight regulation) and rs2943634 IRS1 (related to insulin resistance), were associated with MetS [28]. In 2014 Hashemi *et al.* found that the insertion/deletion polymorphism of 45-bp in UCP2 gene was significantly associated with MetS. The authors demonstrate that the I (insertion) allele decreased the risk of MetS in comparison with the D (deletion) allele [31]. In the Korean population two polymorphisms located near BUD13 (rs11216126, rs180349) were significantly related to MetS [24]. On the other hand, this significance was not confirmed among the Chinese population [32]. Comparative analysis in the African-American population identified 27 SNPs associated with various components of MetS. Unfortunately, only one rs12721054 in APOC1 was associated with all five of the studied components of the syndrome [23]. In 2015, GWAS was carried out on the African population identifying three mutations near RALYL, KSR2, and MBNL1 associated with MetS, and another two near CA10 and CTNNA3. The last two were specific to the African ancestry population [25]. In recent years Mirhafez *et al.* identified another SNP rs964184 in ZPR1, which was associated with MetS [33]. Lin *et al.* showed an association of MetS at the genome-wide significance level with two SNPs: rs16944558/COLEC12 and rs662799/APOA5 [21].

Although there are many reports describing the relation of gene variants and individual MetS components, there are only a few evaluating the most likely genetic basis of the syndrome.

Adipokines

In recent years, adipose tissue has become a main subject of intensive research. It was found that this tissue is not only limited to an energy storage function,

Table 1. Susceptibility gene candidates for Mets

Name/gene ID	Description	Gene location	SNPs candidates	References
ACE	Angiotensin-1-converting enzyme	17q23.3	(I/D) polymorphism	[17]
APOA1	Apolipoprotein A1	11q23.3	rs964184	[18]
APOA4	Apolipoprotein A4	11q23.3	rs964184	[18]
APOA5	Apolipoprotein A5	11q23.3	rs662799; rs3135506, rs2266788	[18–21]
APOB	Apolipoprotein A5	2p24.1	rs673548; rs6728178	[18]
APOC1	Apolipoprotein C1	19q13.32	rs4420638	[22, 23]
APOC3	Apolipoprotein C3	11q23.3	rs2854117; rs2854116	[18, 19]
BRAP	BRCA1 associated protein	12q24.12	rs11065987	[22]
BUD13	BUD13 homolog	11q23.3	rs10790162	[20, 24]
CA10	Carbonic anhydrase 10	17q21.33-q22	rs146816516	[25]
CETP	Cholesteryl ester transfer protein genes	16q13	rs708272; rs173539	[18, 19]
CIDEA	Cell death-inducing DNA fragmentation factor-like effector A	18p11.21; 18	rs11545881	[26]
COLEC12	Collectin subfamily member 12	18p11.32	rs16944558	[21]
CTNNA3	Catenin 3	10q21.3	rs77244975	[25]
ESR1	Oestrogen receptor	6q25.1-q25.2	rs9340799; rs2234693	[27]
FTO	Fat mass and obesity-associated gene	16q12.2	rs9939609	[19]
IL6	Interleukin 6	7p15.3	rs1800795	[19]
IRS1	Insulin receptor substrate 1	2q36.3	rs2943634	[28]
KSR2	Kinase suppressor of ras 2	12q24.22-q24.23	rs7964157	[25]
LPL	Lipoprotein lipase	8p21.3	rs7841189	[18]
MBNL1	Muscleblind like splicing regulator 1	3q25.1-q25.2	rs146816516	[25]
MC4R	Melanocortin 4 receptor	18q21.32	rs17782312	[28]
PLCG1	Phospholipase C g1	20q12	rs753381	[22]
PON	Paraoxonase	7q21.3	rs705379	[29]
RALYL	RALY RNA binding protein like	8q21.2	rs76822696	[25]
TCF7L2	Transcription factor 7-like 2	10q25.2-q25.3	rs7903146	[19]
TNF	Tumor necrosis factor	6p21.33	rs1800629	[30]
UCP2	Uncoupling protein 2	11q13.4	45bp (I/D) in exon 8	[31]
ZPR1 (ZNF259)	ZPR1 zinc finger	11q23.3	rs2266788	[20]

but it is also an active endocrine organ. Numerous compounds demonstrating hormonal properties, produced and secreted by adipocytes, have been identified – all defined as adipokines. The metabolic role of adipokines is varied – appetite regulation, maintaining energy balance, regulation of fat and carbohydrate metabolism, influence on insulin action, as well as adipose tissue remodelling – to name a few. It has been shown that adipokines are involved in angiogenesis and vascular remodelling, also in the formation of atherosclerotic plaque, as well as in the regulation of blood pressure and modulation of inflammatory and immunological processes. The number of newly discovered adipokines increases each year, three being particularly studied in the context of MetS.

Vaspin (SERPINA12) was first identified from visceral adipose tissue of a rat model with type 2 diabetes [34]. Initially, vaspin was classified as a member of the serpine (serine protease inhibitors) family, which was confirmed in 2013 based on a crystal structure [35].

The core structure consists of three-sheets and nine-helices. It was also shown that the reactive centre loop (RCL) is flexible and located between G364 and P381. Unfortunately, the mechanism of action was not established, but it was shown that the most likely target for vaspin is the kallikrein-related peptidase 7 (hK7) [35, 36]. The physiological functions of the vaspin target are diverse. The main role of kallikrein is the proteolysis of intercellular cohesive structures that precede desquamation, the shedding of the outermost layer of the epidermis. In recent years, an overexpression of hK7 was linked with ovarian, breast, and testicular cancer. An interesting fact is that the vaspin–hK7 system is linked to obesity-associated skin diseases such as psoriasis. It was also reported that vaspin exhibits glucose lowering effects. The mechanism of glucose level regulation is based on increasing the half-life of insulin rather than improving insulin-mediated glucose uptake [35, 37].

Several studies reported higher vaspin concentrations in adult women compared with men [38–40], whereas others did not [41]. Körner *et al.* showed that gender differences arise during pubertal progression in girls and are not present in pre-pubertal children. It was also observed that vaspin increased with puberty in girls, but not in boys [42]. Xu *et al.* reported that plasma vaspin increased with aging in both males and females, but to a lesser extent in males [43]. Plasma vaspin levels were increased in both the midcycle and the luteal phases compared to the follicular phase in women, these increases being proportional to the changes in oestrogen and 17-OH progesterone levels [44]. As it was shown, the vaspin concentration was varied and dependent on many physiological factors.

Various positive associations between a serum vaspin concentration and obesity indicators have been demonstrated [38, 41, 45–50]. The most significant was observed between vaspin concentration and the percentage of body fat [45]. In 2014 Feng *et al.* conducted a meta-analysis based on databases of Medline, PubMed, and EMBASE. It was found that the level of vaspin was 0.52 ng/ml higher ($p < 0.05$) in obese subjects than in non-obese healthy control subjects [48]. Liu *et al.* demonstrated that vaspin is able to promote the differentiation of 3T3-L1 preadipocytes and may increase their sensitivity to insulin and suppress obesity [51]. Choi *et al.* also noted positive correlations between plasma vaspin concentrations and body mass index, waist circumference, and percentage of body fat – but only in men [52]. Farmazi *et al.* showed that training for 12 weeks (three sessions per week, 1 h per session) in overweight women (BMI > 25 kg/m²) had a significant effect on the decrease of BMI ($p < 0.05$), waist circumference (WC) ($p < 0.05$), body fat ($p = 0.05$), and vaspin ($p < 0.05$) [53]. On the other hand, Auguet *et al.* and Sperling *et al.* stated that

there is no correlation between vaspin concentration and obesity [54, 55].

A new approach was presented by Wada in 2008. Based on *in vivo* studies, it was shown that an injection of recombinant vaspin in subject mice improved glucose tolerance and increased insulin sensitivity [56]. Many researchers suggest that this increased expression of vaspin genes plays an important compensatory role in obesity and insulin resistance [57, 58]. An interesting observation was demonstrated in the independent research of Ataya *et al.* and Feng *et al.* Considering the duration of diabetes, the negative correlation between time and vaspin concentration was shown [48, 59]. Based on these results, Dimova *et al.* suggested that vaspin plays a compensatory role in glucose metabolism disorders at the outset of type 2 diabetes (T2DM), and its secretion capacity gradually declines with the increase of the diabetes duration [60]. However, the results of studies conducted on humans are ambiguous. Most of them did not show increased levels of vaspin in patients with diabetes [38, 58, 61–63]. Moreover, some of the results showed decreased vaspin concentrations in patients with diabetes [64, 65]. The investigation into the relation of the vaspin variant and type 2 diabetes show that the AA genotype of vaspin rs2236242 confers an increased risk of type 2 diabetes when compared with the TT genotype. Patients who were homozygous for the rs2236242 A allele had a 2.33-fold increased risk of type 2 diabetes [66]. Hida *et al.* confirmed that, in vivo, serum vaspin levels are elevated in individuals with impaired fasting glucose or impaired glucose tolerance and type 2 diabetes. Vaspin levels did not correlate with HOMA or insulin levels; however, they correlated with fasting plasma glucose, suggesting a role in glucose metabolism, particularly in the fasting state [39]. The previously mentioned research by Feng *et al.*, based on meta-analysis, demonstrated that the level of vaspin is 0.36 ng/ml higher in patients with type 2 diabetes compared with the control subjects [48]. Two years of prospective studies confirmed that a low serum concentration of vaspin is a risk factor for the progression of type 2 diabetes. The authors have shown that decreased baseline serum vaspin is an independent risk factor for the subsequent occurrence of diabetes in non-diabetic subjects and a higher risk for insulin treatment in diabetic patients [67]. The most recent results conducted by Abdel Ghany *et al.* in 2017 described the novel, protective role of vaspin variant in obesity. The minor A allele of vaspin rs2236242 polymorphism plays a protective role against obesity and diabetes, but this association is largely ascribed to its effect on insulin resistance [68].

As mentioned before, there are many associations between vaspin and various physiological and patho-physiological processes. It has been shown that an increased vaspin concentration is related to polycystic ovary syndrome (PCOS) [45, 69]. Moreover, Serum

vaspin levels reflect the severity of polycystic ovary syndrome [69]. Kohan *et al.* suggest that allele A of vaspin rs2236242 gene polymorphism decreases the risk of PCOS compared to the T allele. This relation was not shown to be statistically significant after adjusting genotypes for BMI. It was suggested that this relationship is affected by obesity status [70]. A relationship between the plasma vaspin concentration and the presence of coronary artery disease was also observed [71, 72]. Choi *et al.* demonstrate that vaspin concentrations are associated with the presence and severity of coronary atherosclerosis, but only in female patients [52]. Some results suggest that vaspin cannot be used as an independent marker for the presence of coronary artery disease in the general population. However, recent results have confirmed that the vaspin level is associated with the presence of coronary artery disease in patients with type 2 diabetes [58, 73].

Another correlation was observed between vaspin concentration and the limitation of endothelial cell apoptosis caused by free fatty acids [74]. It was also implied that vaspin alleviates the dysfunction of endothelial progenitor cells induced by high glucose [75]. It can be assumed that vaspin indirectly affects many metabolic functions, which may be crucial in the development of MetS.

According to many authors, the exact relationship between many metabolic disorders, such as obesity, diabetes, polycystic ovary syndrome, and coronary artery disease, and vaspin has become a potential biomarker for metabolic syndrome.

In the earliest analysis of reports from 2011, it was shown that plasma vaspin concentrations were significantly higher in men with metabolic syndrome (Me = 0.60 ng/ml) compared with those without MetS (Me = 0.40 ng/ml). These relationships were not found in women [52]. Esteghamati *et al.* detected elevated vaspin levels in the presence of MetS in both genders and assigned vaspin as a predictor for MetS. Moreover, vaspin was found to be the most significant predictor for reduced HDL-cholesterol and raised waist circumference, fasting plasma glucose, and triglycerides, after controlling for age in both sexes [76]. Karbek *et al.* confirmed that serum vaspin levels are significantly higher in patients with MetS than age-matched control subjects [77]. In 2016, Alnory *et al.* analysed vaspin concentrations in Egyptian women with MetS and in control subjects. Significantly higher serum levels of vaspin were observed in patients with MetS (3.34 ±0.52 ng/ml) in comparison to non-MetS cases (1.87 ±0.54 ng/ml). The researchers concluded that serum vaspin concentrations can be used as diagnostic markers of metabolic syndrome [78]. Other researchers have demonstrated that non-alcoholic fatty liver disease and related entities, found in as many as 90% of subjects with MetS, have also been associated with an elevated levels of serum vaspin [79]. Based on re-

search conducted on obese patients (BMI ≥ 30 kg/m²), Mirzaei *et al.* noted that the concentration of vaspin is significantly higher in participants with MetS compared to non-MetS subjects [80]. In 2014 Lu *et al.* came to the same conclusion after an examination of patients undergoing bariatric surgery (BMI ≥ 40 or BMI ≥ 35 kg/m² with associated comorbidities). There were significant associations of high vaspin levels with glucose and lipid-related metabolic parameters in severely obese patients, as well as post-operative increases in vaspin levels, and correlations of higher pre- and postoperative vaspin concentrations with better metabolic profile [81]. Studies carried out on the Caucasian population demonstrate no overt fluctuations in vaspin levels in the early stages of glucose intolerance and MetS [60]. Opposing results were previously reported by Kim *et al.* The authors demonstrated that serum vaspin concentration was significantly lower in men with MetS than in men without MetS. This research was conducted on the Korean population. It was shown that serum vaspin levels tended to decrease with an increasing number of metabolic syndrome components, and was negatively correlated with waist circumference, serum triglyceride level, and systolic and diastolic blood pressure, but positively correlated with HDL-cholesterol level. However, after adjusting for sex, this correlation disappeared [40]. Auguet *et al.* reported that serum vaspin levels were not increased in morbidly obese women (BMI ≥ 40 kg/m²) and that they did not correlate with BMI and markers of glucose or lipid metabolism [54]. Amouzad Mahdirejei *et al.* demonstrated that serum vaspin levels do not correlate with anthropometric and metabolic parameters, and an 8-week resistance training programme significantly improved the insulin resistance index. However, this form of exercise failed to result in significant changes in serum vaspin concentration and lipid profiles [82].

A new approach considers the association of vaspin variants and MetS prevalence. Hashemi *et al.* demonstrated that genotype frequencies of vaspin rs2236242 were significantly different between subjects with and without MetS, in both genders. The minor allele frequency (A allele) of rs2236242 polymorphism in subjects with and without MetS was 0.334 and 0.490, respectively. In patients carrying the A allele, the risk of MetS was found to be significantly lower (OR = 0.52 (0.37–0.72)). Furthermore, it was shown that vaspin rs2236242 polymorphism was resistant against MetS in dominant, codominant, and recessive tested inheritance models, and the associations remained almost unchanged after adjusting for age and gender [83]. In the Egyptian population of woman, Mahanna confirmed that the minor A allele of vaspin rs2236242 polymorphism plays a protective role against MetS (OR = 1.973 (1.227–3.171)). The carriers of vaspin rs2236242 TA and AA genotypes also significantly decreased BMI, waist circumference, sys-

tolic and diastolic blood pressures, fasting blood glucose (FBG), fasting serum insulin, insulin resistance, TG, total cholesterol (TC), and LDL-C and increased HDL-C compared with the carriers of the TT genotype [84]. Opposing results were published by Alnory *et al.* They showed no significant difference in the allele and genotype frequency of vaspin rs2236242 polymorphism between the MetS and non-MetS groups. In addition, no significant difference in the vaspin levels between different polymorphic forms of vaspin rs2236242 was detected [78].

Chemerin is also known as *tazarotene-induced gene 2* (TIG2) or retinoic acid receptor response protein 2 (RARRES2). The gene encoding preprochemerin (RARRES2) is located on 7q36.1 in humans. Interestingly, chemerin is mainly produced in the liver and adipose tissue, but it is also expressed in many other locations including the adrenal glands, placenta, pancreas, lungs, and skin [85].

It has been shown that chemerin has been secreted as an inactive precursor, prochemerin, which is an amino acid 143. Proteolytic processing of the C-terminus of prochemerin is required for this protein to become an active chemoattractant [86]. Recently, many isoforms of chemerin have been identified in various tissues. It is already known that chemerin is a multifunctional protein due to the significance of receptors. Chemerin is primarily identified as the natural ligand of chemokine-like receptor 1 (CMKLR1), which is expressed on several immune cell subsets, such as plasmacytoid dendritic cells, macrophages, and natural killer cells [87]. Therefore the response to chemerin arises through chemotaxis or the modulation of their defence function. In recent years, new functions of chemerin have been discovered, linking this protein with metabolism regulation. Chemerin is an adipocyte signalling molecule important in adipogenesis, and it also plays a role in angiogenesis, osteoblastogenesis, myogenesis, and in regulating glucose homeostasis [85, 88].

There are many studies which evaluate the correlation between chemerin levels and gender, producing ambiguous results. Stejskal *et al.* found no statistically significant difference in chemerin levels between men and women [89]. Bozaoglu *et al.* and Lehrke *et al.* noted higher chemerin levels in older individuals compared with younger individuals. Significant differences were observed in females compared with males, amounting to 188.5 ±65.3 and 168.2 ±55.7 ng/ml, respectively [90–92].

The same studies carried out on the Chinese population showed different dependencies. Chemerin levels were significantly higher in male than in female subjects [93]. Landgraf *et al.* demonstrated that in a group of non-obese and healthy children (age 7–18 years), chemerin serum concentrations showed a negative correlation with age ($r = -0.31$) and pubertal stage ($r = -0.24$). There was a significant decrease

in serum chemerin concentrations between prepubertal, pubertal, and postpubertal boys, but not girls [94]. Differences in chemerin concentration were also present in correlation with physiological stages in woman. The concentrations of chemerin were lower in peri- and premenopausal women (median = 118.0 ng/ml (99.2–135.0)), compared with postmenopausal women (median = 140.0 ng/ml (121.0–167.0)) [95].

There is an increasingly prominent premise that chemerin is involved in the pathophysiology of several metabolic and non-metabolic disorders. It has been reported that chemerin concentrations were significantly higher in obese compared to lean children and correlated with obesity-related parameters such as BMI SD score, leptin, and skinfold thickness [94]. It was also shown that in adults, chemerin levels were significantly associated with measures of body fat (weight, BMI, waist/hip ratio (WHR), fat mass – mainly visceral) [90, 96–98] and with adipocyte volume [99]. Cătoi *et al.* demonstrate that serum levels of chemerin were increased in morbidly obese men and women (74.20 ng/ml (58.31–116.90)) when compared with normal weight, healthy control subjects (25.45 ng/ml (19.75–30.10)) [100]. According to Bozaoglu *et al.*, plasma chemerin levels could be a stimulator of angiogenesis. This function of chemerin suggests a role in the development of obesity through the promotion of angiogenesis within the expanding adipose tissue mass [101]. Additionally, partial correlation analyses showed that the serum chemerin was positively correlated with waist circumference and WHR, but not with BMI [102]. However, Stejskal *et al.* demonstrated that after adjustments for age and gender, chemerin levels were not corelated with fat indicators (BMI, WC) [89]. Research conducted by Sell *et al.* showed that the average chemerin concentration was significantly higher in women with severe obesity (BMI > 50.0 kg/m^2) in comparison with healthy woman ($p < 0.001$). The concentration amounted to 353.8 ±18.0 ng/ml and 191.0 ±14.0 ng/ml, respectively. Chemerin levels were re-examined 1 year after the subjects' bariatric operation, which induced the weight loss. Serum chemerin concentrations decreased significantly to an average value of 253.0 ±14.9 ng/ml, and after 2 years a greater decrease was observed [103]. Similar research was conducted by Ress *et al.* Eighteen months after bariatric surgery a significant decrease of serum chemerin concentrations was observed (175.91 ±24.5 ng/ml before surgery and 145.53 ±26.44 ng/ml after surgery) [104]. Chakaroun *et al.* investigated the chemerin level variation in three groups of obese subjects after three types of intervention – including 12 weeks of exercise, six months of calorie-restricted diet, and bariatric surgery. All interventions led to significantly reduced serum chemerin concentrations. There are many reports demonstrating that after diversified training, serum chemerin levels decreased in overweight or obese individuals [53, 105–107].

In many reports, it is also suggested that chemerin participates in the regulation of carbohydrate metabolism, and its serum levels correlate with fasting blood glucose, fasting insulin, HOMA-IR, glycated haemoglobin (HbA$_{1c}$), independently of age and BMI [103, 108–111]. However, the relationship between chemerin and diabetes remains controversial. Increased levels of chemerin that occur with obesity are hypothesised to be a causal factor in the development of type 2 diabetes as a consequence of the dysregulation of the key physiological processes regulated by this adipokine [112]. Many researchers report that serum chemerin levels are significantly elevated in individuals with diabetes [99, 108, 109, 111, 113]. Fatima *et al.* suggest that chemerin may serve as a potential screening marker in the diagnosis of diabetes or predicting the risk of the development of diabetes in asymptomatic individuals [110]. According to Bozaoglu *et al.* and Weigert *et al.*, plasma chemerin levels were not significantly different between subjects with type 2 diabetes and normal control subjects [90, 91, 114]. Moreover, Gateva *et al.*, in the latest research, detected no significant differences between subjects with prediabetes (impaired fasting glucose and/or impaired glucose tolerance) and obese subjects with normoglycaemia [115]. Takahashi *et al.* established that there is a significant difference in chemerin concentration in patients with diabetes (164.9 ±6.3 ng/ml) compared with control subjects (218.7 ±7.3 ng/ml). It was also reported that fasting glucose levels were negatively associated with serum chemerin levels – but only in male subjects [93]. Controversial results were also obtained after a comparison of serum chemerin levels in pregnant women with gestational diabetes and healthy pregnant women [116, 117].

Weigert *et al.* showed that serum chemerin concentration was elevated in T2DM subjects with higher CRP levels (> 5 ng/ml) and positively correlated with CRP in normal-weight, overweight, and T2DM subjects, after adjusting for BMI and WC. The authors proposed that systemic chemerin levels are related to inflammation rather than obesity in T2DM subjects [114]. Serum chemerin levels were significantly higher in the group with coronary artery disease (CAD), in comparison with those who did not have CAD [118–121]. In addition, serum chemerin concentration was correlated with the severity of the disease [119]. Although significantly high serum chemerin levels were found in CAD, it is not known if this increased level represents a predictor for CAD or if it is a result of atherosclerotic plaque morphology [92, 122]. Hart *et al.* reported that chemerin stimulates the adhesion of macrophages to extracellular matrix protein fibronectin and vascular cell adhesion molecule 1 (VCAM-1). This process has been proposed to contribute to the progression of atherosclerosis [123]. Prospective studies demonstrate that there is a strong positive association between chemerin concentrations at baseline and

risk of heart failure. Participants in the fourth quartile of chemerin had more than four-times higher a risk of heart failure [124]. According to Aydin *et al.*, chemerin was not found to be an independent risk factor for predicting atherosclerosis in diabetes and prediabetes [125]. Ebert *et al.* demonstrated that chemerin, showing the strongest association with MetS components in the general population, suggests that adverse adipose tissue function is a major contributor to these metabolic abnormalities [126].

Lehrke *et al.* found that chemerin is associated with markers of inflammation and components of metabolic syndrome, but does not predict coronary atherosclerosis [92]. On the other hand, Aronis *et al.* were not able to show chemerin as a predictor of acute coronary syndrome [127]. Some studies showed a significant increase of chemerin level in non-alcoholic fatty liver disease (NAFLD) patients [128, 129]. It was implied that this increase is connected with obesity [130]. The ambiguous results of a met-analysis conducted in 2016 did not confirm the relationship between chemerin and NAFLD [131]. Increased serum chemerin in women with PCOS, with or without obesity, suggest that chemerin may be involved in the development of the pathogenesis of PCOS [132]. It has also been shown that there is no significant association between chemerin rs17173608 gene polymorphism and PCOS, after adjusting genotypes for BMI; notedly, this relationship was affected by obesity status [133]. An interesting result was published by Adrych *et al.* According to the authors, there is an association between chronic pancreatitis in humans and an increased serum chemerin concentration [134]. It can also be concluded that chemerin may also be a distinctive regulator of blood pressure because of its significant (high) correlation with diastolic pressure [110]. This effect of chemerin on blood pressure may also be related to its high expression by the kidneys, which is the primary regulator of blood pressure [89].

Numerous studies have demonstrated the relationship between chemerin and MetS components, including triglycerides, HDL-cholesterol, and blood pressure [89, 90, 92, 135–137]. In 2008, Stejskal *et al.* determined that serum chemerin levels correlated with a number of metabolic syndrome risk factors (r = 0.47) [89]. However, a meta-analysis consisting of eight studies (1787 patients) demonstrated that among six MetS components, only WC and TG were positively correlated with chemerin concentration [97]. From a number of reports analysing the correlation between serum chemerin concentration and MetS as a whole, no individual components demonstrate that the level of serum chemerin was significantly elevated in MetS patients compared to healthy control subjects [102, 118, 138, 139]. It was shown that after adjustments for body fat percentage, the chemerin concentration was 3.0 ng/ml higher in those with metabolic syndrome than in those without [140]. In a study of Caucasian

individuals, at a serum chemerin cut-off level of 240 µg/l, the presence of metabolic syndrome was diagnosed with 75% sensitivity and 67% specificity [89]. A meta-analysis of GWAS combined with mRNA expression studies in three independent cohorts from Europe highlighted the role of genetic variation in the RARRES2 locus in the regulation of circulating chemerin concentrations [141]. Analysis of RARES2 expression demonstrate a strong association with MetS ($p = 1.9 \times 10^{-5}$) and with the individual components of MetS: waist circumference ($p = 1.6 \times 10^{-8}$), HDL ($p = 2.0 \times 10^{-5}$), and diastolic blood pressure ($p = 1.5 \times 10^{-4}$) [142]. Hashemi *et al.* observed a positive association between chemerin rs17173608 polymorphism and the risk of MetS. The minor allele frequency (G allele) of rs17173608 polymorphism in subjects with and without MetS was 0.21 and 0.13, respectively. The risk of MetS occurrence significantly increases in patients carrying the G allele (OR = 1.78, 95% CI: 1.14–2.75, $p = 0.021$). According to the authors, chemerin rs17173608 polymorphism increases the risk of MetS in codominant and dominant tested inheritance models (OR = 2.13, 95% CI: 1.23–3.70, $p = 0.007$, TT vs. TG; and OR = 2.03, 95% CI: 1.22–3.40, $p = 0.007$, TT vs. TG-GG, respectively) [83]. Mehanna *et al.* confirmed that in Egyptian females, the minor G allele of the chemerin rs17173608 polymorphism had a significantly higher frequency in metabolic syndrome patients than in the control subjects (OR = 0.351, 95% CI: 0.198–0.625, $p = 0.0001$), and the frequencies of TG and GG genotypes were significantly higher in metabolic syndrome patients (OR = 0.320, 95% CI: 0.166–0.619, $p = 0.0001$). The carriers of the G allele in the homozygous and heterozygous forms (GG and TG genotypes) also showed significantly higher BMI, waist circumference, systolic and diastolic blood pressures, fasting blood glucose, fasting serum insulin, insulin resistance, triglycerides, and total and LDL cholesterol, and lower HDL-cholesterol, compared with the carriers of the TT genotype [84].

Omentin, also known as intelectin 1 (ITLN1), was described in 2003 as a new adipokine secreted from omental adipose tissue. ITLN1 is coded by two genes (1 and 2) from which corresponding isoforms are formed. The arising mRNA is primarily expressed in the stromal vascular fraction. The final hydrophilic protein contains 313 amino acids (35 kDa) in which a secretory signal sequence and a fibrinogen-related domain can be distinguished. The role of omentin is not fully understood, but it is likely that ITLN1 enhances insulin-mediated glucose uptake in adipocytes and activates protein kinase Akt/PKB [143]. Based on the latest research, it can be assumed that omentin takes part in the connection between many organs and in the regulation of many physiological and pathological processes. There is a supposition that omentin inhibits TNF-α-induced cyclooxygenase-2 (COX-2) expression via pathway AMPK active

(eNOS)/NO, which inhibits Jun N-terminal kinase (JNK) signalling, and following this, acts as an anti-inflammatory in endothelial cells. As a consequence of the activation of eNOS/NO path, vasodilation occurs in isolated blood vessels and decreases the agonist-induced increase in blood pressure [144, 145]. Moreover, the omentin-induced AMPK phosphorylation can reduce the RAS/ERK signalling cascade. These actions can be accompanied by the reduction of cardiac hypertrophy and smooth muscle cell (SMC) proliferation [146].

In 2014, Kataoka *et al.* established that omentin can promote the AMPK/AKT pathway directly by suppressing myocyte apoptosis in acute ischaemic heart injury, and can decrease the expression of pro-inflammatory mediators, including TNF, IL-6, and the monocyte chemotactic protein-1 (MCP-1) in macrophages [143]. In 2011, Duan *et al.* proposed that omentin inhibited osteoblastic differentiation of CVSMCs through the PI3K/Akt signalling pathway. It was also suggested that the lower omentin levels in obese (especially in visceral obese) subjects contribute to the development of arterial calcification, with omentin playing a protective role against arterial calcification [147].

It was also suggested that omentin inhibited NOX/p38/HSP27 pathways to prevent platelet-derived growth factor (PDGF-BB)-induced smooth muscle cell (SMC) migration. These may be related to the protective role of omentin in neointimal hyperplasia [148]. However, specific receptors for omentin have not yet been identified.

Major parts of these reports demonstrate that serum omentin-1 concentration is higher in the case of females in comparison with males [149, 150]. Opposing results were published by Moreno-Navarette *et al.* [151]. Lesná *et al.* and Vu *et al.* claimed that there is no significant difference between omentin concentrations in males and females [152, 153]. Until now, there have been no reports demonstrating a correlation between serum omentin-1 and age.

It was previously shown that baseline and post-weight loss omentin-1 concentration were significantly higher in obese men than women, and averaged 48.1 ±8.3 vs. 40.3 ±8.6 ng/ml in baseline serum, respectively, and 56.4 ±8.7 vs. 49.5 ±8.03 ng/ml in post-weight loss serum, respectively [151]. Tan *et al.* demonstrated that the expression of ITLN1 mRNA in adipose tissue and serum concentration of omentin-1 were negatively corelated with 17-oestradiol [154]. According to Luque-Ramirez *et al.*, gender, BMI, and free testosterone explained 48% of variability of ITLN1 values in the areas under the oral glucose tolerance rest curve [155]. Numerous reports show that serum omentin-1 was lower in obese than in lean individuals and negatively correlated with body weight, weight gain, BMI, waist and hip circumferences, fat mass, and visceral fat area [54, 100, 149–151, 156, 157]. Additionally, in

morbidly obese subjects, omentin-1 levels were decreased when compared with normal-weight healthy subjects [100, 158]. Furthermore, it was demonstrated that omentin-1 probably plays an protective role in obesity-related inflammation [100, 159]. A study conducted on a population of pregnant women demonstrate that pre-existing maternal obesity is associated with lower omentin-1 expression in the placenta, adipose tissue, and maternal plasma [160]. Opposing results were obtained in 2017 by Montazerifar *et al.* According to these authors, serum omentin-1 levels did not correlate with BMI, whereas a negative correlation was found between serum omentin-1 and waist circumference, suggesting that BMI is a weaker surrogate for body fat distribution than WC [161]. As previously mentioned, there are no reports establishing a correlation between serum omentin and age. However, it has been shown that in children and adolescents, likewise in adults, serum omentin-1 is lower in the obese than in the lean [162–164]. Furthermore, Oświęcimska *et al.* reported that the mean serum omentin concentration in girls with anorexia nervosa (46.1 ±3.8 ng/ml) was statistically significantly higher than that of healthy (34.3 ±2.6 ng/ml) and obese girls (30.7 ±2.5 ng/ml) [163]. Hamnvik *et al.* found that omentin-1 does not display any day-night variation and that omentin-1 levels remain unaltered in both chronic and acute energy deprivation [165]. Recent findings by Nway *et al.* suggest that omentin may also be involved in the regulation of appetite. Omentin expression correlated with neuropeptide Y expression in both types of adipose tissue [166]. It was also proposed that omentin-1 variants may be important in obesity. However, Splichal *et al.* identified that polymorphism Val109Asp in the omentin gene did not differ in genotype distribution and/or allele frequency between the obese and non-obese cohorts. Nevertheless, there were significant differences in genotype distributions of rs2274907 Val109Asp polymorphism in the omentin gene between the obese and morbidly obese cohorts. It was also found that the TT genotype of rs2274907 polymorphism was associated with the lowest (7877 ±2780 J/day) and the AA genotype with the highest (8764 ±2467 J/day) energy intake [167]. In the Kyrgyz population, significant associations between Val109Asp polymorphism in omentin gene and abdominal obesity was noted. An increased risk of abdominal obesity was associated with homozygous genotype Val109Val. Frequencies of Asp109Asp, Val109Asp, and Val109Val genotypes among individuals with abdominal obesity (48, 40, and 12%, respectively) were different from those among control subjects (Asp109Asp – 53%, Val109Asp – 43%, and Val109Val – 4%) [168]. Saremi *et al.* examined the effects of 12 weeks of aerobic training on serum omentin-1 concentrations [169]. Omentin-1 concentration was significantly increased after the aerobic programme and correlated with changes in waist circumference, insulin resistance,

glucose concentration, and aerobic fitness. Ouergh *et al.* found an increase in plasma omentin levels following an 8-week high-intensity interval training in both overweight/obese and normal-weight untrained young men [170]. Wilms *et al.* showed a strong relationship between exercise performance and circulating omentin-1 levels as well as an increase of the adipokine in response to a 6-week endurance training programme in obese women [171]. A 16-week exercise training programme resulted in a significant increase in serum omentin-1 concentrations in obese children. The authors suggest that exercise-induced changes in omentin-1 may be associated with the beneficial effects of exercise on reduced insulin and weight loss [172]. Numerous research papers show that omentin concentration was inversely correlated with glucose metabolism markers [54, 113, 150, 173]. In Caucasians, the correlation between ITLN1 gene variants and type 2 diabetes occurrence was not identified [174]. El-Mesallamy *et al.* observed significantly reduced serum omentin-1 concentration in type 2 diabetes patients (19.7 ±1.0 ng/ml), compared with healthy control subjects (27.4 ±2.6 ng/ml) [113]. Akour *et al.*, in a cross-sectional study, found lower omentin-1 concentrations in plasma in pre- or diabetic obese patients compared to normoglycaemic subjects [175]. It is thought that omentin-1 levels are closely associated with the endogenous insulin reserve [176]. Serum and vitreous omentin-1 levels in patients with proliferative diabetic retinopathy were markedly decreased compared with those without diabetic retinopathy, with non-proliferative diabetic retinopathy, and with the healthy control subjects [177]. Meta-analysis conducted by Tang *et al.* suggested that circulating omentin-1 levels are significantly lower in women with polycystic ovary syndrome compared with control subjects, which indicates that omentin-1 may play a role in the pathologic processes of polycystic ovary syndrome [178]. In analysing obstructive sleep apnoea syndrome, it was found that the omentin serum levels were low [179, 180]. The same results were obtained after analysing serum omentin levels in inflammatory diseases [148, 181]. It has also been suggested that omentin-1 rs2274907 polymorphism might be a candidate genetic factor for susceptibility to nonalcoholic fatty liver disease [70]. However, according to Wittenbecher *et al.*, despite inverse associations of omentin-1 with measures of body fat, no indication of a diabetes protective role of omentin-1 was found in prospective analyses [182]. In studies conducted on patients in the range of 62–81 years of age, the correlation between higher serum levels of omentin-1 and increases in fasting glucose, 2-h glucose, HbA_{1c}, and with incident type 2 diabetes, were significant [183]. Research conducted by Yilmaz *et al.* demonstrate that omentin levels were elevated in nonalcoholic fatty liver disease, which is a medical condition co-occurring with obesity and diabetes, although obesity and diabetes are

associated with low concentrations of omentin [184]. According to Montazerifar, there is no significant difference between serum omentin level between nonalcoholic fatty liver disease patients and control subjects [161]. Wang considers that these contradictory results may indicate an adaptation response [158].

In recent findings, Harada *et al.* demonstrated that plasma omentin levels were lower in patients with coronary artery disease compared with control subjects (343 ±158 ng/ml vs. 751 ±579 ng/ml) and were negatively associated with the expression of omentin in epicardial adipose tissue in patients with coronary artery disease. There was no significant difference between patients with coronary artery disease and control subjects regarding omentin Val109Asp polymorphism [185]. However, a 2.5-fold increase in Val/Val genotype was detected in subjects with coronary artery disease [186]. The results of Jamshidi *et al.* indicate that the Asp allele of Val109Asp (T allele of rs2274907) is more frequent among men with coronary artery disease than among healthy men [187]. In the Pakistani population, individuals having Val/Asp heterozygous genotype of omentin-1 gene polymorphism are at higher risk of developing coronary artery disease in comparison to Asp/Asp and Val/Val genotypes [188].

In most reports, the analysis was based only on the correlation between serum omentin concentration and MetS components. Less often the analysis considered omentin and MetS as a syndrome.

Shibata *et al.* reported that circulating omentin-1 levels were inversely correlated with the number of metabolic risks, such as increased waist circumference, dyslipidaemia, high blood pressure, and glucose intolerance. This was found in a study done on Japanese men who were taking no medications [189]. Liu *et al.* show that omentin-1 is closely related to MetS and might play an important role in atherosclerosis in MetS patients [190]. It was also reported that omentin-1 was negatively associated with waist circumference, systolic blood pressure, and fasting blood glucose. However, a significant difference was observed between men with metabolic syndrome, who had 20% lower plasma omentin-1 levels, and women with metabolic syndrome [153].

Circulating levels of omentin-1 were useful predictors of metabolic health status in overweight and obese individuals, but no association was seen between omentin-1 and metabolic health status in normal-weight subjects [191]. Jialal *et al.* reported that plasma levels of omentin-1 were 41% lower in patients with nascent MetS as compared with control subjects [137]. Moreover, omentin was associated with high-density lipoprotein cholesterol and inversely with triglycerides and glucose. Opposing results were found by Vu *et al.* According to these authors, plasma omentin-1 concentrations did not differ significantly between individuals with and without MetS (145.7

±70 ng/ml vs. 157.4 ±79.3 ng/ml, $p > 0.05$) [153]. However, men with metabolic syndrome had significantly lower omentin-1 levels than men without metabolic syndrome (129.9 ±66 ng/ml vs. 186.3 ±84.3 ng/ml, $p = 0.03$). Plasma omentin-1 concentrations were significantly correlated with HDL cholesterol in the entire study cohort ($r = 0.26$; $p = 0.01$), which was primarily driven by a correlation in men ($r = 0.451$, $p = 0.002$) and participants with metabolic syndrome ($r = 0.36$; $p = 0.003$). In the female population, there were no significant differences between plasma omentin-1 concentrations and metabolic parameters [192]. In prepubertal children (age 7 ±1 years), increased circulating omentin-1 was associated with a poorer metabolic profile, with higher fasting triglycerides and blood pressure, and familial prevalence of diabetes. In studies conducted by Kilic *et al.*, the plasma omentin concentration was similar in non-diabetic MetS patients and healthy control subjects, although the plasma omentin levels were correlated with high triglyceride and low high-density lipoprotein-cholesterol levels [193]. In an obese group of children, the omentin-1 level was negatively correlated with BMI, insulin, HOMA-IR, and WC, while no significant correlation was observed with systolic blood pressure (SBP), diastolic blood pressure (DBP), and triglyceride levels [162]. In obese children (12–17 years old), serum omentin-1 levels were significantly lower in the MetS group compared to the group without MetS (289.5 ±51.9 ng/ml vs. 268.2 ±60 ng/ml) [194]. To the best of our knowledge, there are no reports regarding omentin variants in MetS.

Conclusions

The adipokines that have been described in this paper significantly influence human metabolic homeostasis. However, current research sometimes presents ambiguous results. Consequently, precise evaluation of their role in the pathogenesis of some metabolic diseases, including the pathogenesis of MetS, is difficult. Further studies are necessary in order to determine whether the increased vaspin serum concentration observed in obese people is due to a compensation mechanism to increased insulin sensitivity, and if vaspin concentration could be a biomarker for insulin resistance. Similarly, it should be clarified if the increased concentration of chemerin accompanying obesity and type 2 diabetes is associated with the visceral fat accumulation in obese patients or with chronic inflammation. It would also be indispensable to study the association between ITLN1 polymorphisms and MetS prevalence. Furthermore, studies on the identification of omentin receptors are essential, as well as an evaluation of omentin concentration fluctuations depending on age.

A thorough understanding the pathomechanisms of MetS, involving vaspin, chemerin, and omentin,

may in the future allow us to use these adipokines as potential biomarkers of metabolic disorder risk. Those adipokines may also be vital to extend pharmacological strategies of metabolic disease treatment.

Conflict of interest

The authors declare no conflict of interest.

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