Review

The Role of Anti-Inflammatory Adipokines in Cardiometabolic Disorders: Moving beyond Adiponectin

Han Na Jung 1,2 and Chang Hee Jung 1,2,*

Citation: Jung, H.N.; Jung, C.H. The Role of Anti-Inflammatory Adipokines in Cardiometabolic Disorders: Moving beyond Adiponectin. Int. J. Mol. Sci. 2021, 22, 13529. https://doi.org/10.3390/ijms222413529

Abstract: The global burden of obesity has multiplied owing to its rapidly growing prevalence and obesity-related morbidity and mortality. In addition to the classic role of depositing extra energy, adipose tissue actively interferes with the metabolic balance by means of secreting bioactive compounds called adipokines. While most adipokines give rise to inflammatory conditions, the others with anti-inflammatory properties have been the novel focus of attention for the amelioration of cardiometabolic complications. This review compiles the current evidence on the roles of anti-inflammatory adipokines, namely, adiponectin, vaspin, the C1q/TNF-related protein (CTRP) family, secreted frizzled-related protein 5 (SFRP5), and omentin-1 on cardiometabolic health. Further investigations on the mechanism of action and prospective human trials may pave the way to their clinical application as innovative biomarkers and therapeutic targets for cardiovascular and metabolic disorders.

Keywords: adipokines; adiponectin; vaspin; CTRP9; SFRP5; omentin-1

1. Introduction

Obesity has been a growing threat worldwide owing to its association with various cardiometabolic disorders, including insulin resistance, type 2 diabetes mellitus (T2DM), fatty liver disease, and cardiovascular disease [1]. Accumulated evidence suggests that obesity-induced inflammation plays a key role in the pathogenesis of these disorders [1–3]. Obesity initiates chronic low-level inflammation, possibly by means of increased expression of pro-inflammatory genes and oxidative stress [2].

Contrary to the traditional concept of adipose tissue as an inert storage site for redundant energy, it is now highlighted as an endocrine organ that is involved in metabolic homeostasis. Since the characterization of leptin in 1994 [4], a number of adipocyte-derived compounds have been identified. These substances known as adipokines modulate appetite control, energy expenditure, insulin secretion, cardiovascular function, inflammation, immunity, adipogenesis, reproduction, and bone metabolism [5]. The inflammation and dysfunction of adipose tissue induce an alteration in adipokine secretion toward a pro-inflammatory, diabetogenic, and atherogenic pattern. Adipokines act not only locally by mediating the crosstalk between adipocytes, endothelial cells, and macrophages but also at the systemic level [2].

Most adipokines, including leptin, tumor necrosis factor-alpha (TNF-α), interleukin 6 (IL-6), resistin, or retinol-binding protein 4 (RBP4), are augmented in the obese state and promote inflammatory reactions, leading to obesity-associated comorbidities [6]. Contrarily, a smaller number of adipokines are produced by metabolically healthy adipose tissue to decrease inflammation and have protective effects on metabolic dysfunction [1]. This review focuses on the beneficial role of several anti-inflammatory adipokines of our interest in cardiometabolic disorders.
2. Adiponectin

2.1. Biological Actions

Adiponectin is one of the most extensively investigated adipokines since its first description in 1995 [7]. It is primarily produced by white adipose tissue, although additional sources, such as skeletal muscles or cardiomyocytes, have been known [8,9]. Circulating adiponectin exists in three different oligomers: low-molecular-weight trimer, middle-molecular-weight hexamer, and high-molecular-weight (HMW) multimer. HMW adiponectin is the principal bioactive form in metabolic tissues [10]. Activation of the two recognized receptors for adiponectin, AdipoR1 and R2, is linked to the stimulation of AMP-activated protein kinase (AMPK), p38 mitogen-activated protein kinase, and peroxisome proliferator-activated receptor alpha (PPARα) [11].

Adiponectin suppresses M1, which induces inflammation and insulin resistance while activating M2, which intensifies the anti-inflammatory response and oxidative metabolism [12–14]. Anti-inflammatory cytokines such as IL-10 are stimulated, and pro-inflammatory factors including TNF-α, interferon-gamma (IFN-γ), and vascular cell adhesion molecule-1 (VCAM-1) are inhibited by adiponectin [15,16]. Meanwhile, adiponectin inhibits hepatic glucose production, as well as promotes glucose utilization and fatty acid oxidation of the skeletal muscles via the stimulation of the AMPK and PPARα pathways [17–20] (Figure 1). Cytokine- or ceramide-induced β cell apoptosis is blocked by adiponectin, further contributing to insulin sensitivity [21,22]. Moreover, augmented nitric oxide (NO) synthesis by AMPK following the adiponectin-mediated phosphorylation of endothelial nitric oxide synthase (eNOS) attenuates vasoconstriction and progression of atherosclerosis [23,24]. Adiponectin also interferes with vascular smooth muscle cell (VSMC) hypertrophy [25]. Collectively, adiponectin has anti-inflammatory, insulin-sensitizing, and anti-atherogenic effects.

![Figure 1](image-url)

**Figure 1.** Anti-diabetic potential of adiponectin. Adiponectin enhances insulin sensitivity through multiorgan involvement to alleviate the progression of diabetes mellitus. Cumulative evidence has supported the favorable actions of anti-diabetic medications on adiponectin. The up arrows denote the increase, while the down arrows denote the opposite.
Several anti-diabetic medications are also recognized to intensify adiponectin expression (Figure 1). For instance, pioglitazone not only upregulates the adiponectin levels in adipose tissue but also affects the multimerization of adiponectin into the potent, HMW form [26]. Likewise, glucagon-like peptide-1 (GLP-1) analogs directly enhance the secretion of adiponectin via protein kinase A (PKA) signaling in vitro [27]. Lastly, T2DM mice administered with sodium-glucose cotransporter-2 (SGLT2) inhibitors exhibit elevation of plasma adiponectin levels [28]. Although further studies are needed, adiponectin may be the mediator of the cardiovascular benefits of pioglitazone, GLP-1 analogs, and SGLT2 inhibitors, which have been established by randomized controlled trials [29–31].

Recently, adiponectin is suggested to be a downstream mediator of fibroblast growth factor (FGF) 21, which is another potent modulator of glucose and lipid metabolism produced in adipose tissue [32]. The expression of adiponectin is stimulated by the acute injection of FGF21 through activating peroxisome proliferator-activated receptor gamma (PPARγ) [33]. In addition, the resistance to FGF21 inhibits adiponectin secretion [34]. Laboratory studies have advocated that adiponectin mediates the metabolic effects of FGF21, although the direct mechanism needs to be specified.

2.2. Human Relevance

Plasma adiponectin levels are reduced in patients with obesity [35], T2DM [36,37], atherosclerosis [38], or hypertension [39]. Clinical studies have shown that the VLDL and HDL levels are inversely and positively correlated with the adiponectin levels, respectively [40,41]. A recent cohort study proposed that low adiponectin levels may predict the diminished capability of cholesterol efflux regardless of body mass index (BMI) [42]. Along with an inverse relationship to total fat mass [35], adiponectin secretion is also regulated by the quality of adipose tissue [43]. Metabolically healthy but obese individuals tend to have higher levels of adiponectin compared with their unhealthy counterparts with a similar amount of adipose tissue [44]. In addition, the disorganized formation of adiponectin isoforms may be associated with cardiometabolic disorders. Patients with coronary artery disease (CAD) show a lower proportion of HMW multimer in contrast to a higher trimeric form. Likewise, only HMW adiponectin is increased following weight loss in obese patients [45]. The augmentation of adiponectin action through increasing its level or enhancing the signaling pathways may be a therapeutic approach for cardiometabolic diseases. Human levels of circulating adiponectin are positively affected by weight loss with a low-calorie diet [46]; medications, such as sibutramine or phentermine/topiramate [47,48]; and bariatric surgery [49].

Recently, some studies emphasized the contradictory results indicating that high adiponectin levels are associated with unfavorable cardiovascular and other metabolic outcomes [50–52]. This contradiction, referred to as the adiponectin paradox, might be attributed to a compensatory response in cardiovascular disorders, instead of precipitating them. Reduced adiponectin clearance is another possible explanation considering that hyperadiponectinemia is frequently observed in patients who have both cardiovascular diseases and hepatic or renal damage [43]. Finally, adiponectin isoforms rather than concentration may have a detrimental role in cardiovascular homeostasis. Even though the adiponectin paradox makes it cumbersome to apply adiponectin as a biomarker, it is still a promising therapeutic target for cardiometabolic disorders.

3. Vaspin

3.1. Biological Actions

Visceral adipose tissue-derived serpin protease inhibitor (vaspin) belongs to serpin family A member 12 (serpin A12) in accordance with the serpin nomenclature [53]. It was first isolated from the Otsuka Long-Evans Tokushima fatty (OLETF) rat, a T2DM animal model with obesity [54]. Vaspin is expressed in not only visceral and subcutaneous adipose tissues but also other organs, including the pancreas, liver, stomach, and skin [55]. Vaspin binds to a 78 kDa glucose-regulated protein and initiates multiple kinase signaling
pathways such as AMPK and Akt [56]. Two protease targets of vaspin have been discovered so far, that is, kallikrein 7 and kallikrein 14, which are inhibited by vaspin through the classical serpin mechanism [57,58].

Vaspin has beneficial effects on glucose metabolism, vascular health, appetite control, and lipid profile (Figure 2). Vaspin expression in adipose tissue and plasma vaspin concentration increases in the highest point of insulin resistance and obesity but decreases with the aggravation of T2DM and body weight loss in the OLETF rat [54]. This conflicting tendency of vaspin contrary to adiponectin may imply the compensatory role of vaspin in metabolic dysfunction. Obviously, in vivo, the infusion of recombinant vaspin or transgenic vaspin overexpression enhances glucose tolerance and insulin sensitivity [54,59,60]. Vaspin promotes pancreatic islet cell secretion, protects β cells from nuclear factor-kappa B (NF-κB)-mediated inflammatory damage, and reduces glucose production in the liver [61,62].

Counteracting vascular inflammation is one of the major capacities of vaspin for preserving endothelial function. Vaspin attenuates NF-κB activity in response to the reduced secretion of inflammatory cytokines in the AMPK-dependent pathway [63–65]. The macrophage phenotype is shifted by vaspin toward anti-inflammatory M2 rather than M1 with the downregulation of NF-κB and upregulation of PPARγ [59]. Moreover, vaspin dampens the generation of reactive oxygen species (ROS) and oxidative stress-induced apoptosis of mesenchymal stem cells (MSCs) [66–69]. The progression of aortic atherosclerosis is mitigated by vaspin through impeding intimal proliferation and plaque instabil-
ity [59,70]. We also demonstrated that vaspin was involved in the aortic vasorelaxation following the augmentation of eNOS activity via favorable effects on the signal transducer and activator of transcription 3 and asymmetric dimethylarginine system [71]. Furthermore, vaspin modulates feeding regulation and lipid metabolism. Both the peripheral and central application of vaspin reduce food intake [72], partly due to the downregulated expression of the hypothalamic orexigenic neuropeptides [73]. High-dose vaspin infusion decreases the free fatty acid and triglyceride levels as well as promotes cholesterol efflux via the upregulation of ATP-binding cassette transporter A1 (ABCA1) in macrophages [59,74]. These biological actions of vaspin support its role as an anti-atherogenic adipokine.

3.2. Human Relevance

Compared with non-obese controls, serum levels of vaspin are higher in obese subjects with even normal body weight [75]. A meta-analysis verified significantly higher vaspin concentrations in subjects with T2DM compared with non-diabetic subjects [76]. Increased vaspin concentrations in T2DM patients are also associated with the elevated risk of diabetic complications, such as CAD or diabetic retinopathy [77,78]. The vaspin levels decrease as insulin sensitivity improves through exercise, anti-diabetic medication such as metformin and rosiglitazone, and bariatric surgery [79–82]. Meanwhile, variants of the vaspin rs2236242 gene have been found to be correlated with the development of T2DM independently of obesity [83]. Contrarily, treatment with atorvastatin or rosuvastatin has been shown to increase the vaspin levels in patients with non-significant carotid atherosclerosis and acute coronary syndrome, respectively [84,85]. Low plasma vaspin levels are significantly associated with a higher risk of preclinical carotid atherosclerosis [84], acute coronary syndrome, coronary in-stent restenosis after percutaneous coronary intervention (PCI) [86], and poorer prognosis after myocardial infarction (MI) [87]. The contrasting results of the association between the vaspin levels and cardiometabolic health might have originated from the different study designs.

Vaspin has been investigated as a diagnostic tool for cardiometabolic disorders. A retrospective observational study on individuals with chest pain implied the availability of vaspin as a predictive biomarker of major adverse cardiovascular events (MACE) [88]. The vaspin expression levels significantly indicated the risk of ischemic stroke in a prospective study of T2DM patients [89]. In women with polycystic ovary syndrome (PCOS), serum vaspin concentrations can make a distinction between individuals with a higher diabetogenic risk [90]. The vaspin levels also predict metabolic syndrome as a single entity, as well as some of its components [91,92]. Taken together, beginning with the identification from the diabetic animals, vaspin is expected to be applicable in cardiometabolic diseases.

4. C1q/TNF-Related Protein (CTRP) Family

The CTRP family is a conserved group of adiponectin paralogs, containing a structural similarity to adiponectin. Along with the epicardial adipose tissue, which is the main secretory organ, various sources, such as the heart, liver, kidney, and muscles, have been recognized [93]. Each member of the 15 identified CTRP isoforms has a distinct function. To sum up the latest research, CTRP1, CTRP3, CTRP5, CTRP6, CTRP9, CTRP12, CTRP13, and CTRP15 engage in the development of cardiometabolic diseases, among which CTRP1 and CTRP5 promote the pro-inflammatory response, whereas the others favor the opposite [94] (Figure 3).

4.1. CTRP9

4.1.1. Biological Actions

Of all its family members, CTRP9 has attracted the most attention following its discovery in 2009 [95]. CTRP9 shares the greatest homology with adiponectin involving 51% amino acid overlap [95]. In contrast to adiponectin that maintains the full length in the plasma, the major circulatory and biologically active structure of CTRP9 is the globular form produced by the proteolytic cleavage of trimeric complexes [96]. The heart is the third
richest organ for CTRP9 distribution, and cardiac function is significantly influenced by CTRP9, making CTRP9 not only an adipokine but also a cardiokine [97]. Currently, two receptors have been introduced: AdipoR1 and N-cadherin, which is a cell surface marker of MSCs [98,99].

Figure 3. Major C1q/TNF-related protein (CTRP) isoforms participating in cardiometabolic homeostasis. The respective members of the CTRP family exert different actions on each organ, among which CTRP3, CTRP6, CTRP9, CTRP12, and CTRP13 promote an anti-inflammatory response. CTRP1 and CTRP5 are recognized to trigger inflammation and atherogenesis, whereas CTRP1 plays a protective function in insulin sensitivity and ischemic heart disease. However, the role of CTRP5 in diabetes and cardiac disease is still unclear.

The administration of CTRP9 exerts anti-inflammatory effects by downregulating TNF-α with the downstream mediators through the activation of the AdipoR1/AMPK/NF-κB signaling cascade [100,101]. In addition, it interferes with macrophage polarization, stimulating the M1 to M2 transition [102]. The targeted deletion of murine CTRP9 leads to obesity, insulin resistance, and hepatic steatosis through both the central and peripheral mechanisms with the overexpression of orexigenic peptides in the hypothalamus, blunting hepatic insulin signaling, and upregulating the lipogenic genes [103]. Recombinant globular CTRP9 elevates the HDL levels while reducing the LDL and triglyceride levels, via the enhancement of cholesterol efflux by accelerating AdipoR1/AMPK signaling and inhibition of lipoprotein uptake by suppressing lectin-like oxidized low-density lipoprotein receptor 1 [100,104–106]. In vivo and in vitro studies have shown that the inhibitory effect of CTRP9 on VSMC proliferation, neointimal hyperplasia, and platelet activation prevents the progression of atherosclerosis [107–109]. The trans-differentiation of VSMCs into macrophage-like cells aggravates the inflammatory and proliferative response as well as debilitates the vascular contractile function, which is antagonized by CTRP9 [100]. Furthermore, CTRP9 serves as a defender of endothelial function by facilitating vascular relaxation and ischemia-induced revascularization through the AMPK/Akt/eNOS pathway [110–112]. It downregulates ROS production and apoptosis of endothelial cells [113–115], along with promoting the phagocytic removal of apoptotic cells to deter subsequent necrosis and
inflammation [116]. Likewise, we have shown that palmitic acid-dependent endothelial senescence, which is a significant risk factor of vascular atherosclerosis, was abrogated by CTRP9-mediated restoration of AdipoR1-/AMPK-mediated autophagy [117]. In addition, the anti-fibrotic action of CTRP9 alleviates the post-MI pathologic cardiac remodeling and ventricular dysfunction [118]. Altogether, these actions of CTRP9 contribute to anti-inflammatory and anti-atherogenesis.

4.1.2. Human Relevance

Two retrospective clinical studies on the association of the CAD and CTRP9 levels presented conflicting results [119,120]. Nonetheless, numerous human data favor the protective effects of CTRP9 on the cardiovascular system. Serum levels of CTRP9 along with CTRP3 are reduced in proportion to the severity of heart failure with reduced ejection fraction [121]. In patients who underwent kidney transplantation, plasma CTRP9 concentration is an improving factor of the aortic calcification [122]. In addition, elevated CTRP9 levels are correlated with less restenosis following the implantation of cerebrovascular stent [123].

Similar to coronary atherosclerosis, antecedent reports on plasma CTRP9 concentrations in patients with metabolic syndrome showed inconsistent trends [124,125]. Obese patients are associated with higher CTRP9 levels, which are downregulated following bariatric surgery [126]. Conversely, serum CTRP9 levels are significantly lower in patients with gestational diabetes mellitus (GDM) [127]. It is cautiously supposed that the CTRP9 levels fluctuate to compensate in the early stage of metabolic dysfunction, taking into account that the CTRP9 expression is increased at 8 weeks of age but decreased 4 weeks later in leptin-deficient obese mice [95]. Several clinical studies of diabetic patients suggested plasma CTRP9 levels as reliable biomarkers for cardiac autonomic neuropathy, carotid intima-media thickness (IMT), and arterial stiffness represented by brachial-ankle pulse wave velocity (baPWV) [128–130]. Likewise, CTRP9 levels are independent risk factors for the aggravation of GDM [131].

4.2. Other Members of the CTRP Family with Anti-Inflammatory Effects

4.2.1. Biological Actions

In conjunction with the most renowned CTRP9, other anti-inflammatory isoforms, such as CTRP3, CTRP12, and CTRP13, exert insulin-sensitizing, anti-atherosclerotic, and cardioprotective properties. CTRP3 remarkably decreases the inflammatory cytokines, suppresses cellular apoptosis, and equilibrates the opposing effects of endothelin-1 and NO by prompting the phosphatidylinositol 3-kinase (PI3K), Akt, and eNOS expressions [132]. CTRP12, also referred to as adipolin, is inversely correlated with IL-6 and TNF-α, and encourages the M2 phenotype of macrophage polarization [133,134]. CTRP3 inhibits hepatic glucose output [135], and both CTRP12 and CTRP13 repress gluconeogenesis, intensify the glucose uptake of various organs, and relieve hepatic insulin resistance [136-ijms-1473452,B137-ijms-1473452]. Additionally, CTRP12 disturbs the neointimal thickening by alleviating vascular cell proliferation and lipid accumulation following the promotion of ABCA1-mediated cholesterol efflux [134,138]. CTRP13-infused mice are protected from atherosclerotic plaque formation with accelerated autophagy, downregulated lipid uptake, and inhibited foam cell migration [139].

Post-MI cardiac impairment is mitigated with the overexpression of CTRP3 by preserving the survival, migration, and antioxidant capacity of MSCs [140]. The anti-fibrotic, anti-apoptotic, and angiogenic functions of CTRP3 further ameliorate adverse cardiac remodeling after MI [141,142]. Conversely, CTRP3 is activated in dysfunctional human hearts, and it rather develops cardiac hypertrophy in response to overpressure [143]. This discrepancy may have derived from different trial models, which needs to be further elucidated. For CTRP12, the beneficial effects on myocardial survival and ventricular contractile function have been confirmed recently [144].
4.2.2. Human Relevance

A longitudinal study demonstrated that the circulating CTRP3 levels are negatively related to obesity, non-alcoholic fatty liver disease, and the indicators of pancreatic β-cell function [145]. Reflecting the compensative role, serum CTRP3 levels are increased in the pre-diabetic state but decreased in T2DM patients [146,147]. Metformin treatment upregulates the concentrations of CTRP3 and CTRP12 in humans [148,149]. Likewise, the CTRP13 levels present an inverse relationship with the adverse metabolic factors including BMI, insulin, lipidemia, and carotid IMT [150].

The CTRP3 levels are reduced in patients with CAD, acute aortic dissection, and heart failure [151–153]. Similarly, the CTRP12 levels are negatively correlated with the severity of CAD [154]. In the meantime, complement 1q (C1q), a complement subcomponent that provokes the classical immune pathway, can bind to adiponectin [155]. Plasma C1q-adiponectin/total adiponectin ratio is positively associated with atherosclerosis measured by vascular ultrasonography and can serve as an indicator of CAD [156–159].

To date, the anti-inflammatory members of the CTRP family show a generally compatible contribution to cardiovascular and metabolic homeostasis, despite the inconsistent findings in some studies.

5. Secreted Frizzled-Related Protein 5 (SFRP5)

5.1. Biological Actions

Wingless-type family member 5a (WNT5A), a glycopeptide secreted by adipose tissue macrophages, belongs to a non-canonical member of the Wnt family [160]. WNT5A has been implicated in cellular inflammation, proliferation, and migration to notably develop atherosclerosis and insulin resistance [6,161]. In persistent low-grade inflammation, the actions of WNT5A are offset by SFRP5 which is produced by healthy adipose tissues [162] (Figure 4). SFRP5 is one of the five identified SFRP families, which is the largest group of Wnt inhibitors. According to Ouchi et al., SFRP5 is substantially expressed in white adipose tissue in addition to other insulin targets, including the liver, muscle, and beta cells [163]. Although both the canonical and non-canonical Wnt pathways are impeded by SFRP5, the blockage of WNT5A signaling has been established to play a dominant role in the modulation of metabolic homeostasis [164,165].

The anti-inflammatory function of SFRP5 is exerted by the neutralization of c-Jun N-terminal kinases (JNK) in the downstream of the Wnt signaling pathway, to repress the production of inflammatory cytokines [162,166] (Figure 4). SFRP5 facilitates adipogenic differentiation and adipocyte expansion [167,168]. Despite the augmented expression of SFRP5 in adipose tissues, it seems to decline following the aggravation of metabolic dysfunction, considering the transient upregulation of SFRP5 with milder inflammation in adipocytes and ensuing drop after the development of obesity. In the same way, SFRP5 knockout mice acquire severe insulin resistance and hepatic steatosis with a greater macrophage accumulation in their adipocytes [162]. SFRP5 suppresses beta cell proliferation but enhances glucose-dependent insulin production, indicating the protective role on beta cell function [169]. Moreover, the central infusion of SFRP5 in vivo ameliorates glucose metabolism through brain-hepatic circuits, with less food intake, more energy expenditure, and potentiated hypothalamic neurons engaged in insulin activity, while inhibiting hepatic gluconeogenesis and lipogenesis via the hepatic vagus nerve [170].

The upregulation of SFRP5 significantly attenuates apoptosis of human endothelial cells, whereas the overexpression of WNT5A or knockdown of SFRP5 exhibits the opposite outcomes [171,172]. We have previously substantiated that SFRP5 dose dependently reverses impaired vasorelaxation by increasing the NO production via blockage of the WNT5A/JNK pathway [173]. SFRP5 also restricts VSMC proliferation and migration as well as decreases ROS generation in the murine aorta [174]. Meanwhile, SFRP5 exerts the restoring function in ischemic heart disease, as evidenced by SFRP5-deficient mice presenting more extensive inflammation, apoptosis, infarct size, and cardiac dysfunction.
consequent to ischemia/reperfusion injury [175]. SFRP5 also interferes with the survival, proliferation, and migration of cardiac fibroblasts [176].

**Figure 4.** Schematic view on the association of secreted frizzled-related protein 5 (SFRP5) and wingless-type family member 5a (WNT5A)/c-Jun N-terminal kinases (JNK). WNT5A and the downstream JNK signaling facilitate inflammation and cardiometabolic impairment, which is antagonized by SFRP5.

5.2. Human Relevance

Obesity predisposes to decreased SFRP5 and increased WNT5A expression, which has been confirmed in human cohorts with atherosclerosis [177]. Cross-sectional studies have demonstrated that higher SFRP5 levels are negatively associated with odds of prediabetes and T2DM, along with multiple risk factors, such as systolic blood pressure, BMI, and C-reactive protein levels [178,179]. Likewise, lifestyle intervention with significant weight loss and anti-diabetic medications, including metformin and liraglutide, increase the SFRP5 levels in humans [180–182]. Numerous clinical trials showed the association between higher SFRP5 levels and a favorable lipid profile [178,179,183,184]. Contrarily, another study suggested that elevated SFRP5 concentrations are rather correlated with a higher risk of T2DM [185]. Further investigation is needed to determine whether the SFRP5 levels vary according to the progression of metabolic dysfunction.

Corresponding to in vitro and in vivo studies, clinical trials have indicated the salutary effects of SFRP5 on vascular health. In the adipocytes of patients with the peripheral arterial disease (PAD), the plasma concentrations of WNT5A are significantly increased but those of SFRP5 are significantly decreased [186]. Similarly, the serum SFRP5 levels are lower in chronic kidney disease subjects with vascular calcification compared with those without calcification [187]. On the other hand, we reported the positive correlation between SFRP5 concentrations and baPWV based on the multivariate linear regression analysis of T2DM patients. This discrepancy in the SFRP5 levels may be interpreted as a compensatory rise in incipient atherosclerosis, taking into account the restoration of endothelial NO synthesis by SFRP5 [173].

Human data concerning the role of SFRP5 on CAD have been discordant. CAD patients have higher plasma WNT5A levels and lower SFRP5 levels compared with those without CAD, independent of the conventional risk factors [177]. An experiment using the mRNA levels of SFRP5 and WNT5A from epicardial adipose tissue biopsies of CAD patients reconfirmed the results [188]. Additionally, the WNT5A concentration is independently correlated with the occurrence and advancement of coronary calcification [177]. In the acute phase of ST-segment elevation MI, high SFRP5 concentrations are significantly related to early myocardial recovery after primary PCI [189]. Furthermore, a prospective cohort study proposed SFRP5 as a novel prognostic marker for heart failure on the basis of enhanced discrimination by conjoining SFRP5 to the traditional risk factors [190]. On the contrary, elevated SFRP5 levels predicted the incidence of MACE in a 4-year prospective study [191].
In spite of the conflicting outcomes regarding the relationship of the SFRP5 levels with insulin resistance and CAD, the majority of up-to-date research supports the beneficial role of SFRP5 in cardiometabolic health. Future research on the temporal variation of SFRP concentration during the disease course as well as the mechanism of action is required.

6. Omentin-1

6.1. Biological Actions

Omentin is a novel adipokine comprising 313 amino acids [192]. It is preferentially produced by visceral adipose tissue rather than subcutaneous adipose tissue. Omentin-1 and omentin-2 are two identified isoforms showing analogous gene expression, among which omentin-1 is a dominant form in the human circulation [193]. Cumulative experimental studies have demonstrated the direct intervention of omentin-1 in anti-inflammation, insulin sensitization, and cardiovascular health mainly through the cascade of AMPK/Akt/NF-kB/extracellular signal-regulated kinase (ERK), JNK, and p38 [194]. The antagonistic effects of omentin-1 on inflammation and atherosclerosis have been confirmed by various in vivo and in vitro studies. Transgenic mice with the human omentin gene show decreased expression of pro-inflammatory cytokines via the stimulation of Akt [195]. Omentin-1 also suppresses macrophage aggregation, apoptosis, foam cell formation, and M1 phenotype [195–197]. Previously built atherosclerotic lesions are diminished by omentin-1 through reducing lipid content and necrotic core [195,196]. Neointimal hyperplasia and VSMC proliferation are attenuated by omentin via the AMPK/ERK pathway [198]. Likewise, omentin-1 overexpression mitigates arterial calcification through PI3K/Akt-dependent mechanisms [199].

Cardiovascular dysfunction is also ameliorated by omentin-1. Bioavailability of NO is improved by omentin-mediated phosphorylation of eNOS to promote vasorelaxation and revascularization in contracted artery [200–202]. Omentin-derived activation of the canonical pathway of AMPK/Akt/ERK attenuates myocyte apoptosis, hypertrophy, and fibrosis following myocardial ischemia [203,204]. Similarly, overexpression of omentin-1 enhances parameters of cardiac function and cardiac mitochondrial activities possibly through upregulating glycogen synthase kinase-3 beta pathway in the rat model [205].

6.2. Human Relevance

Investigations on the correlation of human plasma levels of omentin-1 and cardiometabolic disorders display remarkably consistent results. Cross-sectional studies determined significantly lower omentin-1 levels in obese individuals compared with lean controls [193,206]. Even after adjusting for BMI, both serum and adipocyte levels of omentin-1 are inversely associated with the presence of metabolic syndrome [207]. A negative correlation of the serum omentin-1 levels with T2DM and GDM has also been reported [206,208]. Moreover, plasma omentin-1 is further reduced in T2DM patients with diabetic complications including retinopathy, peripheral neuropathy, nephropathy, and PAD than in those without complications [209,210]. In addition to decreased omentin-1 levels, patients with diabetic nephropathy exhibit significantly increased IL-6 which plays a critical role in immune response [211]. Serum IL-6 levels are independent factors determining omentin-1 levels, indicating the crosstalk between the adipose tissue and immune system [212].

Decreased plasma omentin-1 levels are not only significantly associated with CAD but also reflective of the disease severity, with lower values in acute coronary syndrome than in stable angina pectoris [213,214]. Biscetti et al. performed a prospective cohort study with T2DM subjects who have PAD and chronic limb-threatening ischemia to reveal that declined omentin-1 levels at baseline are related to higher risks of MACE and major adverse limb events [215]. On the other hand, higher plasma omentin levels are associated with enhanced cardiac function in patients with MI and heart failure [203,216]. Omentin-1 is also thought to influence blood pressure and lipid profile regulation. Individuals with stage 1 and 2 hypertension have significantly lower omentin-1 in circulation compared
with their normotensive counterparts [217]. HDL and VLDL concentrations are correlated with omentin-1 levels positively and negatively, respectively [193,207].

The possibility of using circulating omentin-1 levels as biomarkers for cardiovascular diseases has been raised. Reduced baseline levels of omentin-1 predict worse functional prognosis, carotid plaque instability, and 1-year mortality in patients with acute ischemic stroke [218–221], as well as poorer clinical outcomes for acute intracerebral hemorrhage [222]. Lower omentin-1 levels are also prognostic markers of frequent MACE, severe angiographic CAD, and incomplete coronary collateral circulation [215,223,224]. In addition, plasma omentin-1 levels are independent determinants of several vascular complications of diabetic patients including carotid plaque, arterial stiffness measured by baPWV, PAD, and retinopathy [210,225–227].

Upregulation of circulating omentin-1 levels may be a novel therapeutic approach to delay the progression of cardiometabolic diseases. A recent prospective cohort study of obese or overweight children discovered that both short-term and long-term lifestyle interventions correlated positively with omentin-1 levels [228]. Similarly, a high-intensity exercise program of 12-week duration and weight loss after biliopancreatic diversion surgery augments plasma omentin-1 levels [229,230]. The widely prescribed medications such as metformin and atorvastatin are also expected to increase serum levels of omentin-1 [84,231].

In conclusion, coherent results of animal and human data on the favoring effect of omentin-1 on the cardiometabolic system may allow omentin-1 to be developed as a predictive marker or therapeutic medium.

7. Conclusions

Obesity, beyond its definition indicating the static state of excessive fat accumulation, accompanies chronic low-grade inflammation and is associated with a broad spectrum of cardiometabolic diseases, including T2DM, dyslipidemia, CAD, and fatty liver disease. Likewise, the pleiotropic effects of adipokines on metabolic homeostasis have also been investigated. Together with the autocrine and paracrine actions on local adipose tissue and macrophages, adipokines reach the systemic vasculature to actively interact with the central nervous system, pancreatic islets, or liver. This review specifically summarizes the cardiometabolic function of anti-inflammatory adipokines, covering from prototypical adiponectin to the more recently discovered omentin-1. The present review is distinguished by its explicit partition of experimental and clinical data as well as the introduction of diverse, up-to-date research on humans, especially regarding the applicability as biomarkers and therapeutic targets. These advantages allow for a better understanding of current knowledge and constraints, along with an outline of future study.

A number of retrospective clinical studies have implied the predictive value of adipokines for the risk of cardiovascular disorders and the capability as biomarkers replacing more complicated diagnostic tests. Contrary to the consistent tendency presented in the animal data, human trials showed incompatible results of the associations between the serum adipokine levels and diseases (Table 1). More mechanistic explanations and prospective human trials are needed to overcome the limitations of animal studies and contradictory outcomes. The exploration of the dynamic expression of adipokines, rather than the single serum concentration, will confirm their role as prognostic markers for cardiovascular diseases. Additionally, further clinical investigation concerning the relationship of demographic factors such as age, sex, and ethnicity with the cardiometabolic effects of adipokines may be valuable. Furthermore, expanding from the gathered animal data indicating that the upregulation or exogenous administration of each substance exhibits therapeutic effects on vascular and metabolic function, the manipulation of the axis connecting the anti-inflammatory adipokines and target organs may be the blueprint for the future approaches in managing cardiometabolic disorders. Reasonable strategies for applying adipokines as biotargets are manufacturing the analogs which are stable in the circulation to sustain enough therapeutic concentration, in addition to influencing directly the action target and downstream signaling.
Table 1. Summary of the human studies for the association of adipokine levels with cardiometabolic parameters.

| Author, Year [ref]  | Study Design | Participants | Mean Age (years) | Men (%) | Ethnicity † | Outcomes or Parameters | Cardiometabolic Health Association ‡ |
|---------------------|--------------|--------------|------------------|---------|-------------|------------------------|--------------------------------------|
| Adiponectin         | PC           | 193 overweight and obese subjects | 36.0             | 7.0     | Asian       | Visceral fat            | Positive                             |
| Gariballa et al., 2019 [35] | PC         | 666 patients with STEMI without diabetes | 63.5             | 74.3    | White       | Incident T2DM          | Positive                             |
| Lindberg et al., 2014 [37] | PC         | 309 subjects | N/R             | N/R     | Asian       | Atherogenic index of plasma | Positive                             |
| Kou et al., 2018 [38] | CC           | 56 patients with T2DM | N/R             | N/R     | Asian       | VLDL levels            | Positive                             |
| Yoshida et al., 2005 [40] | CS          | 174 subjects without diabetes | 67.9             | 45.4    | Asian       | HDL levels             | Positive                             |
| Tomono et al., 2018 [41] | CS          | 822 subjects and/or MetS | 43.3             | 44.3    | Black       | Obesity and MetS       | Positive                             |
| Doumatay et al., 2012 [44] | CS          | 475 subjects with prediabetes | 52.0             | 35.2    | Multiracial | Phentermine/topiramate | Positive                             |
| Garvey et al., 2014 [48] | RC           | 4046 men | 68.7             | 100     | White       | All-cause and CVD mortality | Negative                             |
| Wannamethee et al., 2007 [51] | PC          | 47 patients with CAD | 67.3             | 83.0    | White       | HF and cachexia        | Negative                             |
| Vaspin              | CS           | 70 women | 29.0             | 0       | Asian       | Obesity                | Negative                             |
| Taheri et al., 2020 [55] | CS          | 348 subjects | 52.8             | 58.0    | Asian       | T2DM and CAD           | Negative                             |
| Yang et al., 2021 [57] | CS           | 372 patients with T2DM | 53.0             | 55.6    | Asian       | Diabetic retinopathy   | Negative                             |
| Jia et al., 2018 [79] | RC           | 474 patients with NAFLD | N/R             | N/R     | Asian       | Exercise               | Negative                             |
| Tan et al., 2008 [80] | NRI          | 21 women with PCOS | 28.0             | 0       | White       | Metformin              | Negative                             |
| Zhang et al., 2011 [81] | NRI          | 31 patients with T2DM | 55.3             | 35.5    | Asian       | Rosiglitazone          | Negative                             |
| Golpaei et al., 2011 [82] | NRI          | 30 obese subjects | 32.5             | 30.0    | Asian       | Restrictive bariatric surgery | Negative                             |
| Kadoglu et al., 2021 [84] | NRI          | 84 subjects with preclinical carotid atherosclerosis | 62.0             | 46.4    | White       | Atovastatin            | Positive                             |
| Al-Kuraishi et al., 2018 [85] | RC          | 110 patients with ACS | 48.6             | 65.5    | Asian       | Rosuvastatin           | Positive                             |
| Kodali et al., 2020 [86] | PC           | 85 patients with CAD | 64.0             | 77.6    | White       | In-stent restenosis    | Positive                             |
| Zhang et al., 2016 [87] | PC           | 80 patients with MI | 68.0             | 79.2    | Asian       | MACE                   | Positive                             |
| Ji et al., 2020 [88] | RC           | 197 subjects with chest pain | 65.0             | 56.9    | Asian       | MACE                   | Positive                             |
| Rashad et al., 2020 [89] | PCC          | 90 patients with T2DM | 58.7             | 55.6    | Asian       | IS                     | Negative                             |
| Cakal et al., 2011 [90] | CS           | 71 women | N/R             | 0       | Asian       | Diabetogenic risk      | Negative                             |
| Esteghamati et al., 2014 [91] | CS          | 145 subjects | 49.4             | 42.8    | Asian       | MetS                   | Negative                             |
| Buyukatay et al., 2018 [92] | CS          | 121 obese children | N/R             | 34.7    | Asian       | MetS                   | Negative                             |
| CTRP9               | CS           | 362 subjects | 62.1             | 72.1    | Asian       | CAD                    | Positive                             |
| Wang et al., 2015 [119] | CS           | 337 subjects | 58.0             | 70.0    | Asian       | CAD and T2DM           | Positive                             |
| Moradi et al., 2018 [120] | CS          | 344 subjects | 56.2             | 69.2    | Asian       | HF, EF                  | Positive                             |
| Gao et al., 2019 [121] | RC           | 50 recipients of kidney transplantation | 31.5             | 66.0    | Asian       | Aortic calcification   | Positive                             |
| Miyatake et al., 2020 [122] | RC          | 128 CI patients with cerebrovascular stent | 54.0             | 58.6    | Asian       | Restenosis after cerebrovascular stent | Positive                             |
| Pan et al., 2020 [123] | CS           | 363 subjects | 52.0             | 48.0    | Asian       | Incident T2DM and obesity | Negative                             |
| Jia et al., 2017 [124] | CS           | 221 subjects | 46.0             | 63.3    | Asian       | MetS                   | Positive                             |
| Hwang et al., 2014 [125] | CS           | 21 obese subjects | N/R             | 14.0    | Multiracial | Bariatric surgery      | Negative                             |
| Wolf et al., 2016 [126] | NRI          | 259 pregnant women | N/R             | 0       | Asian       | GDM                    | Positive                             |
| Xia et al., 2020 [127] | CS           | 55 patients with T2DM | 55.0             | 68.3    | Asian       | Cardiac autonomic neuropathy | Positive                             |
| Yang et al., 2021 [128] | CS           | 258 patients with T2DM without CKD | 62.0             | 54.3    | Asian       | Canoid IIT            | Negative                             |
| Jia et al., 2014 [129] | CS           | 279 patients with T2DM | 58.3             | 60.8    | Asian       | bPWV                   | Negative                             |
| Na et al., 2020 [130] | CS           | 133 pregnant women | N/R             | 0       | Asian       | GDM                    | Positive                             |
| Author, Year [ref]   | Study Design † | Participants | Mean Age (years) | Men (%) | Ethnicity ‡ | Outcomes or Parameters Cardiometabolic Health Association § |
|----------------------|---------------|--------------|------------------|---------|-------------|------------------------------------------------------------|
| Zhou et al., 2018 [145] | PC            | 313 subjects | N/R              | N/R     | Asian       | Incident NAFLD                                             |
| Choi et al., 2012 [146] | CS            | 345 subjects | 51.8             | 38.2    | Asian       | Prediabetes, T2DM, and MetS                                |
| Moradi et al., 2019 [147] | CS            | 164 subjects | 58.0             | 62.8    | Asian       | T2DM and diabetic nephropathy                              |
| Flehmig et al., 2014 [148] | CS            | 141 obese subjects | 48.0       | 47.5    | White       | Metformin                                                 |
| Choi et al., 2014 [151] | CS            | 362 subjects | 60.4             | 67.4    | Asian       | ACS and SAP                                                |
| Jiang et al., 2018 [152] | CS            | 108 subjects | 56.3             | 71.3    | Asian       | Acute aortic dissection                                    |
| Yildirim et al., 2015 [153] | CS            | 118 subjects | 64.4             | 66.1    | Asian       | HFrEF and VT                                              |
| Tan et al., 2014 [149] | NRI           | 21 women with PCOS | 28.0      | 0       | White       | Metformin                                                 |
| Nadimi et al., 2021 [154] | CS            | 250 subjects | 58.5             | 54.8    | Asian       | CAD severity                                               |
| Tan et al., 2014 [180] | PC            | 31 obese children | 11.0      |         | Asian       | Lifestyle intervention                                     |
| He et al., 2020 [181] | NRI           | 111 patients with T2DM | 57.0      |         | Asian       | Metformin                                                 |
| Hu et al., 2013 [182] | NRI           | 30 patients with T2DM | 57.0      |         | Asian       | T2DM                                                      |
| Almario et al., 2015 [183] | CS            | 84 women    | 26.1             | 51.8    | Asian       | Vascular calcification                                     |
| Xu et al., 2017 [184] | CS            | 284 subjects | 53.4             | 53.9    | Asian       | PAD                                                       |
| Lu et al., 2013 [185] | CS            | 124 subjects | 59.5             | 56.5    | Asian       | Early improvement of LVEF                                  |
| Wang et al., 2021 [186] | CS            | 114 subjects | 67.3             | 51.8    | Asian       | CAD                                                       |
| Oh et al., 2020 [187] | CS            | 120 subjects | 51.7             | 19.3    | Asian       | Composite of all-cause mortality or HF rehospitalization   |
| Cho et al., 2018 [173] | CS            | 282 patients with T2DM | 58.0      |         | Asian       | MACE                                                      |
| Tong et al., 2020 [188] | PC            | 87 subjects | 61.5             | 56.3    | Asian       | Positive                                                  |
| Du et al., 2019 [189] | PC            | 85 patients with STEMI | 55.7      | 76.5    | Asian       | CAD                                                       |
| Wu et al., 2020 [190] | PC            | 833 patients with HF | 65.9      | 57.4    | Asian       | Composite of all-cause mortality or HF rehospitalization   |
| Li et al., 2017 [191] | PC            | 168 subjects | 65.0             | 55.4    | Asian       | MACE                                                      |
| Batista et al., 2007 [192] | CS            | 91 subjects | 43.7             | 42.9    | White       | Obesity                                                   |
| Zhang et al., 2014 [206] | CS            | 120 subjects | 66.3             | 51.7    | Asian       | T2DM and obesity                                          |
| Jialal et al., 2013 [207] | CS            | 75 subjects | 51.6             | 78.7    | White       | MetS                                                      |
| Pesta-Cano et al., 2021 [208] | CS            | 231 pregnant women | 29.5      | 0       | Hispanic    | GDM                                                      |
| Latif et al., 2021 [209] | CS            | 500 patients with T2DM | 53.0      | 52.0    | Asian       | Diabetic complications                                    |
| Biscetti et al., 2019 [210] | S             | 600 patients with T2DM | 74.7      | 68.2    | White       | PAD                                                       |
| Senthilkumar et al., 2018 [211] | CS            | 82 patients with T2DM | 48.5      | N/R     | Asian       | Early improvement of LVEF                                  |
| El-Mesallamy et al., 2011 [212] | CS            | 90 subjects | 57.3             | 74.4    | Asian       | T2DM                                                      |
| Bai et al., 2021 [213] | CS            | 600 subjects | 52.5             | 61.2    | Asian       | CAD                                                       |
| Zhong et al., 2011 [214] | CS            | 207 subjects | 61.2             | 69.1    | Asian       | ACS and SAP                                               |
| Biscetti et al., 2020 [215] | PC            | 207 patients with T2DM and CTLI | 75.0      | 69.6    | White       | MACE and MALE                                             |
| Kataoka et al., 2014 [216] | CS            | 20 patients with acute MI | 62.5      | 65.0    | Asian       | Myocardial salvage index and EF                            |
| Narumi et al., 2014 [217] | PC            | 136 patients with HF | 72.0      | 55.9    | Asian       | Cardiac death or HF rehospitalization                     |
| Çelik et al., 2021 [218] | CS            | 121 subjects | 49.6             | 48.8    | Asian       | Hypertension                                              |
| Xu et al., 2016 [219] | PC            | 266 patients with IS | N/R      | N/R     | Asian       | Functional outcome                                        |
| Yang et al., 2020 [220] | PC            | 109 patients with CI | 62.8      | 62.4    | Asian       | Functional prognosis                                      |
Table 1. Cont.

| Author, Year [ref] * | Study Design † | Participants | Mean Age (years) | Men (%) | Ethnicity ‡ | Outcomes or Parameters | Cardiometabolic Health Association § |
|---------------------|----------------|--------------|-----------------|---------|-------------|------------------------|-------------------------------------|
| Xu et al., 2018 [220] | CS             | 173 patients with IS | N/R            | N/R     | Asian       | Unstable carotid plaque | Positive                           |
| Xu et al., 2020 [221] | PC             | 303 patients with IS | 66.8           | 64.7    | Asian       | 1 year mortality       | Positive                           |
| Onur et al., 2014 [222] | PC             | 104 patients with hemorrhagic stroke | 68.0           | 54.8    | Asian       | Functional outcome     | Positive                           |
| Zhou et al., 2017 [223] | CS             | 142 patients with CAD | N/R            | N/R     | Asian       | Coronary collateral circulation | Positive                           |
| Yoo et al., 2011 [224] | CS             | 90 subjects | 54.5           | 41.1    | Asian       | T2DM and carotid plaque | Positive                           |
| Onur et al., 2014 [225] | CS             | 173 subjects | N/R            | N/R     | Asian       | PAD                    | Positive                           |
| Yasir et al., 2019 [226] | CS             | 167 patients with T2DM | N/R            | N/R     | Asian       | Diabetic retinopathy   | Positive                           |
| Siegrist et al., 2021 [227] | NRI          | 156 overweight and obese children | 14.0           | 44.9    | White       | Lifestyle intervention | Positive                           |
| Atashak et al., 2021 [228] | RC             | 30 obese men | N/R            | 100     | Multiracial | Exercise               | Positive                           |
| Luis et al., 2018 [229] | NRI           | 24 obese subjects | N/R            | N/R     | White       | Biliopancreatic diversion surgery | Positive                           |
| Kadoglou et al., 2021 [84] | NRI          | 84 subjects with preclinical carotid atherosclerosis | 62.0           | 46.4    | White       | Atorvastatin           | Positive                           |
| Alkuraishy et al., 2015 [230] | CS             | 85 patients with T2DM and acute MI | 57.5           | 60.0    | White       | Metformin              | Positive                           |

* Articles were listed in the order of citation in the text. Meta-analyses were excluded. † RC, randomized controlled; NRI, nonrandomized interventional; PC, prospective cohort; RC, retrospective cohort; CC, case-control; PCC, prospective case-control; CS, cross-sectional. ‡ One of the following ethnic groups: white, Asian, Hispanic, black, and multiracial. § Labeled as positive if the increasing adipokine levels are associated with the positive direction of cardiometabolic health, and as negative in the case of the inverse association.
Author Contributions: Conceptualization, C.H.J.; investigation, H.N.J. and C.H.J.; writing—original draft preparation, H.N.J.; writing—review and editing, C.H.J. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: This work was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF-2020R1A2C1101977: C.H.J.). These funding sources had no roles in the design of the study; the collection, analysis, and interpretation of data; writing of the article; or the decision to submit the article for publication.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations
STEMI, ST-segment elevation MI; T2DM, type 2 diabetes mellitus; N/R, not reported; MetS, metabolic syndrome; CVD, cardiovascular disease; HF, heart failure; CAD, coronary artery disease; NAFLD, non-alcoholic fatty liver disease; PCOS, polycystic ovary syndrome; ACS, acute coronary syndrome; MI, myocardial infarction; MACE, major adverse cardiac events; IS, ischemic stroke; HFrEF, heart failure with reduced ejection fraction; GDM, gestational diabetes mellitus; CKD, chronic kidney disease; IMT, intima-media thickness; baPWV, brachial ankle pulse wave velocity; SAP, stable angina pectoris; VT, ventricular tachycardia; BMI, body mass index; FPG, fasting plasma glucose; TC, total cholesterol; PAD, peripheral arterial disease; LVEF, left ventricular ejection fraction; CTLI, chronic limb-threatening ischemia; MALE, major adverse limb events; CI, cerebral infarction.

References
1. Ouchi, N.; Parker, J.L.; Lugus, J.J.; Walsh, K. Adipokines in inflammation and metabolic disease. Nat. Rev. Immunol. 2011, 11, 85–97. [CrossRef] [PubMed]
2. Shoelson, S.E.; Herrero, L.; Naaz, A. Obesity, inflammation, and insulin resistance. Gastroenterology 2007, 132, 2169–2180. [CrossRef] [PubMed]
3. Wellen, K.E.; Hotamisligil, G.S. Inflammation, stress, and diabetes. J. Clin. Investig. 2005, 115, 1111–1119. [CrossRef] [PubMed]
4. Zhang, Y.; Proenca, R.; Maffei, M.; Barone, M.; Leopold, L.; Friedman, J.M. Positional cloning of the mouse obese gene and its human homologue. Nature 1994, 372, 425–432. [CrossRef]
5. Blüher, M. Adipokines—Removing road blocks to obesity and diabetes therapy. Mol. Metab. 2014, 3, 230–240. [CrossRef] [PubMed]
6. Recinella, L.; Orlando, G.; Ferrante, C.; Chiavaroli, A.; Brunetti, L.; Leone, S. Adipokines: New Potential Therapeutic Target for Obesity and Metabolic, Rheumatic, and Cardiovascular Diseases. Front. Physiol. 2020, 11, 578966. [CrossRef] [PubMed]
7. Scherer, P.E.; Williams, S.; Fogliano, M.; Baldini, G.; Lodish, H.F. A Novel Serum Protein Similar to C1q, Produced Exclusively in Adipocytes. J. Biol. Chem. 1995, 270, 26746–26749. [CrossRef]
8. Martinez-Huenchullan, S.F.; Tam, C.S.; Ban, L.A.; Ehrenfeld-Slater, P.; Mclennan, S.V.; Twigg, S.M. Skeletal muscle adiponectin induction in obesity and exercise. Metabolism 2020, 102, 154008. [CrossRef] [PubMed]
9. Natarajan, R.; Salloum, F.N.; Fisher, B.J.; Kukreja, R.C.; Fowler, A.A. Hypoxia Inducible Factor-1 Upregulates Adiponectin in Diabetic Mouse Hearts and Attenuates Post-Ischemic Injury. J. Cardiovasc. Pharmacol. 2008, 51, 178–187. [CrossRef]
10. Achari, A.E.; Jain, S.K. Adiponectin, a Therapeutic Target for Obesity, Diabetes, and Endothelial Dysfunction. Int. J. Mol. Sci. 2017, 18, 1321. [CrossRef]
11. Fang, H.; Judd, R.L. Adiponectin Regulation and Function. Compr. Physiol. 2011, 8, 1031–1063.
12. Xuan, D.; Han, Q.; Tu, Q.; Zhang, L.; Yu, L.; Murry, D.; Tu, T.; Tang, Y.; Lian, J.B.; Stein, G.S.; et al. Epigenetic Modulation in Periodontitis: Interaction of Adiponectin and MJID3-IRF4 Axis in Macrophages. J. Cell. Physiol. 2015, 231, 1090–1096. [CrossRef]
13. Luo, Y.; Liu, M. Adiponectin: A versatile player of innate immunity. J. Mol. Cell Biol. 2016, 8, 120–128. [CrossRef]
14. Bourlier, V.; Bouloumie, A. Role of macrophage tissue infiltration in obesity and insulin resistance. Diabetes Metab. 2009, 35, 251–260. [CrossRef] [PubMed]
15. Wolf, A.M.; Wolf, D.; Rumpold, H.; Enrich, B.; Tilig, H. Adiponectin induces the anti-inflammatory cytokines IL-10 and IL-1RA in human leukocytes. Biochim. Biophys. Res. Commun. 2004, 323, 630–635. [CrossRef] [PubMed]
16. Okamoto, Y.; Kihara, S.; Ouchi, N.; Nishida, M.; Arita, Y.; Kumada, M.; Ohashi, K.; Sakai, N.; Shimomura, I.; Kobayashi, H.; et al. Adiponectin Reduces Atherosclerosis in Apolipoprotein E-Deficient Mice. *Circulation* **2002**, *106*, 2767–2770. [CrossRef] [PubMed]

17. Combs, T.P.; Berg, A.H.; Obici, S.; Scherer, P.E.; Rossetti, L. Endogenous glucose production is inhibited by the adipose-derived protein Acrp30. *J. Clin. Investig.* **2001**, *108*, 1875–1881. [CrossRef]

18. Combs, T.P.; Marliß, E.B. Adiponectin signaling in the liver. *Rev. Endocr. Metab. Disord.* **2014**, *15*, 137–147. [CrossRef] [PubMed]

19. Schindler, M.; Pendzialek, M.; Gribel, K.; Seeling, T.; Gürke, J.; Fischer, B.; Santos, A.N. Adiponectin stimulates lipid metabolism via AMPK in rabbit blastocystcs. *Hum. Reprod.* **2017**, *32*, 1382–1392. [CrossRef]

20. Yamauchi, T.; Kamon, J.; Minokoshi, Y.; Ito, Y.; Waki, H.; Uchida, S.; Yamashita, S.; Noda, M.; Kita, S.; Ueki, K.; et al. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMPK-activated protein kinase. *Nat. Med.* **2002**, *8*, 1288–1295. [CrossRef] [PubMed]

21. Rakatzi, I.; Mueller, H.; Ritzeler, O.; Tennagels, N.; Eckel, J. Adiponectin counteracts cytokine- and fatty acid-induced apoptosis in the pancreatic beta-cell line INS-1. *Diabetologia* **2004**, *47*, 249–258. [CrossRef]

22. Holland, W.L.; Miller, R.A.; Wang, Z.V.; Sun, K.; Barth, B.M.; Bui, H.H.; Davis, K.E.; Bikman, B.T.; Halberg, N.; Rutkowski, J.M.; et al. Receptor-mediated activation of ceramidase activity initiates the pleiotropic actions of adiponectin. *Nat. Med.* **2011**, *17*, 55–63. [CrossRef] [PubMed]

23. Deng, G.; Long, Y.;Yu, Y.R.; Li, M.R. Adiponectin directly improves endothelial dysfunction in obese rats through the AMPK-eNOS Pathway. *Int. J. Obes.* **2010**, *34*, 165–171. [CrossRef] [PubMed]

24. Cai, X.; Li, X.; Li, L.; Huang, X.Z.; Liu, Y.S.; Chen, L.; Zhang, K.; Wang, L.; Li, X.; Song, J.; et al. Adiponectin reduces carotid atherosclerotic plaque formation in Apo-E/- mice: Roles of oxidative and nitrosative stress and inducible nitric oxide synthase. *Mol. Med. Rep.* **2015**, *11*, 1715–1721. [CrossRef]

25. Nour-Eldine, W.; Ghantous, C.M.; Zibara, K.; Dib, L.; Issaa, H.; Itani, H.A.; El-Zein, N.; Zeidan, A. Adiponectin Attenuates Atherosclerotic plaque formation in ApoE-/- mice: Roles of oxidative and nitrosative stress and inducible nitric oxide synthase. *Mol. Med. Rep.* **2015**, *11*, 1715–1721. [CrossRef]

26. Bodles, A.M.; Banga, A.; Rasouli, N.; Ono, F.; Kern, P.A.; Owens, R.J. Pioglitazone increases secretion of high-molecular-weight adiponectin from adipocytes. *Am. J. Physiol. Metab.* **2006**, *291*, E1100–E1105. [CrossRef] [PubMed]

27. Chung, L.T.K.; Hosaka, T.; Yoshida, M.; Harada, N.; Sakaue, H.; Sakai, T.; Nakaya, Y. Exendin-4, a GLP-1 receptor agonist, directly induces adiponectin expression through protein kinase A pathway and prevents inflammatory adipokine expression. *Biochem. Biophys. Res. Commun.* **2016**, *376*, 613–618. [CrossRef] [PubMed]

28. Tahara, A.; Takasu, T.; Yokono, M.; Imamura, M.; Kuroasaki, E. Characterization and comparison of sodium-glucose cotransporter 2 inhibitors: Part 2. Antidiabetic effects in type 2 diabetic mice. *J. Pharmacol. Sci.* **2016**, *131*, 198–208. [CrossRef]

29. Dormandy, J.A.; Charbonnel, B.; Eckel, J.D.A.; Erdmann, E.; Massi-Benedetti, M.; Moules, I.K.; Scobie, J.; Fischer, B.; Santos, A.N. Adiponectin stimulates lipid metabolism via AMPK in rabbit blastocystcs. *Hum. Reprod.* **2017**, *32*, 1382–1392. [CrossRef]

30. Zelniker, T.A.; Wiviott, S.D.; Lazar, M.A. Adiponectin mediates the metabolic effects of FGF21 on glucose homeostasis and insulin sensitivity in mice. *Cell Metab.* **2013**, *17*, 790–797. [CrossRef] [PubMed]

31. Liu, C.; Feng, X.; Li, Q.; Wang, Y.; Li, Q.; Hua, M. Adiponectin, TNF-α and inflammatory cytokines and risk of type 2 diabetes: A systematic review and meta-analysis. *Cytokine* **2016**, *86*, 100–109. [CrossRef]

32. Lindberg, S.; Jensen, J.S.; Pedersen, S.H.; Galatius, S.; Frystyk, J.; Flyvbjerg, A.; Bjerring, M.; Mogelvang, R. Low Adiponectin Levels and Increased Risk of Type 2 Diabetes in Patients with Myocardial Infarction. *Diabetes Care* **2014**, *37*, 3003–3008. [CrossRef]

33. Kou, H.; Deng, J.; Gao, D.; Song, A.; Han, Z.; Wei, J.; Jin, X.; Ma, R.; Zheng, Q. Relationship among adiponectin, insulin resistance and atherosclerosis in non-diabetic hypertensive patients and healthy adults. *Clin. Exp. Hypertens.* **2018**, *40*, 656–663. [CrossRef]

34. Kim, D.H.; Kim, D.; Ding, E.L.; Townsend, M.K.; Lipsitz, L.A. Adiponectin levels and the risk of hypertension: A systematic review and meta-analysis. *Hypertension* **2013**, *62*, 27–32. [CrossRef]

35. Yoshida, H.; Hirokawa, Y.; Kurosawa, H.; Tada, N. Implications of decreased serum adiponectin for type IIb hyperlipidaemia and increased cholesterol levels of very-low-density lipoprotein in type II diabetic patients. *Clin. Sci.* **2005**, *109*, 297–302. [CrossRef]
41. Tomono, Y.; Hiraishi, C.; Yoshida, H. Age and sex differences in serum adiponectin and its association with lipoprotein fractions. *Ann. Clin. Biochem. Int. J. Lab. Med.* 2018, 55, 165–171. [CrossRef]

42. Marsche, G.; Zelzer, S.; Meinitz, A.; Kern, S.; Meissl, S.; Pregartner, G.; Weghuber, D.; Almer, G.; Mangge, H. Adiponectin Predicts High-Density Lipoprotein Cholesterol Efflux Capacity in Adults Irrespective of Body Mass Index and Fat Distribution. *J. Clin. Endocrinol. Metab.* 2017, 102, 4117–4123. [CrossRef] [PubMed]

43. Zhao, S.; Kusminski, C.M.; Scherer, P.E. Adiponectin, Leptin and Cardiovascular Disorders. *Circ. Res.* 2021, 128, 136–149. [CrossRef] [PubMed]

44. Doumatay, A.P.; Bentley, A.R.; Zhou, J.; Huang, H.; Adevemo, A.; Rotimi, C.N. Paradoxical Hyperadiponectinemia is Associated with the Metabolically Healthy Obese (MHO) Phenotype in African Americans. *J. Endocrinol. Metab.* 2012, 2, 51–65. [CrossRef]

45. Kobayashi, H.; Ouchi, N.; Kihara, S.; Walsh, K.; Kumada, M.; Abe, Y.; Funahashi, T.; Matsuzawa, Y. Selective Suppression of Endothelial Cell Apoptosis by the High Molecular Weight Form of Adiponectin. *Circ. Res.* 2004, 94, e27–e31. [CrossRef] [PubMed]

46. Salehi-Abargouei, A.; Izadi, V.; Azadbakhsh, L. The Effect of Low Calorie Diet on Adiponectin Concentration: A Systematic Review and Meta-Analysis. *Horm. Metab. Res.* 2015, 47, 549–555. [CrossRef]

47. De Vincentis, A.; Pedone, C.; Gentilucci, U.V.; Picardi, A.; Derosa, G.; Maffioli, P.; Sahebkar, A. Effect of Sibutramine on Plasma C-Reactive Protein, Leptin and Adiponectin Concentrations: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Curr. Pharm. Des.* 2017, 23, 870–877. [CrossRef]

48. Garvey, W.T.; Ryan, D.H.; Henry, R.; Bohnannan, N.J.; Toplak, H.; Schwiers, M.; Troupin, B.; Day, W.W. Prevention of Type 2 Diabetes in Subjects with Prediabetes and Metabolic Syndrome Treated with Phentermine and Topiramate Extended Release. *Diabetes Care* 2013, 37, 912–921. [CrossRef]

49. Khosravi-Largani, M.; Nojomi, M.; Aghili, R.; Otaghvar, H.A.; Tanha, K.; Seyedi, S.H.S.; Mottaghi, A. Evaluation of all Types of Metabolic Bariatric Surgery and its Consequences: A Systematic Review and Meta-Analysis. *Obes. Surg.* 2019, 29, 651–690. [CrossRef]

50. Woodward, L.; Akoumianakis, I.; Antoniades, C. Unravelling the adiponectin paradox: Novel roles of adiponectin in the reg-ulation of cardiovascular disease. *Br. J. Pharmacol.* 2017, 144, 4007–4020. [CrossRef]

51. Wannamethee, S.G.; Whincup, P.; Lennon, L.; Sattar, N. Circulating Adiponectin Levels and Mortality in Elderly Men with and Without Cardiovascular Disease and Heart Failure. *Arch. Intern. Med.* 2007, 167, 1510–1517. [CrossRef]

52. McEntegart, M.B.; Awede, B.; Petrie, M.C.; Sattar, N.; Dunn, F.G.; Macfarlane, N.G.; McMurray, J.J. Increase in serum adiponectin concentration in patients with heart failure and cachexia: Relationship with leptin, other cytokines, and B-type natriuretic peptide. *Eur. Heart J.* 2007, 28, 829–835. [CrossRef]

53. Tindall, C.A.; Dommel, S.; Riedel, V.; Ulbricht, D.; Hanke, S.; Strätter, N.; Heiker, J.T. Membrane Phospholipids and Polyphosphates as Cofactors and Binding Molecules of SERPINA12 (vaspin). *Molecules* 2020, 25, 1992. [CrossRef] [PubMed]

54. Hida, K.; Wada, J.; Eguchi, J.; Zhang, H.; Baba, M.; Seida, A.; Hashimoto, I.; Okada, T.; Yasuhara, A.; Nakatsuka, A.; et al. Visceral adipose tissue-derived serine protease inhibitor: A unique insulin-sensitizing adipocytokine in obesity. *Proc. Natl. Acad. Sci. USA* 2005, 102, 10610–10615. [CrossRef] [PubMed]

55. Weiner, J.; Zieger, K.; Pippel, J.; Heiker, J.T. Molecular Mechanisms of Vaspin Action—From Adipose Tissue to Skin and Bone, from Blood Vessels to the Brain. *Adv. Exp. Med. Biol.* 2019, 1111, 159–188. [PubMed]

56. Kurowska, P.; Myczynśka, E.; Dawid, M.; Jurk, M.; Klimeczk, D.; Dupont, J.; Rak, A. Review: Vaspin (SERPINA12) Expression and Function in Endocrine Cells. *Cells* 2021, 10, 1710. [CrossRef]

57. Heiker, J.T.; Klötting, N.; Kovacs, P.; Kuettner, E.B.; Sträter, N.; Schultz, S.; Kern, M.; Stumvoll, M.; Blüher, M.; Beck-Sickerling, A.G. Vaspin inhibits kallikrein 7 by serpin mechanism. * experientia* 2013, 70, 2569–2583. [CrossRef]

58. Ulbricht, D.; Tindall, C.A.; Oertwig, K.; Hanke, S.; Strätter, N.; Heiker, J.T. Kallikrein-related peptidase 14 is the second KLK protease targeted by the serpin vaspin. *Biochem. Biophys. Acta* 2018, 1894, 1079–1084. [CrossRef] [PubMed]

59. Satô, K.; Shirai, R.; Yamaguchi, M.; Yamashita, T.; Shibata, K.; Okano, T.; Morì, Y.; Matsuyama, T.A.; Ishibashi-Ueda, H.; Hirano, T.; et al. Anti-Atherogenic Effects of Vaspin on Human Aortic Smooth Muscle Cell/Macrophage Responses and Hyper-lipidemic Mouse Plaque Phenotype. *Int. J. Mol. Sci.* 2018, 19, 1732. [CrossRef]

60. Nakatsuka, A.; Wada, J.; Iseda, I.; Teshigawara, S.; Hигashio, K.; Murakami, K.; Kanzaki, M.; Inoue, K.; Terami, T.; Katayama, A.; et al. Vaspin is an adipokine ameliorating ER stress in obesity as a ligand for cell-surface GRP78/MTJ-1 complex. *Diabetes* 2012, 61, 2823–2832. [CrossRef]

61. Liu, S.; Li, X.; Wu, Y.; Duan, R.; Zhang, J.; Du, F.; Zhang, Q.; Li, Y.; Li, N. Effects of vaspin on pancreatic β cell secretion via PISK/Akt and NF-κB signaling pathways. *PloS ONE* 2017, 12, e0189722. [CrossRef] [PubMed]

62. Luo, X.; Li, K.; Zhang, C.; Yang, G.; Yang, M.; Jia, Y.; Zhang, L.; Ma, Z.A.; Boden, G.; Li, L. Central administration of vaspin inhibits glucose production and augments insulin signaling in high-fat-diet-fed rat. *Int. J. Obes.* 2016, 40, 947–954. [CrossRef] [PubMed]

63. Liu, S.; Dong, Y.; Wang, T.; Zhao, S.; Yang, K.; Chen, X.; Zheng, C. Vaspin inhibited proinflammatory cytokine induced activation of nuclear factor-kappa B and its downstream mol-eules in human endothelial EA.hy926 cells. *Diabetes Res. Clin. Pract.* 2014, 103, 482–488. [CrossRef]

64. Jung, C.H.; Lee, M.J.; Kang, Y.M.; La Lee, Y.; Yoon, H.K.; Kang, S.-W.; Lee, W.J.; Park, J.-Y. Vaspin inhibits cytokine-induced nuclear factor-kappa B activation and adhesion molecule expression via AMP-activated protein kinase activation in vascular endothelial cells. *Cardiovasc. Diabetol.* 2014, 13, 41. [CrossRef]
65. Zieger, K.; Weiner, J.; Krause, K.; Schwarz, M.; Kohn, M.; Stumvoll, M.; Blüher, M.; Heiker, J.T. Vaspin suppresses cytokine-induced inflammation in 3T3-L1 adipocytes via inhibition of NFκB pathway. Mol. Cell. Endocrinol. 2018, 460, 181–188. [CrossRef] [PubMed]
66. Sakamoto, Y.; Kameshima, S.; Kakuda, C.; Okamura, Y.; Kodama, T.; Okada, M.; Yamawaki, H. Visceral adipose tissue-derived serine protease inhibitor prevents the development of monocrotaline-induced pulmonary arterial hypertension in rats. Pflugers Arch. 2017, 469, 1425–1432. [CrossRef] [PubMed]
67. Qi, D.; Wang, D.; Zhang, C.; Tang, X.; He, J.; Zhao, Y.; Deng, W.; Deng, X. Vaspin protects against LPS-induced ARDS by inhibiting inflammation, apoptosis and reactive oxygen species generation in pulmonary endothelial cells via the Akt/GSK-3β pathway. Int. J. Mol. Med. 2017, 40, 1803–1817.
68. Jung, C.H.; Lee, W.J.; Hwang, J.Y.; Seol, S.M.; Kim, Y.M.; La Lee, Y.; Park, J.-Y. Vaspin protects vascular endothelial cells against free fatty acid-induced apoptosis via a phosphatidylinositol 3-kinase/Akt pathway. Biochem. Biophys. Res. Commun. 2011, 413, 264–269. [CrossRef]
69. Zhu, X.; Zhang, L.; Chen, Y.; Chen, B.; Huang, H.; Lv, J.; Hu, S.; Shen, J. Vaspin protects mice mesenchymal stem cells from oxidative stress-induced apoptosis through the MAPK/p38 pathway. Mol. Cell. Biochem. 2019, 462, 107–114. [CrossRef]
70. Nakatsuji, K.; Wada, J.; Iseda, I.; Teshigawara, S.; Higashio, K.; Murakami, K.; Kanzaki, M.; Inoue, K.; Terami, T.; Katayama, A.; et al. Visceral adipose tissue-derived serine protease inhibitor inhibits apoptosis of endothelial cells as a ligand for the cell-surface GRP78/voltage-dependent anion channel complex. Circ. Res. 2013, 112, 771–780. [CrossRef]
71. Jung, C.H.; Lee, W.J.; Hwang, J.Y.; Lee, M.J.; Seol, S.M.; Kim, Y.M.; La Lee, Y.; Kim, H.S.; Kim, M.-S.; Park, J.-Y. Vaspin Increases Nitric Oxide Bioavailability through the Reduction of Asymmetric Dimethylarginine in Vascular Endothelial Cells. PLoS ONE 2012, 7, e52346. [CrossRef] [PubMed]
72. Klöting, N.; Kovacs, P.; Kern, M.; Heiker, J.T.; Fasshauer, M.; Schön, M.R.; Stumvoll, M.; Beck-Sickinger, A.G.; Blüher, M. Central vaspin administration acutely reduces food intake and has sustained blood glucose-lowering effects. Diabetologia 2011, 54, 1819–1823. [CrossRef] [PubMed]
73. Brunetti, L.; Di Nisio, C.; Recinella, L.; Chiavaroli, A.; Leone, S.; Ferrante, C.; Orlando, G.; Vacca, M. Effects of vaspin, chemerin and omentin-1 on feeding behavior and hypothalamic peptide gene expression in the rat. Peptides 2011, 32, 1866–1871. [CrossRef] [PubMed]
74. Gao, J.H.; Zeng, M.Y.; Yu, X.H.; Zeng, G.F.; He, L.H.; Zheng, X.L.; Zhang, D.W.; Ouyang, X.P.; Tang, C.K. Visceral adipose tissue-derived serine protease inhibitor accelerates cholesterol efflux by up-regulating ABCA1 expression via the NF-κb/miR-33a pathway in THP-1 macrophage-derived foam cells. Biochem. Biophys. Res. Commun. 2018, 500, 318–324. [CrossRef]
75. Taheri, E.; Hosseini, S.; Qorbani, M.; Mirmiran, P. Association of adipokines with lipid and glycemic profiles in women with type 2 diabetes mellitus: A meta-analysis. Diabetes Res. Clin. Pract. 2014, 106, 88–94. [CrossRef] [PubMed]
76. Hao, F.; Zhang, H.; Zhu, J.; Kuang, H.; Yu, Q.; Bai, M.; Mu, J. Association between vaspin level and coronary artery disease in patients with type 2 diabetes. Diabetes Res. Clin. Pract. 2016, 113, 26–32. [CrossRef]
77. Yang, H.; Huang, Y.; Gai, C.; Chai, G.; Lee, S. Serum vaspin levels are positively associated with diabetic retinopathy in patients with type 2 diabetes mellitus. J. Diabetes Investig. 2020, 12, 566–573. [CrossRef] [PubMed]
78. Jia, G.Y.; Han, T.; Gao, L.; Wang, L.; Wang, S.C.; Yang, L.; Zhang, J.; Guan, Y.Y.; Yan, N.N.; Yu, H.Y.; et al. Effect of aerobic exercise and resistance exercise in improving non-alcoholic fatty liver disease: A randomized controlled trial. Zhonghua Gan Zang Bing Za Zhi 2018, 26, 34–41.
79. Tan, B.K.; Heutling, D.; Chen, J.; Farhatullah, S.; Adya, R.; Keay, S.D.; Kennedy, C.R.; Lehnter, H.; Randeva, H.S. Metformin Decreases the Adipokine Vaspin in Overweight Women with Polycystic Ovary Syndrome Concomitant with Improvement in Insulin Sensitivity and a Decrease in Insulin Resistance. Diabetes 2018, 57, 1501–1507. [CrossRef]
80. Zhang, L.; Li, L.; Yang, M.; Liu, H.; Yang, G. Elevated circulating vaspin levels were decreased by rosiglitazone therapy in T2DM patients with poor glycemic control on metformin alone. Cytokine 2011, 56, 399–402. [CrossRef]
81. Golpaie, A.; Tajik, N.; Masoudkabir, F.; Karbaschian, Z.; Talebpour, M.; Hosseini, M.; Hosseinzadeh-Attar, M.J. Short-term effect of weight loss through restrictive bariatric surgery on serum levels of vaspin in morbidly obese subjects. Eur. Cytokine Netw. 2011, 22, 181–186. [CrossRef]
82. Li, J.; Li, Q.; Zhu, Y.; Wang, Y.; Gao, C.; Li, X.; Ji, T.; Bai, S. Association of vaspin rs2236242 gene variants with type 2 diabetes and obesity in a Chinese population: A prospective, single-center study. J. Cell. Physiol. 2019, 234, 16097–16101. [CrossRef] [PubMed]
83. Kadoglu, N.P.; Kassimis, G.; Patsoyarakos, N.; Kanonidis, I.; Valsami, G. Omentin-1 and vaspin serum levels in patients with preclinical carotid atherosclerosis and the effect of statin therapy on them. Cytokine 2021, 138, 153564. [CrossRef]
84. Al-Kuraishy, H.M.; Al-Gareeb, A.I.; Al-Buhadilly, A.K. Rosuvastatin Improves Vaspin Serum Levels in Obese Patients with Acute Coronary Syndrome. Diseases 2018, 6, 9. [CrossRef] [PubMed]
85. Kastl, S.P.; Katsaros, K.M.; Krychtiuk, K.A.; Jägersberger, G.; Kaun, C.; Huber, K.; Wojta, J.; Speidel, W.S. The adipokine vaspin is associated with decreased coronary in-stent restenosis in vivo and inhibits migration of human coronary smooth muscle cells in vitro. PloS ONE 2020, 15, e0232483. [CrossRef]
86. Zhang, B.; Peng, W.; Wang, K.; Li, H.; Xu, Y. Vaspin as a Prognostic Marker in Patients with Acute Myocardial Infarction. Heart Lung Circ. 2016, 25, 257–264. [CrossRef]
111. Yamaguchi, S.; Shibata, R.; Ohashi, K.; Enomoto, T.; Ogawa, H.; Otaka, N.; Hiramatsu-Ito, M.; Masutomi, T.; Kawanishi, H.; Murohara, T.; et al. Clq/TNF-Related Protein 9 Promotes Revascularization in Response to Ischemia via an eNOS-Dependent Manner. Front. Pharmacol. 2020, 11, 1313. [CrossRef] [PubMed]

112. Li, Y.; Geng, X.; Wang, H.; Cheng, G.; Xu, S. CTRP9 Ameliorates Pulmonary Arterial Hypertension Through Attenuating Inflammation and Improving Endothelial Cell Survival and Function. J. Cardiovasc. Pharmacol. 2016, 67, 394–401. [CrossRef] [PubMed]

113. Cheng, L.; Li, B.; Chen, X.; Su, J.; Wang, H.; Yu, S.; Zheng, Q. CTRP9 induces mitochondrial biogenesis and protects high glucose-induced endothelial oxidative damage via AdipoR1 -SIRT1- PGC-1α activation. Biochem. Biophys. Res. Commun. 2016, 477, 685–691. [CrossRef] [PubMed]

114. Sun, H.; Zhu, X.; Zhou, Y.; Cai, W.; Qiu, L. Clq/TNF-Related Protein-9 Ameliorates Ox-LDL-Induced Endothelial Dysfunction via PGC-1α/AMPK-Mediated Antioxidant Enzyme Induction. Int. J. Mol. Sci. 2017, 18, 1097. [CrossRef]

115. Niemann, B.; Li, L.; Siegler, D.; Siegler, B.H.; Knapp, F.; Hanna, J.; Aslam, M.; Kracht, M.; Schulz, R.; Rohrbach, S. CTRP9 Mediates Protective Effects in Cardiomyocytes via AMPK- and Adiponectin Receptor-Mediated Induction of Anti-Oxidant Response. Cells 2020, 9, 1229. [CrossRef]

116. Song, C.X.; Chen, J.Y.; Li, N.; Guo, Y. CTRP9 Enhances Efferocytosis in Macrophages via MAPK/Drp1-Mediated Mitochondrial Fission and Adi-poR1-Induced Immunometabolism. J. Inflamm. Res. 2021, 14, 1007–1017. [CrossRef]

117. Lee, J.; Yoo, J.H.; Kim, H.S.; Cho, Y.K.; La Lee, Y.; Lee, W.J.; Park, J.-Y.; Jung, C.H. Clq/TNF-related protein-9 attenuates palmitic acid-induced endothelial cell senescence in vivo. Mol. Cell. Endocrinol. 2021, 521, 111114. [CrossRef]

118. Sun, Y.; Yi, W.; Yuan, Y.; Lau, W.B.; Yi, D.; Wang, X.; Wang, Y.; Su, H.; Wang, X.; Gao, E.; et al. Clq/Tumor Necrosis Factor–Related Protein-9, a Novel Adipocyte-Derived Cytokine, Attenuates Adverse Remodeling in the Ischemic Mouse Heart via Protein Kinase a Activation. Circulation 2013, 128 (Suppl. 1), S113–S120. [CrossRef] [PubMed]

119. Wang, J.; Hang, T.; Cheng, X.M.; Li, D.M.; Zhang, Q.G.; Wang, L.J.; Peng, Y.P.; Gong, J.B. Associations of C1q/TNF-Related Protein-9 Levels in Serum and Epicardial Adipose Tissue with Coronary Atherosclerosis in Humans. Biomed. Res. Int. 2015, 2015, 971683. [CrossRef] [PubMed]

120. Moradi, N.; Fadaei, R.; Emamgholipour, S.; Kazemian, E.; Panahi, G.; Vahedi, S.; Fallah, S. Association of circulating CTRP9 with soluble adhesion molecules and inflammatory markers in patients with type 2 diabetes mellitus and coronary artery disease. PloS ONE 2018, 13, e0192159. [CrossRef]

121. Gao, C.; Zhao, S.; Lian, K.; Mi, B.; Su, J.; Wang, H.; Yu, S.; Zheng, Q. CTRP9 induces mitochondrial biogenesis and protects high glucose-induced endothelial oxidative damage via AdipoR1 -SIRT1- PGC-1α activation. Biochem. Biophys. Res. Commun. 2016, 477, 685–691. [CrossRef] [PubMed]

122. Miyatake, N.; Adachi, H.; Nomura-Nakayama, K.; Okada, K.; Okino, K.; Hayashi, N.; Fujimoto, K.; Furuiuchi, K.; Yokoyama, H. Circulating CTRP9 correlates with the prevention of aortic calcification in renal allograft recipients. PLoS ONE 2020, 15, e0226526. [CrossRef]

123. Pan, J.; Cui, X.; Wang, G.; Xue, K.; Hu, J.; Zhou, L. Predictive value of serum CTRP9 and STIM1 for restenosis after cerebrovascular stent implantation and its relationship with vasoactive substances and inflammatory cytokines. Exp. Ther. Med. 2020, 20, 2617–2622. [CrossRef] [PubMed]

124. Jia, Y.; Luo, X.; Ji, Y.; Xie, J.; Jiang, H.; Fu, M.; Li, X. Circulating CTRP9 levels are increased in patients with newly diagnosed type 2 diabetes and correlated with insulin resistance. Diabetes Res. Clin. Pract. 2017, 131, 116–123. [CrossRef]

125. Hwang, Y.-C.; Oh, S.W.; Park, S.-W.; Park, C.-Y. Association of serum C1q/TNF-Related Protein-9 (CTRP9) concentration with visceral adiposity and metabolic syndrome in humans. Int. J. Obes. 2014, 38, 1207–1212. [CrossRef] [PubMed]

126. Wolf, R.M.; Steele, K.E.; Peterson, L.A.; Zeng, X.; Jaffe, A.; Schweitzer, M.A.; Magnuson, T.H.; Wong, G.W. C1q/TNF-Related Protein-9 (CTRP9) Levels Are Associated with Obesity and Decrease Following Weight Loss Surgery. PLoS ONE 2020, 15, e0226526. [CrossRef] [PubMed]

127. Jia, Y.; Luo, X.; Ji, Y.; Xie, J.; Jiang, H.; Fu, M.; Li, X. Circulating CTRP9 levels are increased in patients with newly diagnosed type 2 diabetes mellitus. Diabetes Res. Clin. Pract. 2017, 131, 116–123. [CrossRef]

128. Asada, M.; Morioka, T.; Yamazaki, Y.; Kakutani, Y.; Kawarabayashi, R.; Motoyama, K.; Mori, K.; Fukushima, S.; Shiioi, A.; Shoji, T.; et al. Plasma C1q/TNF-Related Protein 9 Levels are Associated with Atherosclerosis in Patients with Type 2 Diabetes without Renal Dysfunction. J. Diabetes Res. 2016, 2016, 8624313. [CrossRef]

129. Jung, C.H.; Lee, M.J.; Kang, Y.M.; Jang, J.E.; Leem, J.; La Lee, Y.; Seol, S.M.; Yoon, H.K.; Lee, W.J.; Park, J.-Y. Association of Serum C1q/TNF-Related Protein-9 Concentration with Arterial Stiffness in Subjects with Type 2 Diabetes. J. Clin. Endocrinol. Metab. 2014, 99, E2477–E2484. [CrossRef] [PubMed]

130. Na, N.; Ji, M. Role of First-Trimester Serum C1q/TNF-Related Protein 9 in Gestational Diabetes Mellitus. Clin. Lab. 2020, 66. [CrossRef] [PubMed]

131. Chen, L.; Qin, L.; Liu, X.; Meng, X. CTRP3 Alleviates Ox-LDL-Induced Inflammatory Response and Endothelial Dysfunction in Mouse Aortic Endothelial Cells by Activating the PI3K/Akt/eNOS Pathway. Inflammation 2019, 42, 1350–1359. [CrossRef]
156. Hirata, A.; Kishida, K.; Kobayashi, H.; Nakatsuji, H.; Funahashi, T.; Shimomura, I. Correlation between serum C1q-adiponectin/totai adiponectin ratio and polyvascular lesions detected by vascular ultrasonography in Japanese type 2 diabetics. *Metabolism* 2013, 62, 376–385. [CrossRef] [PubMed]

157. Hirata, A.; Kishida, K.; Nakatsuji, H.; Kobayashi, H.; Funahashi, T.; Shimomura, I. High serum C1q-adiponectin/totai adiponectin ratio correlates with coronary artery disease in Japanese type 2 diabetics. *Metabolism* 2013, 62, 578–585. [CrossRef]

158. Kishida, K.; Nakagawa, Y.; Kobayashi, H.; Yanagi, K.; Funahashi, T.; Shimomura, I. Increased serum C1q-binding adiponectin complex to total-adiponectin ratio in men with multi-vessel coronary disease. *Diabetol. Metab. Syndr.* 2014, 6, 64. [CrossRef] [PubMed]

159. Hong, E.S.; Lim, C.; Choi, H.Y.; Ku, E.J.; Kim, K.M.; Moon, J.H.; Lim, S.; Park, K.S.; Jang, H.C.; Choi, S.H. The amount of C1q-secreted frizzled-related protein complex is higher in the serum and the complex localizes to perivascular areas of fat tissues and the intimal-medial layer of blood vessels of coronary artery disease patients. *Cardiovase. Diabetol.* 2015, 14, 50. [CrossRef]

160. Bilkovski, R.; Schulte, D.M.; Oberhauser, F.; Mauer, J.; Hampel, B.; Gutschow, C.; Krone, W.; Laudes, M. Adipose tissue macrophages inhibit adipogenesis of mesenchymal precursor cells via wnt-5a in humans. *Int. J. Obes.* 2011, 35, 1450–1454. [CrossRef]

161. Pashirzad, M.; Shafiee, M.; Rahmani, F.; Behnam-Rassouli, R.; Hoseinikhan, F.; Ryzhikov, M.; Binabazar, M.M.; Parizadeh, M.R.; Avan, A.; Hassanian, S.M. Role of Wnt5a in the Pathogenesis of Inflammatory Diseases. *J. Cell. Physiol.* 2017, 232, 1611–1616. [CrossRef] [PubMed]

162. Ouchi, N.; Higuchi, A.; Ohashi, Y.; Oshima, Y.; Goke, N.; Shibata, R.; Akasaki, Y.; Shimono, A.; Walsh, K. Sfrp5 Is an Anti-Inflammatory Adipokine That Modulates Metabolic Dysfunction in Obesity. *Science* 2010, 329, 454–457. [CrossRef] [PubMed]

163. Rydzewska, M.; Nikolajuk, A.; Matulewicz, N.; Stefanowicz, M.; Karczewska-Kupczewska, M. Serum secreted frizzled-related protein 5 in relation to insulin sensitivity and its regulation by insulin and free fatty acids. *Endocrine 2021*, 74, 300–307. [CrossRef]

164. Tong, S.; Ji, Q.; Du, Y.; Zhu, X.; Zhu, C.; Zhou, Y. Sfrp5/Wnt Pathway: A Protective Regulatory System in Atherosclerotic Cardiovascular Disease. *J. Interferon Cytokine Res.* 2019, 39, 472–482. [CrossRef]

165. Wang, D.; Zhang, Y.; Shen, C. Research update on the association between SFRP5, an anti-inflammatory adipokine, with obesity, type 2 diabetes mellitus and coronary heart disease. *J. Cell. Mol. Med.* 2020, 24, 2730–2735. [CrossRef]

166. Sun, M.; Wang, W.; Min, L.; Chen, C.; Li, Q.; Weng, W. Secreted frizzled-related protein 5 (SFRP5) protects ATDC5 cells against LPS-induced inflammation and apoptosis via inhibiting Wnt5a/JNK pathway. *J. Orthop. Surg. Res.* 2021, 16, 129. [CrossRef] [PubMed]

167. Christodoulides, C.; Lagathu, C.; Sethi, J.K.; Vidal-Puig, A. Adipogenesis and WNT signalling. *Trends Endocrinol. Metab.* 2009, 20, 16–24. [CrossRef] [PubMed]

168. Mori, H.; Prestwich, T.C.; Reid, M.; Longo, K.A.; Gerin, I.; Cavthorn, W.; Susulic, V.S.; Krishnan, V.; Greenfield, A.; MacDougald, O. Secreted frizzled-related protein 5 suppresses adipocyte mitochondrial metabolism through WNT inhibition. *J. Clin. Investig. 2012, 122, 2405–2416. [CrossRef] [PubMed]

169. Carstensen-Kirberg, M.; Röhrig, K.; Niersmann, C.; Ouwens, D.M.; Belgardt, B.F.; Roden, M.; Herder, C. Sfrp5 increases glucose-stimulated insulin secretion in the rat pancreatic beta cell line INS-1E. *PloS ONE 2019*, 14, e0213650. [CrossRef]

170. Li, Y.; Tian, M.; Yang, M.; Yang, G.; Chen, J.; Wang, H.; Liu, D.; Wang, H.; Deng, W.; Zhu, Z.; et al. Central Sfrp5 regulates hepatic glucose flux and VLDL-triglyceride secretion. *Metabolism 2020*, 103, 154029. [CrossRef] [PubMed]

171. Wang, X.; Peng, Q.; Jiang, F.; Xue, L.; Li, J.; Fan, Z.; Chen, P.; Chen, G.; Cai, Y. Secreted frizzled-related protein 5 protects against oxidative stress-induced apoptosis in human aortic endothelial cells via downregulation of Bax. *J. Biochem. Mol. Toxicol. 2017, 31, e21978. [CrossRef] [PubMed]

172. Liu, W.; Ji, Y.; Chu, H.; Wang, M.; Yang, B.; Yin, C. SFRP5 mediates downregulation of the wnt5a/caveolin-1/JNK signaling pathway. *J. Endocrinol. 2020, 247, 263–272. [CrossRef] [PubMed]

173. Cho, Y.K.; Kang, Y.M.; Lee, S.E.; La Lee, Y.; Seol, S.M.; Lee, W.J.; Park, J.-Y.; Jung, C.H. Effect of SFRP5 (Secreted Frizzled–Related Protein 5) on the WNT5A (Wingless-Type Family Member 5A)-Induced Endothelial Dysfunction and Its Relevance with Arterial Stiffness in Human Subjects. *Arterioscler. Thromb. Vasc. Biol.* 2018, 38, 1358–1367. [CrossRef] [PubMed]

174. Teliewubai, J.; Ji, H.; Lu, Y.; Bai, B.; Yu, S.; Chi, C.; Xu, Y.; Zhang, Y. SFRP5 serves a beneficial role in arterial aging by inhibiting the proliferation, migration and inflammation of smooth muscle cells. *Mol. Med. Rep.* 2018, 18, 4682–4690. [CrossRef]

175. Nakamura, K.; Sano, S.; Fuster, J.J.; Kikuchi, R.; Shimizu, I.; Oshima, K.; Katanasaka, Y.; Ouchi, N.; Walsh, K. Secreted Frizzled-Related Protein 5 Diminishes Cardiac Inflammation and Protects the Heart from Ischemia/Reperfusion Injury. *J. Biol. Chem. 2016, 291, 2566–2575. [CrossRef]

176. Bie, Z.-D.; Sun, L.-Y.; Geng, C.-L.; Meng, Q.-G.; Lin, X.-J.; Wang, Y.-F.; Wang, X.-B.; Yang, J. MiR-125b regulates SFRP5 expression to promote growth and activation of cardiac fibroblasts. *Cell Biol. Int.* 2016, 40, 1224–1234. [CrossRef]

177. Akoumianakis, I.; Sanna, F.; Margaritis, M.; Badi, I.; Akawi, N.; Herdman, L.; Coutinho, P.; Fagan, H.; Antonopoulos, A.S.; Oikonomou, E.K.; et al. Adipose tissue-derived WNT5A regulates vascular redox signaling in obesity via USP17/RAC1-mediated activation of NADPH oxidases. *Sci. Transl. Med.* 2019, 11, eaav5055. [CrossRef] [PubMed]

178. Carstensen-Kirberg, M.; Kannenberg, J.M.; Huth, C.; Meisinger, C.; Koenig, W.; Heier, M.; Peters, A.; Rathmann, W.; Roden, M.; Herder, C.; et al. Inverse associations between serum levels of secreted frizzled-related protein-5 (SFRP5) and multiple cardiometabolic risk factors: KORA F4 study. *Cardiovasc. Diabetol.* 2017, 16, 109. [CrossRef]
181. Hu, W.; Li, L.; Yang, M.; Luo, X.; Ran, W.; Liu, D.; Xiong, Z.; Liu, H.; Yang, G. Circulating Sfrp5 Is a Signature of Obesity-Related Metabolic Disorders and Is Regulated by Glucose and Liraglutide in Humans. *J. Clin. Endocrinol. Metab.* 2013, 98, 290–298. [CrossRef]

182. Almario, R.U.; Karakas, S.E. Roles of Circulating WNT-Signaling Proteins and WNT-Inhibitors in Human Adiposity, Insulin Resistance, Insulin Secretion, and Inflammation. *Horm. Metab. Res.* 2015, 47, 152–157. [CrossRef] [PubMed]

183. Almario, R.U.; Karakas, S.E. Roles of Circulating WNT-Signaling Proteins and WNT-Inhibitors in Human Adiposity, Insulin Resistance, Insulin Secretion, and Inflammation. *Horm. Metab. Res.* 2015, 47, 152–157. [CrossRef] [PubMed]

184. Xu, Q.; Wang, H.; Li, Y.; Wang, J.; Lai, Y.; Gao, L.; Lei, L.; Yang, G.; Liao, X.; Fang, X.; et al. Plasma Sfrp5 levels correlate with determinants of the metabolic syndrome in Chinese adults. *Diabetes Metab. Res. Rev.* 2017, 33, e2896. [CrossRef] [PubMed]

185. Lu, Y.C.; Wang, C.P.; Hsu, C.C.; Chiu, C.A.; Yu, T.H.; Hung, W.C.; Lu, L.F.; Chung, F.M.; Tsai, I.T.; Lin, H.C.; et al. Circulating secreted frizzled-related protein 5 (Sfrp5) and wingless-type MMTV integration site family member 5a (Wnt5a) levels in patients with type 2 diabetes mellitus. *Diabetes Metab. Res. Rev.* 2013, 29, 551–556.

186. Wang, B.; Pan, Y.; Yang, G.; Yu, W.; Liu, H.; Bai, B. Sfrp5/Wnt5a and leptin/adiponectin levels in the serum and the periarterial adipose tissue of patients with peripheral arterial occlusive disease. *Clin. Biochem.* 2020, 87, 46–51. [CrossRef]

187. Oh, Y.J.; Kim, H.; Kim, A.J.; Ro, H.; Chang, J.H.; Lee, H.H.; Chung, W.; Jun, H.-S.; Jung, J.Y. Reduction of Secreted Frizzled-Related Protein 5 Levels Associates with Early Improvement of Cardiac Function Following ST-Segment Elevation Myocardial Infarction Treated by Primary Percutaneous Coronary Intervention. *J. Atheroscler. Thromb.* 2019, 26, 868–878. [CrossRef]

188. Wang, B.; Pan, Y.; Yang, G.; Yu, W.; Liu, H.; Bai, B. Sfrp5/Wnt5a and leptin/adiponectin levels in the serum and the periarterial adipose tissue of patients with peripheral arterial occlusive disease. *Clin. Biochem.* 2020, 87, 46–51. [CrossRef]

189. Du, Y.; Zhao, Y.; Zhu, Y.; Hu, C.; Zhang, J.; Ji, Q.; Liu, W.; Han, Y.; Yang, L.; Zhang, D.; et al. High Serum Secreted Frizzled-Related Protein 5 Levels Associates with Early Improvement of Cardiac Function Following ST-Segment Elevation Myocardial Infarction Treated by Primary Percutaneous Coronary Intervention. *J. Atheroscler. Thromb.* 2019, 26, 868–878. [CrossRef]

190. Du, Y.; Zhao, Y.; Zhu, Y.; Hu, C.; Zhang, J.; Ji, Q.; Liu, W.; Han, Y.; Yang, L.; Zhang, D.; et al. High Serum Secreted Frizzled-Related Protein 5 Levels Associates with Early Improvement of Cardiac Function Following ST-Segment Elevation Myocardial Infarction Treated by Primary Percutaneous Coronary Intervention. *J. Atheroscler. Thromb.* 2019, 26, 868–878. [CrossRef]

191. Ji, H.; Li, H.; Zhuang, J.; Su, Y.; Wen, J.; Zhang, J.; Zhao, D.; Zhang, Y.; Xu, Y. High serum level of secreted frizzled-related protein 5 (sfrp5) is associated with future cardiovascular events. *Cardiovasc. Ther.* 2017, 2, e115.

192. Yang, R.-Z.; Lee, M.-J.; Glynn, N.M.; Yu, D.-Z.; Pray, J.; Ndubuizu, K.; Patil, S.; Schwartz, A.; Kligman, M.; et al. Omentin Plasma Levels and Gene Expression Are Decreased in Obesity. *Diabetes* 2007, 56, 1655–1661. [CrossRef]

193. De Souza Batista, C.M.; Yang, R.-Z.; Lee, M.-J.; Glynn, N.M.; Yu, D.-Z.; Pray, J.; Ndubuizu, K.; Patil, S.; Schwartz, A.; Kligman, M.; et al. Omentin Plasma Levels and Gene Expression Are Decreased in Obesity. *Diabetes* 2007, 56, 1655–1661. [CrossRef]

194. Watanabe, T.; Watanabe-Kominato, K.; Takahashi, Y.; Kojima, M.; Watanabe, R. Adipose Tissue-Derived Omentin-1 Function and Regulation. *Compr. Physiol.* 2017, 7, 765–781. [CrossRef] [PubMed]

195. Hiramatsu-Itō, M.; Shibata, R.; Ohashi, K.; Uemura, Y.; Kanemura, N.; Kambara, T.; Enomoto, T.; Yuasa, D.; Matsu, K.; Ito, M.; et al. Omentin attenuates atherosclerotic lesion formation in apolipoprotein E-deficient mice. *Cardiovasc. Res. 2016, 110, 107–117. [CrossRef] [PubMed]

196. Lin, X.; Sun, Y.; Yang, S.; Yu, M.; Pan, L.; Yang, J.; Yang, J.; Shao, Q.; Liu, J.; Liu, Y.; et al. Omentin-1 Modulates Macrophage Function via Integrin Receptors αvβ3 and αvβ5 and Reverses Plaque Vulnerability in Animal Models of Atherosclerosis. *Front. Cardiovasc. Med.* 2021, 8, 757926. [CrossRef] [PubMed]

197. Watanabe, K.; Watanabe, R.; Konii, H.; Shirai, R.; Sato, K.; Matsuyama, T.-A.; Ishibashi-Ueda, H.; Koba, S.; Kobayashi, Y.; Hirano, T.; et al. Counteractive effects of omentin-1 against atherosclerosis. *Cardiovasc. Res. 2016, 110, 118–128. [CrossRef]

198. Uemura, Y.; Shibata, R.; Kanemura, N.; Ohashi, K.; Kambara, T.; Hiramatsu-Itō, M.; Enomoto, T.; Yuasa, D.; Joki, Y.; Matsu, K.; et al. Adipose-derived protein omentin prevents neointimal formation after arterial injury. *FASEB J.* 2015, 29, 141–151. [CrossRef]

199. Xie, H.; Xie, P.-L.; Wu, X.-P.; Chen, S.-M.; Zhou, H.-D.; Yuan, L.-Q.; Sheng, Z.-F.; Tang, S.-Y.; Luo, X.-H.; Liao, E.-Y. Omentin-1 attenuates arterial calcification and bone loss in osteoprotegerin-deficient mice by inhibition of RANKL expression. *Cardiovasc. Res. 2011, 92, 296–306. [CrossRef] [PubMed]

200. Leandro, A.; Queiroz, M.; Azul, L.; Seiça, R.; Sena, C.M. Omentin: A novel therapeutic approach for the treatment of endothelial dysfunction in type 2 diabetes. *Free. Radic. Biol. Med.* 2021, 162, 233–242. [CrossRef]

201. Yamawaki, H.; Tsubaki, N.; Mukohda, M.; Okada, M.; Hara, Y. Omentin, a novel adipokine, induces vasodilation in rat isolated blood vessels. *Biochem. Biophys. Res. Commun.* 2010, 393, 668–672. [CrossRef]
202. Maruyama, S.; Shibata, R.; Kikuchi, R.; Izumiya, Y.; Rokutanda, T.; Araki, S.; Kataoka, Y.; Ohashi, K.; Daida, H.; Kihara, S.; et al. Fat-derived Factor Omentin Stimulates Endothelial Cell Function and Ischemia-induced Revascularization via Endothelial Nitric Oxide Synthase-dependent Mechanism. J. Biol. Chem. 2012, 287, 408–417. [CrossRef]

203. Kataoka, Y.; Shibata, R.; Ohashi, K.; Kambara, T.; Enomoto, T.; Uemura, Y.; Ogura, Y.; Yuasa, D.; Matsuo, K.; Nagata, T.; et al. Omentin Prevents Myocardial Ischemic Injury Through AMP-Activated Protein Kinase- and Akt-Dependent Mechanisms. J. Am. Coll. Cardiol. 2014, 63, 2722–2733. [CrossRef]

204. Matsuo, K.; Shibata, R.; Ohashi, K.; Kambara, T.; Uemura, Y.; Hiramatsu-Ito, M.; Enomoto, T.; Yuasa, D.; Joki, Y.; Ito, M.; et al. Omentin functions to attenuate cardiac hypertrophic response. J. Mol. cell. Cardiol. 2015, 79, 195–202. [CrossRef][PubMed]

205. Jin, Z.; Xia, F.; Dong, J.; Lin, T.; Cai, Y.; Chen, J.; Chen, X.; Huang, Z.; Wang, Q.; Chen, H.; et al. Omentin-1 attenuates glucocorticoid-induced cardiac injury by phosphorylating GSK3β. J. Mol. Endocrinol. 2021, 66, 273–283. [CrossRef]

206. Zhang, Q.; Zhu, L.; Zheng, M.; Fan, C.; Li, Y.; Zhang, D.; He, Y.; Yang, H. Changes of serum omentin-1 levels in normal subjects, type 2 diabetes and type 2 diabetes with overweight and obesity in Chinese adults. Ann. Endocrinol. 2014, 75, 171–175. [CrossRef]

207. Jalal, I.; Devaraj, S.; Kaur, H.; Adams-Huet, B.; Bremer, A.A. Increased Chemerin and Decreased Omentin-1 in Both Adipose Tissue and Plasma in Nascent Metabolic Syndrome. J. Clin. Endocrinol. Metab. 2013, 98, E514–E517. [CrossRef][PubMed]

208. Peña-Cano, M.I.; Valencia-Ortega, J.; Morales-Avila, E.; Díaz-Velázquez, M.F.; Gómez-Díaz, R.; Saucedo, R. Omentin-1 and its relationship with inflammatory factors in maternal plasma and visceral adipose tissue of women with gestational diabetes mellitus. J. Endocrinol. Investig. 2021, 1–10. [CrossRef][PubMed]

209. Latif, A.H.E.; Anwar, S.; Gautham, K.S.; Kadurei, F.; Ojo, R.O.; Hafizyar, F.; Haroon, D.M.; Rakesh, F.; Talpur, A.S. Association of Plasma Omentin-1 Levels with Diabetes and Its Complications. Curr. Issues Circ. 2021, 13, e18203. [CrossRef]

210. Biscetti, F.; Nardella, E.; Rando, M.M.; Cecchini, A.L.; Angelini, F.; Pitocco, D.; Santoliquido, A.; Filipponi, M.; Landolfi, R.; Flex, A. Association between plasma omentin-1 levels in type 2 diabetic patients and peripheral artery disease. Cardiovasc. Diabetol. 2019, 18, 74–77. [CrossRef]

211. Biscetti, F.; Nardella, E.; Bonadini, N.; Angelini, F.; Pitocco, D.; Santoliquido, A.; Filipponi, M.; Landolfi, R.; Flex, A. Association between plasma omentin-1 levels in type 2 diabetic patients and peripheral artery disease. Cardiovasc. Diabetol. 2019, 18, 74–77. [CrossRef]

212. El-Mesallamy, H.O.; El-Derany, M.O.; Hamdy, N.M. Serum omentin-1 and chemerin levels are interrelated in patients with Type 2 diabetes mellitus with or without ischaemic heart disease. Diabet. Med. 2011, 28, 1194–1200. [CrossRef]

213. Bai, P.; Abdullah, F.; Lodi, M.; Sarhadi, M.; Dilip, A.; Shahab, S.; Yasir, F.; Jahangir, M. Association between Coronary Artery Disease and Plasma Omentin-1 Levels. Curr. Issues Cardiovasc. Diabetol. 2021, 13, e17347. [CrossRef]

214. Zhong, X.; Zhang, H-Y.; Tan, H.; Zhou, Y.; Liu, F-L.; Chen, F-Q.; Shang, D-Y. Association of serum omentin-1 levels with coronary artery disease. Acta Pharmacol. Sin. 2011, 32, 873–878. [CrossRef][PubMed]

215. Biscetti, F.; Nardella, E.; Randol, M.M.; Cecchini, A.L.; Angelini, F.; Cina, A.; Iezzi, R.; Filipponi, M.; Santoliquido, A.; Pitocco, D.; et al. Association between omentin-1 and major cardiovascular events after lower extremity endovascular revascularization in diabetic patients: A prospective cohort study. Cardiovasc. Diabetol. 2020, 19, 170. [CrossRef]

216. Narumi, T.; Watanabe, T.; Kadowaki, S.; Kinoshita, D.; Yokoyama, M.; Honda, Y.; Otaki, Y.; Nishiyama, S.; Takahashi, H.; Arimoto, T.; et al. Impact of serum omentin-1 levels on cardiac prognosis in patients with heart failure. Cardiovasc. Diabetol. 2014, 13, 84. [CrossRef][PubMed]

217. Çelik, M.; Nar, R.; Nar, G.; Sökmen, E.; Günver, G. Serum omentin-1 levels in hypertensive patients. J. Hum. Hypertens. 2021, 35, 290–295. [CrossRef]

218. Xu, T.; Zuo, P.; Wang, Y.; Gao, Z.; Ke, K. Serum omentin-1 is a novel biomarker for predicting the functional outcome of acute ischemic stroke patients. Clin. Chim. Lab. Med. 2018, 56, 350–355. [CrossRef][PubMed]

219. Yang, J.; Gao, Y. Clinical relevance of serum omentin-1 levels as a biomarker of prognosis in patients with acute cerebral infarction. Brain Behav. 2020, 10, e01678. [CrossRef][PubMed]

220. Xu, T.; Zuo, P.; Cao, L.; Gao, Z.; Ke, K. Omentin-1 is Associated with Carotid Plaque Instability among Ischemic Stroke Patients. J. Atheroscler. Thromb. 2018, 25, 505–511. [CrossRef][PubMed]

221. Hu, T.; Li, Y.; Su, Y.; Zuo, P.; Gao, Z.; Ke, K. Serum omentin-1 and risk of one-year mortality in patients with ischemic stroke. Clin. Chim. Acta 2020, 505, 167–171. [CrossRef][PubMed]

222. Zhang, G.-H.; Ye, Z.-H.; Guan, H.-J.; Guo, M.; Zhou, X.-X.; Xu, Y.-Y. Impact of serum omentin-1 concentrations on functional outcome among acute intracerebral hemorrhage patients. Clin. Chim. Acta 2020, 503, 169–174. [CrossRef]

223. Onur, I.; Oz, F.; Yildiz, S.; Oflaz, H.; Sigirci, S.; Elitok, A.; Pilten, S.; Kasali, K.; Cizgici, A.Y.; et al. Association of circulating omentin-1 level with arterial stiffness and carotid plaque in type 2 diabetes. Cardiovasc. Diabetol. 2011, 10, 103. [CrossRef][PubMed]

224. Zhou, J.-P.; Tong, X.-Y.; Zhu, L.-P.; Luo, J.-M.; Luo, Y.; Bai, Y.-P.; Li, C.-C.; Zhang, G.-G. Plasma Omentin-1 Level as a Predictor of Good Coronary Collateral Circulation. J. Atheroscler. Thromb. 2017, 24, 940–948. [CrossRef]

225. Yoo, H.J.; Huang, S.Y.; Hong, H.C.; Choi, H.Y.; Yang, S.J.; Seo, J.A.; Kim, S.G.; Kim, N.H.; Choi, K.M.; Choi, D.S.; et al. Association of circulating omentin-1 level with arterial stiffness and carotid plaque in type 2 diabetes. Cardiovasc. Diabetol. 2011, 10, 103. [CrossRef][PubMed]

226. Onur, I.; Oz, F.; Yildiz, S.; Kuplay, H.; Yucel, C.; Sigirci, S.; Elitok, A.; Pilten, S.; Kasali, K.; Cizgici, A.Y.; et al. A decreased serum omentin-1 level may be an independent risk factor for peripheral arterial disease. Int Angiol. 2014, 33, 455–460.
227. Yasir, M.; Senthilkumar, G.P.; Jayashree, K.; Babu, K.R.; Vadivelan, M.; Palanivel, C. Association of serum omentin-1, apelin and chemerin concentrations with the presence and severity of diabetic retinopathy in type 2 diabetes mellitus patients. Arch. Physiol. Biochem. 2019, 1–8. [CrossRef]

228. Siegrist, M.; Heitkamp, M.; Braun, I.; Vogg, N.; Haller, B.; Langhof, H.; Koenig, W.; Halle, M. Changes of omentin-1 and chemerin during 4 weeks of lifestyle intervention and 1 year follow-up in children with obesity. Clin. Nutr. 2021, 40, 5648–5654. [CrossRef]

229. Atashak, S.; Stannard, S.R.; Daraei, A.; Soltani, M.; Saeidi, A.; Moradi, F.; Laher, I.; Hackney, A.C.; Zouhal, H. High-intensity Interval Training Improves Lipocalin-2 and Omentin-1 Levels in Men with Obesity. Int. J. Sports Med. 2021, 1–16. [CrossRef]

230. De Luis, D.A.; Calvo, S.G.; Gomez, J.J.L.; Izaola, O.; Primo, D.; Pacheco, D.; Aller, R. Omentin-1 Changes following Biliopancreatic Diversion and Relationship with Cardiovascular Risk Factors. Ann. Nutr. Metab. 2018, 73, 106–112. [CrossRef]

231. Alkuraishy, H.M.; Al-Gareeb, A.I. New Insights into the Role of Metformin Effects on Serum Omentin-1 Levels in Acute Myocardial Infarction: Cross-Sectional Study. Emerg. Med. Int. 2015, 2015, 283021. [CrossRef] [PubMed]