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REVIEW ARTICLE

Association between Omentin-1 and Coronary Artery Disease: Pathogenesis and Clinical Research

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Abstract: Like other adipokines, omentin-1 is secreted from visceral adipose tissue and plays a vital role in the development of chronic inflammatory diseases, including cardiovascular events. Recent studies have shown that circulating omentin-1 levels are associated with various metabolic risk factors, such as high blood pressure, increased waist circumference, dyslipidemia, and glucose intolerance. The decrease in serum omentin level is an independent predictor of Coronary Artery Disease (CAD) and is associated with the severity of this disease. Since there is no relevant review in the literature, we aimed to summarize the studies on the relationship between omentin-1 and CAD.

Keywords: Acute coronary syndrome, coronary artery disease, omentin-1, vascular smooth muscle cell, adipokines,adipose tissues.

1. INTRODUCTION

Omentin is an adipokine secreted from visceral adipose tissue and is abundant in plasma. Adipokine plays a role in the development of chronic inflammatory diseases, but its effect on cardiovascular events is little known [1]. Omentin-1, also known as intestinal lactoferrin receptor, endothelial lectin HL-1, galactofuranose binding lectin, or intelectin- 1, is a newly identified secretory protein that is selectively expressed in visceral adipose tissue. Mature omentin-1 is a glycoprotein consisting of 295 amino acids and 1-linked oligosaccharide [2].

Omentin homolog called omentin-2 has 83% amino acid similarity with omentin-1. In some populations, two omentin genes, omentin-1 and omentin-2, are localized adjacent to each other in the chromosomal region associated with Type 2 Diabetes (T2D). Omentin-1 is the main isoform in human plasma [3]. Recent studies have found that omentin-1 is low in the circulation of hemodialysis patients. Additionally, there is a strong association between decreased omentin-1 levels and the severity of Peripheral Arterial Disease (PAD) [4, 5]. In patients with metabolic syndrome, there is an inverse relation of omentin-1 levels with the presence of CAD and the degree of angiographic stenosis [6]. In the COSANI study, omentin-1 levels were lower in the Acute Myocardial Infarction (AMI) group than in the healthy subjects. After a 6-month follow-up period, omentin-1 levels increased significantly in the AMI group [7]. We aimed to summarize the studies on the relationship between omentin-1 and CAD.

Plasma omentin-1 levels are associated with metabolic risk factors. In a study, omentin-1 levels showed a positive correlation with Body Mass Index (BMI), waist circumference insulin resistance, leptin, adiponectin, and High-Density Lipoprotein (HDL) levels. Stejskal *et al*. found a weak but positive relationship between omentin-1 and BMI [8-10].

An inverse relationship exists between serum omentin-1 levels and carotid plaque formation. In contrast, there is a positive correlation of omentin with cardiac autonomic neuropathy in patients with T2D [11, 12]. Patients with coronary atherosclerosis have lower omentin-1 levels than healthy ones [13]. Furthermore, studies have reported that serum omentin levels are a significant predictor of cardiovascular events in hemodialysis patients with suspected CAD, heart failure or subclinical atherosclerosis [14-16].

Recently, Benedicte *et al*. identified 400 common genes associated with the extracellular matrix remodeling, thrombosis and inflammation expressed from the peripheral region, periventricular area and Epicardial Adipose Tissue (EAT). The authors also showed that omentin was the highest number of regulated genes in EAT compared to Subcutaneous Adipose Tissue (SAT) [17]. Du *et al*. found that omentin-1 mRNA and protein levels were significantly higher in EAT than in SAT, independent of CAD presence [18]. It is reasonable to estimate that tissue-specific omentin-1 expression in EAT is closely related to local coronary atherosclerosis through paracrine and vasocrine mechanisms.

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Verhagen *et al*. manifested a negative correlation between adipocytokine production from EAT and coronary atherosclerosis [19]. In a study, omentin-1 mRNA levels were significantly decreased in stenotic segments of coronary artery surrounding EAT. Thus, omentin-1 mRNA expression in EAT may be negatively correlated to coronary atherosclerosis [18].

The relationship between EAT-derived adipocytokines and coronary atherosclerosis has been underestimated and the paracrine effects of EAT need to be emphasized. In fact, the balance between pro-inflammatory and anti-inflammatory adipocytokines is complex and susceptible to deterioration in pathological conditions [20]. Verhagen *et al*. showed that adiponectin mRNA expression was not as low as expected in EAT close to stenotic segments when compared with non-stenotic ones. Furthermore, the secretion of pro-inflammatory adipocytokines (IL-la, IL-17, IL-18, and IL-23) from EAT adjacent to the stenotic coronary segments were markedly reduced [19]. In general, the pro-inflammatory proactive profile of adipocytokines from EAT in patients with CAD is more prominent than in healthy individuals [21]. Regulation of adipocytokines from EAT, close to stenotic coronary segments, appears to be sophisticated in CAD patients.

Omentin-1 is secreted by visceral fat, and its local concentration in fat tissue may exceed the amount of it in circulation or SAT [22]. Since Omentin-1 is present in circulation, it can regulate insulin sensitivity and glucose metabolism; this may prevent the progression of CAD in obese patients. Serum omentin-1 negatively correlates with waist circumference and HOMA-IR. In most obese with diabetes who underwent bariatric surgery with low cardiovascular risk, increased diastolic cardiac function, after pioglitazone treatment, is correlated with increased serum omentin-1 levels [23].

Omentin-1, *via in vivo* effect, inhibits the development of atherosclerosis in apolipoprotein E-deficient mice by decreasing macrophage infiltration and pro-inflammatory gene expression [24, 25]. *In vitro*, omentin-1 promotes differentiation of macrophages into the anti-inflammatory M2 phenotype, suppresses inflammatory responses and foam cell formation [20]. Omentin-1 increases vasodilation and survival of endothelial cells by activation of the AMPK/eNOS pathways and alleviates inflammation in endothelial cells by TNF-α inhibition [26, 27]. In addition, it prevents monocyte adhesion to smooth muscle cells by reducing VCAM-1 expression [28]. In patients with Acute Coronary Syndrome (ACS), omentin-1 is increased in macrophage-induced foam cells in coronary plaques, in middle layer vascular smooth muscle cells and circulation. This finding explains the role of omentin-1 in ACS and is vital for targeted therapy [24].

Jha *et al*. [29] showed that the expression of the AT genotype of rs2274907A>T increased sensitivity to CAD. They also found a relationship between rs2274907A>T SNP genotype distribution with total cholesterol, Low-Density Lipoprotein (LDL), and HDL levels. The results are consistent with similar studies in the literature [30, 31]. Omentin-1 has a cardioprotective effect as a nitric oxide-mediated vasodilator [23] and is negatively correlated with carotid intima-media thickness [10]. The genotype distribution of rs2274907A>T between diabetic and non-diabetic groups has shown that this gene may play a role in inducing diabetes. Serum omentin-1 levels are inversely correlated with insulin resistance and T2D [32].

Chen *et al*. demonstrated that omentin-1-based therapy is a new treatment alternative in CAD [33]. They showed that atorvastatin increases serum omentin-1 concentration in patients with CAD, and this effect is dose-dependent. Atorvastatin-induced increase in serum omentin-1 levels represents the different antiatherogenic capacity of the drug. Alkuraishy *et al*. have suggested that metformin therapy increases omentin-1 levels and that metformin can be considered as a potential agent for the prevention of AMI in diabetics [34].

Zhou *et al*. demonstrated that plasma omentin-1 levels were associated with good Coronary Collateral Circulation (CCC), and omentin-1 might play a significant role in the development of these colleterals. However, the mechanism underlying the relationship between high plasma omentin-1 levels and good CCC is unclear [35]. Omentin-1 increases tube formation capacity in human umbilical vein endothelial cells and diminishes apoptotic activity. Furthermore, smooth muscle cell phenotype transformation is crucial to regulate CCC development [36]. Takeda *et al*. showed that the polarization of deformed macrophages towards an M2 phenotype promotes collateral artery development [37]. Omentin-1 may be claimed to regulate macrophage differentiation by inhibiting the pro-inflammatory M1 phenotype and by promoting the pro-angiogenic M2 phenotype [38].

Zhu *et al*. [39] reported that post-infarction myocardial function was significantly associated with omentin-1 levels in AMI. The results shed light on the relationship between omentin-1 and myocardial ischemia/reperfusion, and revealed that omentin-1 is a new adipocytokine that suppresses negative remodeling. Future studies will clear the uncertainty about the issue.

In the study by Tao *et al*., serum omentin-1 concentrations inversely correlated to atrial fibrillation development and atrial remodeling [40]. Onur *et al*. demonstrated that in women with postmenopausal CAD, decreased serum omentin level was an independent predictor of CAD and was associated with the disease severity [41]. Narumi *et al*. showed that serum omentin-1 levels predicted cardiovascular events in patients with heart failure. Serum omentin-1 levels appear to be a new prognostic factor of risk classification in this population [16].

CONCLUSION

A decrease in omentin-1 levels is an independent predictor of CAD and is associated with the severity and progression of the disease. Omentin-1 may act as an alternative diagnostic tool to ensure optimal management of CAD patients. Studies of omentin-1 on the prognosis of CAD are limited; therefore, more comprehensive studies are needed.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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