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

Lutfu Askin, Hakan Duman, Ali Ozyildiz, Okan Tanriverdi and Serdar Turkmen

1Department of Cardiology, Adiyaman Education and Research Hospital, Adiyaman, Turkey; 2Department of Cardiology, Recep Tayyip Erdogan University Medicine of Faculty, Rize, Turkey

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.
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-1α, IL-17, IL-18, and IL-23) from EAT adjacent to the stenotic coronary segments were markedly reduced [19]. In general, the pro-inflammatory 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 monocye 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. Alkuraishi 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 collaterals. 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 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**

Not applicable.
FUNDING

None.

CONFLICT OF INTEREST

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

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Saely CH, Leierher A, Muendlein A, et al. Coronary patients with high plasma omentin are at a higher cardiovascular risk. Data Brief 2015; 6: 158-61. http://dx.doi.org/10.1016/j.dib.2015.11.065 PMID: 26862554

[2] Schaffler A, Neumeier M, Herfarth H, et al. Genomic structure of human omentin, a new adipocytokine expressed in omental adipose tissue. Biochim Biophys Acta 2005; 1732(1-3): 96-102. http://dx.doi.org/10.1016/j.bbamap.2005.11.005 PMID: 16386808

[3] Yang RZ, Lee MJ, Hu H, et al. Identification of omentin as a novel depot-specific adipokine in human adipose tissue: Possible role in modulating insulin action. Am J Physiol Endocrinol Metab 2006; 290(6): E1253-61. http://dx.doi.org/10.1152/ajpendo.00572.2004 PMID: 16531507

[4] Kocijanec M, Vujicic B, Racki S, Cubranic Z, Zapatovic L, Dvornik S. Serum omentin-1 levels as a possible risk factor of mortality in patients with diabetes on haemodialysis. Diabetes Res Clin Pract 2015; 110(1): 44-50. http://dx.doi.org/10.1016/j.diabres.2015.06.008 PMID: 26293449

[5] Onur I, Oz F, Yildiz S, et al. A decreased serum omentin-1 level may be an independent risk factor for peripheral arterial disease. Int Angiol 2014; 33(5): 455-60. PMID: 2394287

[6] Shang FJ, Wang JP, Liu XT, et al. Serum omentin-1 levels are inversely associated with the presence and severity of coronary artery disease in patients with metabolic syndrome. Biomarkers 2011; 16(8): 657-62. http://dx.doi.org/10.3109/1354750X.2011.622789 PMID: 21988056

[7] Kadowgou NP, Tahmatzidis DK, Giannakoulas C, et al. Serum levels of novel adipokines, omentin-1 and chemerin, in patients with acute myocardial infarction: KOZANI STUDY. J Cardiovasc Med (Hagerstown) 2015; 16(5): 341

[8] de Souza Batista CM, Yang RZ, Lee MJ, et al. Omentin plasma levels and gene expression are decreased in obesity. Diabetes 2007; 56(6): 1655-61. http://dx.doi.org/10.2337/db06-1506 PMID: 17329619

[9] Stejskal D, Vaclavik J, Smekal A, Svobodova G, Richterova R, Svestak M. Omentin-1 levels in patients with premature coronary artery disease, metabolic syndrome and healthy controls. Short communication. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2016; 160(2): 219-21. http://dx.doi.org/10.5507/bp.2016.019 PMID: 27108603

[10] Shibata R, Ouchi N, Takahashi R, et al. Omentin as a novel biomarker of metabolic risk factors. Diabetol Metab Syndr 2012; 4(1): 37. http://dx.doi.org/10.1186/1758-5966-4-37 PMID: 22835063

[11] Yoo HJ, Hwang SY, Hong HC, et al. Association of circulating omentin-1 level with arterial stiffness and carotid plaque in type 2 diabetes. Cardioger Diabetol 2011; 10: 103. http://dx.doi.org/10.1186/1475-2840-10-103 PMID: 22108456

[12] Jung CH, Jung SH, Kim BY, Kim CH, Kang SK, Mok JO. Association of serum omentin levels with cardiac autonomic neuropathy in patients with type 2 diabetes mellitus: A hospital-based study. Cardioger Diabetol 2015; 14: 140. http://dx.doi.org/10.1186/s12933-015-0303-3 PMID: 26466574

[13] Shibata R, Ouchi N, Kikuchi R, et al. Circulating omentin is associated with coronary artery disease in men. Atherosclerosis 2011; 219(2): 811-4. http://dx.doi.org/10.1016/j.atherosclerosis.2011.08.017 PMID: 21925659

[14] Saely CH, Leierher A, Muendlein A, et al. High plasma omentin predicts cardiovascular events independently from the presence and extent of angiographically determined atherosclerosis. Atherosclerosis 2016; 244: 38-43. http://dx.doi.org/10.1016/j.atherosclerosis.2015.10.000 PMID: 26590865

[15] Kocijanec M, Cubranic Z, Vujicic B, Racki S, Dvornik S, Zapatovic L. Soluble intracellular adhesion molecule-1 and omentin-1 as potential biomarkers of subclinical atherosclerosis in hemodialysis patients. Int Urol Nephrol 2016; 48(7): 1145-54. http://dx.doi.org/10.1007/s11255-016-1275-2 PMID: 27023478

[16] Narumi T, Watanabe T, Kadowaki S, et al. Impact of serum omentin-1 levels on cardiac prognosis in patients with heart failure. Cardiovasc Diabetol 2014; 13: 84. http://dx.doi.org/10.1186/1475-2840-13-84 PMID: 24755035

[17] Gaborit B, Venteclef N, Ancel P, et al. Human epididymal adipokine tissue has a specific transcriptomic signature depending on its anatomic peri-atrial, peri-ventricular, or peri-coronary location. Cardiovasc Res 2015; 108(1): 62-73. http://dx.doi.org/10.1093/cvr/cvv208 PMID: 26239655

[18] Du Y, Ji Q, Cai L, et al. Association between omentin-1 expression in human epididymal adipose tissue and coronary atherosclerosis. Cardiovasc Diabetol 2016; 15: 90. http://dx.doi.org/10.1186/s12933-016-0406-5 PMID: 27352781

[19] Verhagen SN, Bujsroegge MP, Vink A, van Herwerden LA, van der Graaf Y, Visseren FL. Secretion of adipokine by perivascular adipose tissue near stenotic and non-stenotic coronary artery segments in patients undergoing CABG. Atherosclerosis 2014; 233(1): 242-7. http://dx.doi.org/10.1016/j.atherosclerosis.2013.12.005 PMID: 24529151

[20] Iacobellis G, Corradi D, Sharma AM. Epididymal adipose tissue: Anatomic, biologic and clinical relationships with the heart. Nat Clin Pract Cardiovasc Med 2005; 2(10): 536-43. http://dx.doi.org/10.1038/ncpcardio0319 PMID: 16186852

[21] Cheng KH, Chu CS, Lee KT, et al. Adipokynes and proinflammatory mediators from abdominal and epididymal adipose tissue in patients with coronary artery disease. Int J Obes 2008; 32(2): 268-74. http://dx.doi.org/10.1038/ijo.2007.56 PMID: 17878891

[22] Yang R-Z, Lee MJ, Hu H, et al. Identification of omentin as a novel depot-specific adipokine in human adipose tissue: possible role in modulating insulin action. Am J Physiol Endocrinol Metab 2006; 290(6): 2125-31. http://dx.doi.org/10.1152/ajpendo.00572.2004 PMID: 27352781

[23] Greulich S, Chen WJ, Maxhira B, et al. Cardioprotective properties of omentin-1 in type 2 diabetes: Evidence from clinical and in vitro studies. PLoS One 2013; 8(3): e59697. http://dx.doi.org/10.1371/journal.pone.0059697 PMID: 23555749

[24] Watanabe K, Watanabe R, Konih I, et al. Counteractive effects of omentin-1 against atherosclerosis. Cardiovasc Res 2016; 110(1): 118-28. http://dx.doi.org/10.1093/eurheartj/ehw561 PMID: 26790473

[25] Hiramatsu-Ito M, Shibata R, Ohashi K, et al. Abstract 11475: omentin-1 as a novel adipokine inhibits TNF-induced vascular inflammation in human endothelial cells. Biochem Biophys Res Commun 2011; 408(2): 339-43. http://dx.doi.org/10.1016/j.bbrc.2011.04.039 PMID: 21514279

[26] Kazama K, Usui T, Okada M, Hara Y, Yamawaki H. Omentin plays an anti-inflammatory role through inhibition of TNF-α-induced superoxide production in vascular smooth muscle cells. Eur J Pharmacol 2012; 686(1-3): 116-23. http://dx.doi.org/10.1016/j.ejphar.2012.04.033 PMID: 22554771
[29] Jha CK, Mir R, Elfaki I, et al. Evaluation of the association of omentin-1 rs2274907 A>T and rs2274908 G>A gene polymorphisms with coronary artery disease in Indian population: A case control study. J Pers Med 2019; 9(2): 9.
http://dx.doi.org/10.3390/jpm9020030 PMID: 31174318

[30] Jamshidi J, Ghanbari M, Asnaashari A, Jafari N, Valizadeh GA. Omentin Val109Asp polymorphism and risk of coronary artery disease. Asian Cardiovasc Thorac Ann 2017; 25(3): 199-203.
http://dx.doi.org/10.1177/0218492317699752 PMID: 28325076

[31] Nazar S, Zehra S, Azhar A. Association of single Nucleotide Missense Polymorphism Val109Asp of Omentin-1 gene and coronary artery disease in Pakistani population: Multicenter study. Pak J Med Sci 2017; 33(5): 1128-33.
PMID: 29142551

[32] Elsaid NH, Sadik NA, Ahmed NR, Fayez SE, Mohammed NAE. Serum omentin-1 levels in type 2 diabetic obese women in relation to glycemic control, insulin resistance and metabolic parameters. J Clin Transl Endocrinol 2018; 13: 14-9.
http://dx.doi.org/10.1016/j.jclet.2018.05.003 PMID: 30023310

[33] Chen Q, Shang X, Yuan M, Liang L, Zhong X. Effect of atorvastatin on serum omentin-1 in patients with coronary artery disease. Coron Artery Dis 2017; 28(1): 44-51.
http://dx.doi.org/10.1097/MCA.0000000000000435 PMID: 27749321

[34] Alkuraishy HM, Al-Gareeb AI. 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.
http://dx.doi.org/10.1155/2015/283021 PMID: 26682070

[35] Zhou JP, Tong XY, Zhu LP, et al. Plasma omentin-1 level as a predictor of good coronary collateral circulation. J Atheroscler Thromb 2017; 24(9): 940-8.
http://dx.doi.org/10.5551/jat.37440 PMID: 28123148

[36] Maruyama S, Shibata R, Kikuchi R, 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(1): 408-17.
http://dx.doi.org/10.1074/jbc.M111.261818 PMID: 22081609

[37] Takeda Y, Costa S, Delamarre E, et al. Macrophage skewing by Phd2 haplodeficiency prevents ischaemia by inducing arteriogenesis. Nature 2011; 479(7371): 122-6.
http://dx.doi.org/10.1038/nature10507 PMID: 21983962

[38] De Jager SC, Pasterkamp G. Atheroprotective properties of human Omentin-1 in experimental atherosclerosis. Cardiovasc Res 2016; 110(1): 1-3.
http://dx.doi.org/10.1093/cvr/cvw040 PMID: 26935810

[39] Zhu Y, Hu C, Du Y, et al. Time-dependent change in omentin-1 level correlated with early improvement of myocardial function in patients with first anterior st-segment elevation myocardial infarction after primary percutaneous coronary intervention. J Atheroscler Thromb 2019; 26(10): 856-67.
http://dx.doi.org/10.5551/jat.47043 PMID: 30853697

[40] Tao S, Huang YQ, Cai AP, et al. Association of serum omentin-1 concentrations with the presence of atrial fibrillation. Med Sci Monit 2016; 22: 4749-54.
http://dx.doi.org/10.12659/MSM.898202 PMID: 27915353

[41] Onur I, Oz F, Yildiz S, et al. Serum omentin 1 level is associated with coronary artery disease and its severity in postmenopausal women. Angiology 2014; 65(10): 896-900.
http://dx.doi.org/10.1177/0003319713511322 PMID: 24265251