Adipsin as a novel prognostic biomarker for cardiovascular diseases

Lutfu Askin^a, Husna Sengul Askin^b, Sabri Abus^c, Siho Hidayet^d

^a Department of Cardiology, Adiyaman Education and Research Hospital, Adiyaman, Turkey

^b Department of Infectious Diseases, Adiyaman Education and Research Hospital, Adiyaman, Turkey

^c Department of Cardiology, Kahta State Hospital, Adiyaman, Turkey

^d Department of Cardiology, Inonu University Medicine Faculty, Malatya, Turkey

ARTICLE INFO

Article history:

Submitted: 29. 5. 2021

Revised: 1. 7. 2021

Accepted: 10. 7. 2021

Available online: 8. 2. 2022

Klíčová slova:

Adipsin

Ateroskleróza

Kardiovaskulární onemocnění

Keywords:

Adipsin

Atherosclerosis

Cardiovascular disease

SOUHRN

Zvýšený oxidační stres při cévních onemocněních stimuluje sekreci adipokinů z adipocytů. Řada klinických studií prokázala, že hodnoty adipsinu v plazmě poměrně spolehlivě predikují vznik ischemických příhod. Zvýšené hodnoty adipsinu těsně souvisí s úmrtím z jakýchkoli příčin a s morbiditou. Adipsin je tak novým biomarkerem při sledování rozvoje aterosklerózy. Cílem tohoto přehledu bylo zdůraznit souvislost mezi adipsinem a kardiovaskulárními onemocněními a přínos použití adipsinu v léčbě těchto onemocnění.

© 2022, ČKS.

ABSTRACT

Increased vascular oxidative stress stimulates the secretion of adipokines from adipocytes. Many clinical studies have demonstrated that plasma adipsin levels are successful in predicting ischemic events. Increased adipsin levels are closely related to all-cause death and morbidity. Therefore, adipsin may be a new biomarker for atherosclerosis. In this review, we aimed to emphasize the association of adipsin with cardiovascular diseases (CVDs) and its beneficial role in the therapeutic field of CVDs.

Introduction

Hypertension, diabetes mellitus (DM), dyslipidemia, and smoking are risk factors of cardiovascular diseases (CVDs).¹ The INTERHEART study showed that hypertension, dyslipidemia, diabetes, smoking, and obesity accounted for approximately 80% of CVDs.² Modification of these traditional risk factors provides both primary and secondary protection for CVDs.³ Despite interventional and medical advances in acute myocardial infarction (AMI), hospital mortality rates are still high due to complications of AMI.⁴ One of the adverse events is cardiac arrhythmia, which is an incredibly challenging disease of childhood.⁵ Decompensated heart failure (HF) is the other complication that requires hospitalization and, in this case, is defined, high-risk groups.⁶ Although HF benefits from medical and device therapy, HF is still a social health problem.⁷⁻⁹

The FINMONICA study, the Finnish division of the MONICA project coordinated with the World Health Organization (WHO), covered the provinces of North Karelia and Kuopio in eastern Finland and the surrounding areas

of Turku, Loimaa, and Loimaa in southwestern Finland. This study includes hospitalization and mortality records of patients aged 25–64 years with AMI. The FINMONICA AMI Register's mortality findings are consistent with Finland's official CVD mortality statistics.¹⁰

CRP and other new inflammatory markers may help us properly manage cardiovascular events in AMI patients. The predictive value of CRP is independent of troponin. Aggressive lifestyle changes and preventive medical treatment may regress the increased inflammation in CVD. The early invasive strategy was found beneficial in individuals with high levels of inflammatory biomarkers.¹¹

Circulating cytokines/chemokines and growth factors affect endothelial function,¹² and these develop vascular diseases.^{13,14} Indeed, vascular diseases are processes involving a series of events such as endothelial dysfunction.¹⁵⁻¹⁷ Hypertension, DM, dyslipidemia, smoking, and aging cause vascular diseases by oxidative stress.^{18,19}

The complement system has an active role in the balance of coagulation and fibrinolysis. In contrast, a thrombin-activated fibrinolysis inhibitor neutralizes C3a and

Address: Lutfu Askin, MD, Cardiology Department, Adiyaman Education and Research Hospital, 2230 – Adiyaman, Turkey, e-mail: lutfuaskin23@gmail.com

DOI: 10.33678/cor.2021.086

Please cite this article as: Askin L, Askin HS, Abus S, Hidayet S. Adipsin as a novel prognostic biomarker for cardiovascular diseases. Cor Vasa 2022;64:34–37.

Fig. 1 – The role of adipsin in insulin secretion.

C5a.²⁰ Thrombin-activated fibrinolysis stimulates the intracellular signal and increases vascular remodeling in endothelial cells and vascular smooth muscle cells. Therefore, thrombin-activated fibrinolysis inhibitor plays a vital role in inflammation by aggregating a series of reactions such as complement system regulation, endothelial dysfunction, etc.²¹ Adipsin is an adipocytes-derived biomarker that catalyzes the complement cascades. Adipsin forms fragments such as C3a, C3b, C5a, and C5b with the aid of complementary 3 (C3) convertase.²² For example, thrombin can be divided directly into C3 and activation fragments and divide C5 into C5a.²³

The relationship of adipsin with the alternative complement pathway (ACP) provides clues about the etio-pathogenesis of CVDs. This review tried to summarize whether adipsin is a valuable prognostic biomarker in CVDs by presenting several studies about the issue.

Adipsin in atherosclerosis pathogenesis

Adipokines, released from adipose tissue, may have a role in the development of coronary artery disease (CAD).^{22,23} In a clinical study, plasma adipsin levels predicted ischemic stroke.²⁴ However, few studies refer about the pathogenesis of adipsin in the atherosclerosis process in the literature. High adipsin levels are closely related to all-cause death and morbidity. Therefore, adipsin may be a potential new biomarker for atherosclerosis. Further analysis is required to support this hypothesis.

Adipsin catalyzes the rate restriction step of ACP, which is secreted from adipocytes, monocytes, and macrophages. Also, adipsin may reflect the metabolic status and insulin resistance (IR) in mice. Adipsin has a close link with IR in obesity.²⁵ Adipsin is necessary for pancreatic beta-cell function in patients with type 2 diabetes mellitus (DM).^{22,26}

Adipokines may be the reason for dyslipidemia and unstable atherosclerotic plaques.^{27,28} Adipsin is associated with metabolic disorders.²⁹ Additionally, adipsin accelerates lipid accumulation and adipocyte differentiation.³⁰

Therefore, adipsin may lead to instability of atherosclerotic plaques.

Comparison of adipsin with other biomarkers

In the study of Ohtsuki et al., serum levels of adipsin were compared with other biomarkers (BNP and hs-CRP).³¹ Higher plasma BNP levels predict poor prognosis in cardiovascular events,³² and processed BNP forms (N-terminal proBNP) may predict the incidence of revascularization.³³ Besides, high serum hsCRP levels (>1 mg/L) determine future cardiovascular events. However, serum hsCRP levels are also elevated in many non-specific infections.³⁴ CRP is released mainly from the liver in parallel with cytokine levels.¹⁹ Ohtsuki et al.³¹ examined the definitive role of adipose in combination with other biomarkers in CAD. Eventually, the combination of adipsin and BNP predicted adverse events better than alone. This information was also valid for hsCRP. Thus, the combination of adipsin and other biomarkers may guide us in determining CAD. In our opinion, adipsin usage may provide improvements in the clinical practice of CAD.

Contrary to early studies, some studies reported that low adiponectin levels increase the risk of IR and CVD.^{35,36} Current findings provide a new perspective on the relationship between adipsin and other adiponectin. The distinction between them is due to the level of participation of the immune system. Future studies will help the understanding of the issue.

Adipsin and other CVDs

Gómez-Banoy et al.³⁷ thought that the treatment of adipsin/C3a might be a new approach to achieving beta-cell health in type 2 DM. Wang et al.³⁸ reported that the growth hormone/insulin-like growth factor 1 (GH/IGF-1) axis significantly regulated serum adipsin levels. Adipsin levels were increased in adult growth hormone deficiency cases and associated with glucolipid metabolism disorders. Thus, adipsin may be an early-stage CVD marker.

Brady et al.³⁹ observed higher adipsin and leptin concentrations in those with back pain. Adipsin was found to be an independent determinant of back pain. Korman et al.⁴⁰ revealed higher adipsin levels in systemic sclerosis (SSc) and a close link between pulmonary arterial hypertension (PAH) and adipsin in this population. Adipsin genetic variants may be effective in SSc-PAH. Adipsin potentially might be a new marker of PAH. Also, adipsin may modulate the complement system associated with PAH.

The complement system has a role in the development of inflammation. Adipsin was associated with hs-CRP in polycystic ovary syndrome (PCOS), and adipsin might contribute to the metabolic disorders in PCOS. Despite all this, controversy continues about adipsin in PCOS.² Chedraui et al.⁴¹ found that high adipokine levels reflect metabolic syndrome in a postmenopausal woman.

Conclusion

Circulating adipokines may affect endothelial function and cause the development of vascular damage. Given the active role of adipsin in the complement cascade and increased release in adipose tissue, adipsin may be thought to play a potential role in the etiopathogenesis of CVDs. In our opinion, adipsin, along with other biomarkers, maybe an adjunct marker in determining the presence of atherosclerosis. Further studies will clarify this claim.

Conflict of interest

The authors declare that they have no competing interests.

Funding

All authors report no financial interests or potential conflicts of interest.

References

1. Nguyen HN, Fujiyoshi A, Abbott RD, et al. Epidemiology of cardiovascular risk factors in Asian countries. *Circ J* 2013;77:2851–2859.
2. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case-control study. *Lancet* 2004;364:937–952.
3. Chiuve SE, McCullough ML, Sacks FM, et al. Healthy lifestyle factors in the primary prevention of coronary heart disease among men: Benefits among users and nonusers of lipid-lowering and antihypertensive medications. *Circulation* 2006;114:160–167.
4. Aşkın L, Karakelleoğlu Ş, Değirmenci H, et al. Comparison of the effects of metoprolol or carvedilol on serum gamma-glutamyltransferase and uric acid levels among patients with acute coronary syndrome without ST segment elevation. *Anatol J Cardiol* 2016;16:16–22.
5. Casale M, Mezzetti M, Tulino V, et al. Therapy Of Cardiac Arrhythmias In Children: An Emerging Role Of Electroanatomical Mapping Systems. *Curr Vasc Pharmacol* 2018;16:528–533.
6. Spencer FA, Meyer TE, Gore JM, et al. Heterogeneity in the management and outcomes of patients with acute myocardial infarction complicated by heart failure: the National Registry of Myocardial Infarction. *Circulation* 2002;105:2605–2610.
7. Casale M, Correale M, Laterra G, et al. Effects of Sacubitril/Valsartan in Patients with High Arrhythmic Risk and an ICD: A Longitudinal Study. *Clin Drug Investig* 2021;41:169–176.
8. Casale M, Mezzetti M, Gigliotti De Fazio M, et al. Usefulness of Sacubitril/Valsartan in reduction of atrial fibrillation burden in a patient with ICD delivering inappropriate therapies. A new possibility? *Cor Vasa* 2020;62:336–339.
9. Casale M, Quattrocchi S, Bitto R, et al. Cardiac implantable devices and takotsubo syndrome. A rare but potential eventuality. *Cor Vasa* 2018;60:e500–e502.
10. Mähönen M, Salomaa V, Brommels M, et al. The validity of hospital discharge register data on coronary heart disease in Finland. *Eur J Epidemiol* 1997;13:403–415.
11. Blake GJ, Ridker PM. C-reactive protein and other inflammatory risk markers in acute coronary syndromes. *J Am Coll Cardiol* 2003;41:375–425.
12. Satoh K. AMPKα2 regulates hypoxia-inducible factor-1α stability and neutrophil survival to promote vascular repair after ischemia. *Circ Res* 2017;120:8–10.
13. Satoh K, Satoh T, Kikuchi N, et al. Basigin mediates pulmonary hypertension by promoting inflammation and vascular smooth muscle cell proliferation. *Circ Res* 2014;115:738–750.
14. Shimokawa H. 2014 Williams Harvey Lecture: importance of coronary vasomotion abnormalities – from bench to bedside. *Eur Heart J* 2014;35:3180–3193.
15. Satoh K, Matoba T, Suzuki J, et al. Cyclophilin A mediates vascular remodeling by promoting inflammation and vascular smooth muscle cell proliferation. *Circulation* 2008;117:3088–3098.
16. Satoh K, Kikuchi N, Kurosawa R, et al. PDE1C negatively regulates growth factor receptor degradation and promotes VSMC proliferation. *Circ Res* 2015;116:1098–1100.
17. Shimokawa H, Sunamura S, Satoh K. RhoA/Rho-kinase in the cardiovascular system. *Circ Res* 2016;118:352–366.
18. Satoh K, Nigro P, Matoba T, et al. Cyclophilin A enhances vascular oxidative stress and the development of angiotensin II-induced aortic aneurysms. *Nat Med* 2009;15:649–656.
19. Satoh K, Shimokawa H. High-sensitivity C-reactive protein: still need for nextgeneration biomarkers for remote future cardiovascular events. *Eur Heart J* 2014;35:1776–1778.
20. Rittirsch D, Flierl MA, Ward PA. Harmful molecular mechanisms in sepsis. *Nat Rev Immunol* 2008;8:776–787.
21. Satoh T, Satoh K, Yaoita N, et al. Activated TAFI promotes the development of chronic thromboembolic pulmonary hypertension: a possible novel therapeutic target. *Circ Res* 2017;120:1246–1262.
22. Lo JC, Ljubicic S, Leibiger B, et al. Adipsin is an adipokine that improves β cell function in diabetes. *Cell* 2014;158:41–53.
23. Luc G, Empana JP, Morange P, et al. Adipocytokines and the risk of coronary heart disease in healthy middle aged men: the PRIME Study. *Int J Obes (Lond)* 2010;34:118–126.
24. Prugger C, Luc G, Haas B, et al. Adipocytokines and the risk of ischemic stroke: the PRIME Study. *Ann Neurol* 2012;71:478–486.
25. Vasilenko MA, Kirienkova EV, Skuratovskaia DA, et al. The role of production of adipsin and leptin in the development of insulin resistance in patients with abdominal obesity. *Dokl Biochem Biophys* 2017;475:271–276.
26. Tafere GG, Wondafrash DZ, Zewdie KA, et al. Plasma Adipsin as a Biomarker and Its Implication in Type 2 Diabetes Mellitus. *Diabetes Metab Syndr Obes* 2020;13:1855–1861.
27. Sartipy P, Loskutoff DJ. Monocyte chemoattractant protein 1 in obesity and insulin resistance. *Proc Natl Acad Sci USA* 2003;100:7265–7270.
28. Nasu K, Tsuchikane E, Katoh O, et al. Plaque characterisation by virtual histology intravascular ultrasound analysis in patients with type 2 diabetes. *Heart* 2008;94:429–433.
29. Gursoy CO, Calan M, Yesil SP, et al. Increased adipsin is associated with carotid intima media thickness and metabolic disturbances in polycystic ovary syndrome. *Clin Endocrinol (Oxf)* 2016;85:910–917.
30. Song NJ, Kim S, Jang BH, et al. Small molecule-induced complement factor D (adipsin) promotes lipid accumulation and adipocyte differentiation. *PLoS One* 2016;11:e0162228.
31. Ohtsuki T, Satoh K, Shimizu T, et al. Identification of Adipsin

- as a Novel Prognostic Biomarker in Patients With Coronary Artery Disease. *J Am Heart Assoc* 2019;8:e013716.
32. Wang TJ, Larson MG, Levy D, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. *N Engl J Med* 2004;350:655–663.
 33. Fujimoto H, Suzuki T, Aizawa K, et al. Processed B-type natriuretic peptide is a biomarker of postinterventional restenosis in ischemic heart disease. *Clin Chem* 2013;59:1330–1337.
 34. Ridker PM. High-sensitivity C-reactive protein, inflammation, and cardiovascular risk: from concept to clinical practice to clinical benefit. *Am Heart J* 2004;148:S19–S26.
 35. Martinez HR, Escamilla-Ocas CE, Camara-Lemarroy CR, et al. CSF concentrations of adiponectin and adiponectin in patients with amyotrophic lateral sclerosis. *Acta Neurol Belg* 2017;117:879–883.
 36. Natarajan R, Hagman S, Hamalainen M, et al. Adipsin is associated with multiple sclerosis: a follow-up study of adipokines. *Mult Scler Int* 2015;2015:371734.
 37. Gómez-Banoy N, Guseh JS, Li G, et al. Adipsin preserves beta cells in diabetic mice and associates with protection from type 2 diabetes in humans. *Nat Med* 2019;25:1739–1747.
 38. Wang Y, Zheng X, Xie X, et al. Correlation of increased serum adiponectin with increased cardiovascular risks in adult patients with growth hormone deficiency. *Endocr Pract* 2019;25:446–453.
 39. Brady SRE, Mousa A, Naderpoor N, et al. Adipsin Concentrations Are Associated with Back Pain Independently of Adiposity in Overweight or Obese Adults. *Front Physiol* 2018;9:93.
 40. Korman BD, Marangoni RG, Hinchcliff M, et al. Brief Report: Association of Elevated Adipsin Levels With Pulmonary Arterial Hypertension in Systemic Sclerosis. *Arthritis Rheumatol* 2017;69:2062–2068.
 41. Chedraui P, Pérez-López FR, Escobar GS, et al. Circulating leptin, resistin, adiponectin, visfatin, adiponectin and ghrelin levels and insulin resistance in postmenopausal women with and without the metabolic syndrome. *Maturitas* 2014;79:86–90.