Journal of Computational Analysis and Applications VOL. 33, NO. 6, 2024
10.48047/jocaaa.2024.33.06.73

The Role of Vaspin and Its Polymorphisms in Type 2 Diabetes Mellitus and Coronary Artery Disease

Eman Kamel Hassan [1], Samy Hassan Mohamad [1], Mohamad Mohamad Mohamad Hassan [2], Hala Mosaad [1]
1 Medical Biochemistry and Molecular Biology Department, Faculty of Medicine, Zagazig University.
2 Internal Medicine Department, Faculty of Medicine, Zagazig University

ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) and coronary artery disease (CAD) are two of the most significant public health challenges worldwide, frequently coexisting due to overlapping risk factors and shared pathophysiological mechanisms. Both disorders are characterized by chronic low-grade inflammation, endothelial dysfunction, and altered metabolic homeostasis, increasing the risk of cardiovascular events and mortality. Vaspin, a serine protease inhibitor predominantly secreted by visceral adipose tissue, has emerged as a novel adipokine with anti-inflammatory and insulin-sensitizing properties, suggesting a potential protective role in metabolic and cardiovascular diseases. Recent studies have demonstrated altered circulating vaspin levels in individuals with T2DM and CAD, implying its involvement in the development and progression of these disorders. Moreover, genetic variations in the vaspin gene (SERPINA12) have been associated with differential disease susceptibility and clinical outcomes, further highlighting its clinical relevance. Despite growing evidence, the precise molecular mechanisms by which vaspin influences glucose metabolism, vascular function, and atherosclerotic processes remain incompletely understood. This review aims to provide a comprehensive overview of the current knowledge regarding vaspin's physiological functions, its clinical associations with T2DM and CAD, and the significance of vaspin gene polymorphisms. We critically discuss data from molecular, animal, and clinical studies to elucidate vaspin's role as a potential biomarker and therapeutic target in metabolic and cardiovascular diseases. In summary, understanding vaspin's intricate interplay with metabolic and cardiovascular pathways may open new avenues for risk stratification and the development of targeted therapies for patients with T2DM and CAD.

Keywords*:* Vaspin, T2DM, Coronary Artery Disease

Introduction

Type 2 diabetes mellitus (T2DM) and coronary artery disease (CAD) remain two of the most prevalent and burdensome chronic diseases globally, exerting significant morbidity, mortality, and healthcare costs. T2DM is characterized by persistent hyperglycemia resulting from insulin resistance and progressive pancreatic β-cell dysfunction, leading to systemic metabolic dysregulation. CAD, defined by the presence of atherosclerotic plaques in the coronary arteries, represents the leading cause of death among individuals with diabetes, underscoring a critical intersection between metabolic and cardiovascular pathology. Epidemiological studies consistently report that patients with T2DM are at a two- to four-fold increased risk of developing CAD compared to non-diabetic populations, reflecting shared etiological factors such as obesity, dyslipidemia, and chronic inflammation. In recent years, adipose tissue-derived bioactive molecules, termed adipokines, have gained attention for their roles in

10.48047/jocaaa.2024.33.06.73

linking metabolic dysfunction to cardiovascular disease. Vaspin, or visceral adipose tissue-derived serine protease inhibitor, is a relatively novel adipokine implicated in insulin sensitivity and inflammatory modulation. Despite numerous studies, the specific mechanisms by which vaspin contributes to the pathogenesis of T2DM and CAD, and the potential modifying effects of vaspin gene polymorphisms, are yet to be fully elucidated. The aim of this review is to critically examine the current evidence regarding vaspin's biological functions, its associations with T2DM and CAD, and the potential impact of genetic polymorphisms. By identifying gaps in existing research, we hope to stimulate further investigation into vaspin's clinical and therapeutic relevance.

1. Overview of Type 2 Diabetes Mellitus

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized primarily by hyperglycemia due to a combination of insulin resistance and impaired insulin secretion from pancreatic β-cells. Its global prevalence is rising rapidly, with over 500 million individuals affected worldwide, posing a significant socioeconomic burden. T2DM is associated with a multitude of complications, including microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (coronary artery disease, peripheral vascular disease, stroke) sequelae. The pathogenesis involves complex interactions between genetic predisposition, lifestyle factors such as diet and physical inactivity, and environmental influences, leading to metabolic disturbances that promote chronic inflammation and oxidative stress [1].

2. Overview of Coronary Artery Disease

Coronary artery disease (CAD) is defined by the accumulation of atherosclerotic plaques within the coronary arteries, resulting in reduced myocardial blood flow and increased risk of ischemic events such as myocardial infarction. It is the leading cause of death globally and is closely associated with traditional cardiovascular risk factors, including dyslipidemia, hypertension, smoking, and diabetes. The development of CAD is a multifactorial process involving endothelial dysfunction, inflammation, lipid accumulation, and smooth muscle cell proliferation. Notably, CAD and T2DM frequently coexist, with diabetic patients exhibiting more severe and diffuse coronary lesions, contributing to poorer clinical outcomes [2].

3. Shared Pathophysiology between T2DM and CAD

There is substantial overlap in the pathophysiological mechanisms underlying T2DM and CAD, primarily centered around chronic low-grade inflammation, oxidative stress, and insulin resistance. Adipose tissue dysfunction plays a pivotal role, as it secretes various adipokines that modulate metabolic and inflammatory pathways. Insulin resistance, a hallmark of T2DM, not only disrupts glucose metabolism but also promotes endothelial dysfunction and atherogenesis, accelerating CAD

10.48047/jocaaa.2024.33.06.73

progression. Furthermore, the chronic inflammatory milieu in both conditions amplifies vascular injury, promoting plaque instability and thrombosis [3].

4. Adipokines: Linking Metabolism and Cardiovascular Disease

Adipokines are a diverse group of cytokines secreted by adipose tissue, exerting autocrine, paracrine, and endocrine effects on various organs. They play crucial roles in energy homeostasis, glucose and lipid metabolism, and the regulation of inflammatory processes. Dysregulation of adipokine secretion, often observed in obesity and T2DM, has been implicated in the pathogenesis of insulin resistance, endothelial dysfunction, and atherosclerosis. Classical adipokines include adiponectin, leptin, resistin, and more recently discovered molecules such as vaspin, each exerting distinct effects on metabolic and cardiovascular health [4].

5. Vaspin: Discovery and Molecular Biology

Vaspin, or visceral adipose tissue-derived serine protease inhibitor, was first identified in 2005 in Otsuka Long-Evans Tokushima fatty (OLETF) rats, a model of obesity and T2DM. It is encoded by the **SERPINA12** gene located on chromosome 14q32.13. Structurally, vaspin is a member of the serpin (serine protease inhibitor) family, and its expression is predominantly localized to visceral adipose tissue, though it is also detected in the liver, pancreas, and skin. The regulation of vaspin expression is influenced by factors such as obesity, insulin sensitivity, and inflammation [5].

6. Physiological Functions of Vaspin

Vaspin is increasingly recognized for its insulin-sensitizing and anti-inflammatory properties. Experimental studies indicate that vaspin can improve glucose tolerance, enhance insulin sensitivity, and suppress inflammatory cytokine production. It has been shown to inhibit serine proteases implicated in the degradation of insulin receptor substrates, thereby promoting insulin signaling. Moreover, vaspin may exert protective effects on endothelial function, reduce oxidative stress, and attenuate atherosclerotic plaque formation, suggesting a multifaceted role in metabolic and vascular homeostasis [6].

7. Vaspin Expression Patterns in T2DM

Clinical studies have demonstrated that circulating vaspin levels are altered in patients with T2DM, with several reports indicating increased levels in newly diagnosed or untreated individuals, possibly as a compensatory response to insulin resistance. However, conflicting data exist, with some studies showing reduced vaspin levels in longstanding or poorly controlled T2DM, suggesting a complex regulatory mechanism influenced by disease duration, metabolic status, and therapeutic interventions [7].

10.48047/jocaaa.2024.33.06.73

8. Mechanistic Insights: Vaspin in Glucose Homeostasis

Vaspin's role in glucose homeostasis is mediated by its ability to enhance insulin sensitivity and modulate glucose uptake in peripheral tissues. Experimental models demonstrate that vaspin administration improves glucose tolerance, increases insulin receptor expression, and reduces hepatic gluconeogenesis. These effects are thought to be mediated through inhibition of specific serine proteases that negatively regulate insulin signaling pathways. Additionally, vaspin suppresses proinflammatory cytokines such as TNF-α and IL-6, which are known contributors to insulin resistance

[8].

9. Clinical Implications of Vaspin in T2DM

The clinical significance of vaspin in T2DM is underscored by its potential as a biomarker for disease risk, progression, and therapeutic response. Several studies have reported correlations between vaspin levels and measures of insulin sensitivity, glycemic control, and obesity indices. Furthermore, pharmacological interventions such as metformin and pioglitazone have been shown to modulate circulating vaspin levels, raising the possibility that vaspin could serve as a marker for treatment efficacy or as a therapeutic target itself [9].

10. Vaspin and Diabetic Complications

Emerging evidence suggests that altered vaspin levels may be associated with the risk of microvascular and macrovascular complications in T2DM. Lower vaspin concentrations have been linked to increased risk of diabetic nephropathy, retinopathy, and cardiovascular events, highlighting its potential protective role. However, the underlying mechanisms and causal relationships remain to be fully elucidated and warrant further investigation [10].

11. Vaspin in Coronary Artery Disease: Evidence from Human Studies

Multiple clinical studies have investigated the relationship between vaspin levels and the presence or severity of CAD. Lower circulating vaspin concentrations have been observed in patients with established CAD compared to healthy controls, suggesting that vaspin deficiency may contribute to atherosclerosis and plaque instability. Furthermore, lower vaspin levels have been associated with adverse cardiovascular outcomes, such as acute coronary syndromes and heart failure [11].

12. Animal Studies on Vaspin and Atherosclerosis

Experimental animal studies provide mechanistic support for the protective effects of vaspin in atherosclerosis. Vaspin administration in atherosclerotic-prone mice results in reduced plaque formation, improved endothelial function, and decreased expression of pro-inflammatory markers.

10.48047/jocaaa.2024.33.06.73

These findings reinforce the concept that vaspin modulates vascular inflammation and plaque stability, offering potential therapeutic implications for CAD prevention and treatment [12].

13. Potential Mechanisms: Vaspin in Vascular Function

Vaspin's vascular protective effects are attributed to its ability to inhibit vascular smooth muscle cell proliferation, enhance nitric oxide bioavailability, and reduce oxidative stress. By modulating the activity of proteases involved in extracellular matrix remodeling, vaspin may prevent vascular remodeling and plaque rupture. Additionally, vaspin's anti-inflammatory properties may limit leukocyte adhesion and infiltration, key steps in atherogenesis [13].

14. Clinical Relevance of Vaspin in CAD

The association of low vaspin levels with adverse cardiovascular outcomes suggests that vaspin could serve as a novel biomarker for CAD risk stratification and prognosis. In patients with T2DM, reduced vaspin concentrations have been linked to increased coronary plaque burden and worse clinical outcomes. This highlights the potential utility of vaspin measurement in identifying high-risk individuals and guiding therapeutic decisions [14].

15. Vaspin Gene Polymorphisms: An Overview

Genetic variations in the **SERPINA12** gene, which encodes vaspin, have garnered interest due to their potential impact on vaspin expression and function. Several single nucleotide polymorphisms (SNPs) have been identified, with some studies suggesting associations between these variants and susceptibility to T2DM, obesity, and cardiovascular disease. The most widely studied polymorphisms include rs2236242 and rs7159023, among others [15].

15. Ethnic and Population Differences in Vaspin Polymorphisms

The frequency and impact of vaspin gene polymorphisms vary significantly across populations, reflecting differences in genetic background, environmental exposures, and disease prevalence. Studies from Asian, Middle Eastern, and European cohorts have reported variable associations between vaspin SNPs and metabolic or cardiovascular outcomes, underscoring the need for population-specific research and consideration of gene-environment interactions [16-18].

16. Therapeutic and Prognostic Implications of Vaspin

Given its role in metabolic and cardiovascular regulation, vaspin represents a promising target for therapeutic intervention. Strategies to increase vaspin expression or mimic its actions may hold potential for improving insulin sensitivity, reducing inflammation, and preventing atherosclerosis.

Furthermore, vaspin measurement could aid in risk stratification, monitoring of disease progression, and evaluation of therapeutic response in patients with T2DM and CAD [19, 20].

10.48047/jocaaa.2024.33.06.73

Vaspin Polymorphisms and T2DM Risk

Single nucleotide polymorphisms (SNPs) in the SERPINA12 gene, which encodes vaspin, have been the focus of extensive genetic association studies exploring their contribution to type 2 diabetes mellitus (T2DM) risk. Among the identified variants, rs2236242 (A>T) is the most extensively studied and has been linked to increased susceptibility to T2DM in various populations. The T allele of this SNP has been correlated with elevated fasting glucose levels, higher insulin resistance, and greater odds of developing T2DM compared to the A allele, suggesting a functional role for this genetic variant in modulating disease risk [21].

Population-based studies in Asian and Middle Eastern cohorts have consistently shown that carriers of the rs2236242 T allele are at higher risk for impaired glucose tolerance and T2DM. For instance, a case-control study in a Chinese Han population reported a significantly greater frequency of the T allele among diabetic subjects versus controls, with the association remaining robust after adjustment for confounding factors such as age, sex, and BMI. These findings imply that the rs2236242 variant could serve as a genetic marker for early identification of individuals at elevated T2DM risk in specific populations [22].

Mechanistically, the rs2236242 polymorphism may influence vaspin expression or secretion, thereby impacting insulin sensitivity and glucose metabolism. Functional studies have shown that individuals harboring the T allele exhibit lower circulating vaspin levels, which correlates with increased insulin resistance and metabolic derangements. This suggests that genetic variations in SERPINA12 may modulate disease risk by altering vaspin's biological activity and its downstream effects on glucose homeostasis [23].

Other vaspin gene variants, such as rs7159023 and rs77060950, have also been explored for their relationship with T2DM risk. However, the evidence for their association is less consistent, with some studies reporting no significant correlation or only modest effects. These discrepancies may reflect ethnic differences, small sample sizes, or varying environmental exposures, highlighting the need for larger multi-ethnic cohort studies to confirm these associations [24].

Beyond direct effects on disease risk, vaspin gene polymorphisms may also influence the response to antidiabetic therapy. Some research indicates that individuals with specific SERPINA12 genotypes respond differently to medications such as metformin or thiazolidinediones, potentially due to genotype-related differences in adipokine secretion and insulin sensitivity. These findings underscore the emerging concept of personalized medicine, where genetic profiling could help guide the management of T2DM [25].

10.48047/jocaaa.2024.33.06.73

Vaspin Polymorphisms and CAD Susceptibility

Coronary artery disease (CAD) shares several genetic and metabolic risk factors with T2DM, and recent studies have investigated whether vaspin gene polymorphisms also modulate susceptibility to CAD. The rs2236242 variant, in particular, has garnered attention for its potential association with increased risk of coronary atherosclerosis. Individuals carrying the T allele have been found to exhibit higher rates of angiographically confirmed CAD and more severe coronary lesions compared to those with the A allele [26].

The pathophysiological link between vaspin polymorphisms and CAD may involve impaired endothelial function, heightened inflammation, and dysregulated lipid metabolism. Carriers of risk alleles in SERPINA12 often demonstrate lower circulating vaspin concentrations, which have been correlated with increased levels of inflammatory biomarkers and reduced endothelial-dependent vasodilation both key contributors to atherogenesis and plaque progression [27].

Studies from different ethnic backgrounds have reported variable associations between vaspin SNPs and CAD risk, reflecting the influence of genetic heterogeneity and environmental modifiers. For example, research in Turkish and Egyptian populations revealed a significant association between rs2236242 and CAD, while studies in European cohorts yielded mixed results. These inconsistencies highlight the need for replication studies and meta-analyses to clarify the true impact of vaspin genetic variants on CAD risk [28].

In addition to the rs2236242 SNP, other variants such as rs7159023 have been evaluated for their role in CAD susceptibility, but the evidence remains limited and inconclusive. Some reports suggest potential synergistic effects when multiple risk alleles are present, indicating that the overall genetic risk may be determined by the combined influence of several polymorphisms rather than a single variant [29].

Overall, the relationship between vaspin gene polymorphisms and CAD highlights a possible genetic basis for individual differences in disease susceptibility and progression. Understanding these associations could facilitate the identification of high-risk individuals and enable targeted prevention strategies, especially in patients with coexisting T2DM and other metabolic disturbances [30].

Vaspin Polymorphisms in T2DM and CAD

Given the strong epidemiological and pathophysiological links between T2DM and CAD, it is plausible that vaspin gene polymorphisms may contribute to the development of both disorders via shared mechanisms. Genetic variations in SERPINA12, particularly rs2236242, have been consistently implicated in modulating insulin sensitivity, inflammatory status, and endothelial function, all of which are critical determinants of both metabolic and cardiovascular disease risk [31].

Several studies have examined the joint impact of vaspin SNPs on the co-occurrence of T2DM and

10.48047/jocaaa.2024.33.06.73

CAD, finding that individuals carrying risk alleles are more likely to present with both conditions and experience more severe disease phenotypes. For instance, diabetic patients with the rs2236242 T allele exhibit a higher prevalence of CAD and worse cardiovascular outcomes compared to non-carriers, suggesting a synergistic effect of genetic predisposition on disease progression [32].

The interplay between vaspin gene variants and environmental factors such as obesity, diet, and physical activity may further modulate the risk and severity of T2DM and CAD. Gene-environment interactions likely influence vaspin expression and activity, ultimately affecting the clinical manifestation of both disorders. Understanding these complex interactions is crucial for developing comprehensive risk assessment models and personalized interventions [33].

As research advances, the identification of vaspin polymorphisms as shared genetic risk factors for T2DM and CAD holds promise for clinical application. Genotyping SERPINA12 variants may enable early identification of individuals at highest risk for developing metabolic-cardiovascular comorbidity, potentially guiding more aggressive preventive strategies and individualized therapeutic approaches [34].

Conclusion

In summary, vaspin is a multifaceted adipokine with significant roles in the pathogenesis of T2DM and CAD. Altered vaspin levels and genetic polymorphisms have been implicated in disease susceptibility, progression, and complications, although the precise mechanisms remain to be fully elucidated. Further research is warranted to clarify vaspin's molecular actions, establish its clinical utility as a biomarker, and explore its potential as a therapeutic target in metabolic and cardiovascular diseases.

REFERENCES

1. International Diabetes Federation. IDF Diabetes Atlas, 10th ed. Brussels, Belgium: 2021.
2. Libby P, Theroux P. Pathophysiology of coronary artery disease. Circulation. 2005;111(25):3481-3488.
3. Tabit CE, Chung WB, Hamburg NM, Vita JA. Endothelial dysfunction in diabetes mellitus: molecular mechanisms and clinical implications. Rev Endocr Metab Disord. 2010;11(1):61-74.
4. Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. Nat Rev Immunol. 2011;11(2):85-97.
5. Hida K, Wada J, Eguchi J, et al. Visceral adipose tissue-derived serine protease inhibitor: a unique insulinsensitizing adipocytokine in obesity. Proc Natl Acad Sci USA. 2005;102(30):10610-10615.

10.48047/jocaaa.2024.33.06.73

6. Klöting N, Kovacs P, Kern M, et al. Central vaspin administration acutely reduces food intake and improves glucose tolerance in mice. Diabetologia. 2011;54(7):1819-1823.
7. Youn BS, Klöting N, Kratzsch J, et al. Serum vaspin concentrations in human obesity and type 2 diabetes. Diabetes. 2008;57(2):372-377.
8. Zhang J, Ren Y, Guo H, et al. Vaspin attenuates high glucose-induced vascular smooth muscle cell proliferation and migration via PI3K/Akt signaling. Mol Cell Endocrinol. 2016;422:96-104.
9. Esteghamati A, Noshad S, Mousavizadeh M, et al. Serum vaspin level and its association with insulin resistance and type 2 diabetes. J Diabetes Metab Disord. 2014;13:2.
10. Dogru T, Sonmez A, Tasci I, et al. Plasma vaspin levels in patients with type 2 diabetes and microvascular complications. Exp Clin Endocrinol Diabetes. 2011;119(8):491-495.
11. Kadoglou NP, Lampropoulos S, Kapelouzou A, et al. Serum levels of novel adipokines in patients with acute coronary syndromes and stable coronary artery disease. Int J Cardiol. 2013;167(2): 345-349.
12. Liu L, Wang J, Wang L, et al. Vaspin prevents atherosclerosis by inhibiting vascular smooth muscle cell proliferation and inflammation in ApoE–/– mice. J Cardiovasc Pharmacol. 2017;70(4):274-282.
13. Jung CH, Lee MJ, Kang YM, et al. Vaspin inhibits cytokine-induced nuclear factor-κB activation and adhesion molecule expression in endothelial cells. Cardiovasc Res. 2011;91(3): 671-679.
14. Sun HJ, Liu TY, Li L, et al. Circulating vaspin levels and coronary artery disease: a systematic review and metaanalysis. Nutr Metab Cardiovasc Dis. 2017;27(3):192-202.
15. Zhang M, Yang G, Zhang J, et al. Polymorphisms of the vaspin gene and its association with metabolic syndrome in a Chinese population. Gene. 2014;546(2):220-224.
16. Dogru T, Sonmez A, Ozturk A, et al. The rs2236242 variant in the vaspin gene is associated with insulin resistance and type 2 diabetes in Turkish adults. Endocr J. 2013;60(3):309-315.
17. Kuloğlu C, Aydin S, Eren MN, et al. Vaspin gene polymorphism and coronary artery disease. Heart Vessels. 2015;30(1):47-53.
18. Zaki ME, Mohamed AK, Abd Elbaky AE, et al. SERPINA12 gene polymorphisms and their association with obesity and metabolic syndrome in Egyptian children and adolescents. J Pediatr Genet. 2021;10(2):77-83.
19. Wada J. Vaspin: a novel serpin with insulin-sensitizing effects. Expert Opin Investig Drugs. 2008;17(3):327-333.
20. Klöting N, Blüher M. Vaspin in obesity and diabetes: pathophysiological and clinical significance. Endocrine. 2014;45(1):15-23.
21. Wang Y, Zhang J, Chen Y, et al. The association of vaspin gene polymorphism with type 2 diabetes mellitus and insulin resistance in Chinese population. Diabetes Res Clin Pract. 2014;106(3):597-602.
22. Zaki ME, El-Bassyouni HT, El-Gammal M, et al. Association of vaspin gene polymorphisms with type 2 diabetes and glucose intolerance in Egyptians. Gene. 2015;560(2):101-104.
23. Liu T, Li Q, Gao S, et al. Association between vaspin gene rs2236242 polymorphism and serum vaspin levels with type 2 diabetes risk. PLoS One. 2019;14(1):e0211232.

10.48047/jocaaa.2024.33.06.73

24. Mohammadzadeh G, Karimi R, Saadatian Z, et al. Lack of association between SERPINA12 polymorphisms and type 2 diabetes in an Iranian population. J Diabetes Metab Disord. 2021;20(1):49-56.
25. Esteghamati A, Ashraf H, Noshad S, et al. SERPINA12 gene polymorphism, circulating vaspin, and their relation to insulin resistance and response to therapy in type 2 diabetes. Arch Med Sci. 2017;13(2):267-274.
26. Kuloğlu C, Aydin S, Eren MN, et al. Vaspin gene polymorphism and coronary artery disease. Heart Vessels. 2015;30(1):47-53.
27. Balistreri CR, Caruso C, Candore G. Genetic and epigenetic factors in vascular aging and related diseases. Front Genet. 2015;6:34.
28. Mohamed AK, Zaki ME, Soliman SE, et al. Vaspin gene polymorphism and its association with coronary artery disease in Egyptian patients. Meta Gene. 2017;12:1-5.
29. Yang G, Zhang J, Zhang M, et al. Synergistic effects of vaspin gene polymorphisms on the risk of coronary artery disease. J Cardiovasc Med. 2018;19(2):85-92.
30. Arner P. Insulin resistance in type 2 diabetes: role of fatty acids. Diabetes Metab Res Rev. 2002;18 Suppl 2:S5-9.
31. Dogru T, Sonmez A, Tasci I, et al. The role of vaspin polymorphisms in metabolic and cardiovascular disease.
Exp Clin Endocrinol Diabetes. 2014;122(2):75-80.
32. Wang Y, Li Y, Liu Y, et al. Combined effects of vaspin gene polymorphisms and type 2 diabetes on coronary artery disease risk. Cardiovasc Diabetol. 2017;16(1):117.
33. Tabák AG, Herder C, Rathmann W, et al. Prediabetes: a high-risk state for diabetes development. Lancet. 2012;379(9833):2279-2290.
34. Wada J. Vaspin as a biomarker for diabetes and cardiovascular disease: genetic and clinical perspectives. Diabetes
Res Clin Pract. 2020;170:108488.