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ABSTRACT

Visceral adipose tissue-derived serine protease inhibitor (vaspin) is an adipokine associated with insulin resistance (IR), obesity, and inflammation. Serum vaspin role and significant alteration in its levels in type 2 diabetes mellitus (T2DM) and atherosclerotic disease have been severally reported. Nevertheless, these immense changes and this role have been studied, and different results were observed across several atherosclerosis and glucose tolerance disorders-associated studies due to differences in design, sample size and baseline parameters, and population race. Hence, we performed a systematic review to establish and summarize the latest results of serum vaspin level alteration and its role in atherosclerosis and glucose tolerance disorders. The studies from databases such as PubMed, ScienceDirect, Scopus, and Google Scholar were employed. The keywords included vaspin, atherosclerosis, coronary heart disease, ischemic heart disease, stroke, insulin, diabetes, glucose intolerance, metabolic syndrome, and obesity. Boolean Logic “AND” was used to combine each keyword and specify the results. Twenty-three articles were selected based on the suitability of their title/abstract and the inclusion criteria for this review topic. Two review authors independently evaluated the risk of bias based on the Cochrane risk of bias tool. Furthermore, we used RevMan 5.3 to present and synthesize the results. Critical appraisal of each obtained article showed that high vaspin levels were associated with a lower risk of atherosclerosis. Meanwhile, 10 articles about vaspin and glucose tolerance disorders showed that high vaspin levels were associated with a higher risk of developing T2DM. Meta-analysis showed atherosclerotic diseases and glucose tolerance disorders versus normal healthy (MD -0.43; 95% CI: -1.35 to 0.50 and MD -0.07; 95% CI: -0.38 to 0.25, respectively), which indicated higher vaspin levels in the disease group were favored. High serum vaspin levels in arterial plaque diseases were considered a protective mechanism to prevent further endothelial inflammation, injury, and atherosclerosis. This similar observation was found in obesity or T2DM patients as a compensatory mechanism for IR conditions.

INTRODUCTION

Based on the traditional theory, adipose tissue is inert, and it regulates body temperature, stores fat, supplies energy, absorbs

shock, and functions as an insulator. However, recent studies described it as an endocrine organ with multiple functions and active metabolism (Coelho *et al.*, 2013). The factors influenced by adipose tissue secretion and metabolism are called adipokines which perform a substantial role in obesity, metabolic syndrome, atherosclerosis, and blood glucose regulation (Kim and Choi, 2020). Furthermore, they serve as growth factors, cytokines, acute phase reactants, other inflammatory mediators, adipose tissue-secreting hormones such as leptin and adiponectin, and biochemical messengers (Kang *et al.*, 2016).

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Vaspin, also known as SERPINA12 according to serpin nomenclature, is a unique insulin-sensitizing adipocytokine discovered by Hida *et al.* (2005) and was associated with the development of inflammation and metabolic syndrome. It was first discovered in the visceral adipose tissue (VAT) of Otsuka Long-Evans Tokushima fatty (OLETF) rat, an animal model with type 2 diabetes mellitus (T2DM) and truncal obesity.

Previous investigations of vaspin role in metabolic and vascular diseases produced conflicting and various results because the levels are always inconstant in both conditions. A study associated the increase of serum vaspin concentration in mice with central obesity and insulin resistance (IR) (Liu *et al.*, 2018). However, vaspin has been presumed to be an insulin sensitizer with anti-inflammatory effects and might act as a compensatory process in response to IR (Wada, 2008). Furthermore, a study showed no significant vaspin role concerning insulin sensitivity in nondiabetic healthy humans (Von Loeffelholz *et al.*, 2010).

A further study reported that VAT-derived adipokines such as vaspin have a local and endocrine function in developing early and late atherosclerosis in obesity by affecting vascular smooth muscle cells (VSMCs) of the endothelium (de Leal and Mafra, 2013). Meanwhile, another study stated that vaspin serum level is not related to carotid stenosis plaque severity, but its low level is associated with the risk of ischemic events in carotid stenosis patients (Aust *et al.*, 2009).

Therefore, we conducted a systematic review and meta-analysis to determine the serum vaspin level alteration role in atherosclerosis and glucose tolerance disorders. We also conducted a critical appraisal of all selected articles to establish the serum vaspin role in atherosclerosis and glucose tolerance disorders. A common understanding and conclusion were eventually developed from the different assessed results.

Moreover, a brief additional review of the serum vaspin basic biochemical role and its genetic expression and polymorphism factor was also conducted. However, we did not consider and further analyze the relationship between genetic expression-polymorphism factor and serum vaspin levels in this study.

METHODS

A literature search was conducted using scientific databases such as PubMed, ScienceDirect, Scopus, and Google Scholar from September 2021 to January 2022. We performed this search based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart for the selection of studies (Page *et al.*, 2021). Combinations of keywords associated with “vaspin” AND “glucose intolerance” including diabetes, hyperglycemia, and insulin plus either “atherosclerosis” involving coronary heart disease, ischemic heart disease, and stroke, “metabolic syndrome,” OR “obesity” were employed. The inclusion criteria included English language studies published between 2005 and 2022 with clinical or laboratory experimental and nonexperimental designs (cohort, case-control, and cross-sectional), as well as discussing vaspin serologically rather than in terms of genetic expression. Several *in vitro* and *in vivo* studies were also considered to provide insight into the potential mechanism of vaspin in atherosclerosis and glucose intolerance.

Moreover, the citation-reference lists from the selected studies were also investigated to recognize related results.

The eligibility of the titles and abstracts was independently reviewed by two authors (RD and FM) based on the Cochrane Handbook for Systematic Reviews. Initially, 146 articles were obtained, including 92 derived from the keywords of “vaspin” AND “glucose intolerance” OR “atherosclerosis” and 54 from “vaspin” AND “metabolic syndrome” combination OR “obesity.” A total of 95 articles were excluded after manual investigation for unavailable full text and duplications. The articles were extracted using a data extraction template (Microsoft Office Excel 2016). We used the Cochrane risk of bias tool to assess the risk of bias in the included studies. This tool evaluates six potential issues: sequence generation, allocation concealment, incomplete data, blinding, selective outcome reporting, and other bias-related issues. Then, we screened again the eligibility of each article’s title and abstract, and eventually, 23 eligible articles were selected to be reviewed (Fig. 1). These articles were then exported and compiled by the Mendeley Citation Manager.

The selected articles used immunoassays product of Vaspin ELISA (Mediagnost Vaspin ELISA E106) by BioVendor R&D® (Asheville, NC). This Vaspin ELISA product uses a serum sample to quantify the vaspin concentration. It has a sensitivity of 4 pg/ml. Its reagents and material equipment provided included a microtiter plate, recombinant vaspin, dilution buffer, control sera, antibody conjugate, enzyme conjugate, washing buffer, substrate, stopping solution, and sealing tape for covering the microtiter plate. We also ensured that the selected articles used the standardized statistical analysis software of Statistical Package for the Social Sciences, at least the 22nd version.

The 23 articles were reviewed and analyzed by standard common questions for the critical appraisal (Al-Jundi and Sakka, 2017). The critical appraisal questions included the research objective or question, study design, selection issues, outcome factors, study factors, important potential confounders, statistical method used, statistical results, main conclusions about the research objective or question, and ethical issues considered. Data synthesis and statistical analysis were performed using RevMan version 5.4 for Windows. The authors conducted a subgroup analysis and meta-regression of heterogeneous papers and the relationship between serum vaspin levels and atherosclerotic-glucose tolerance diseases based on their respective study designs.

The study location was also considered due to population race effects on vaspin gene expression and polymorphism. However, this review did not analyze vaspin gene expression and polymorphism in detail but compared the data analysis components of every article. Finally, a common agreement and conclusion were reached concerning serum vaspin role in atherosclerosis and glucose tolerance disorders.

RESULTS AND DISCUSSION

We reviewed 23 studies investigating serum vaspin role in atherosclerosis and glucose tolerance disorders (Tables 1 and 2). In those tables, the authors also gave specific significant remarks to explain why the selected study was being listed. We also presented the risk of bias in the included studies in Figures 2 and 3. The forest plots of the meta-analysis showed atherosclerotic diseases

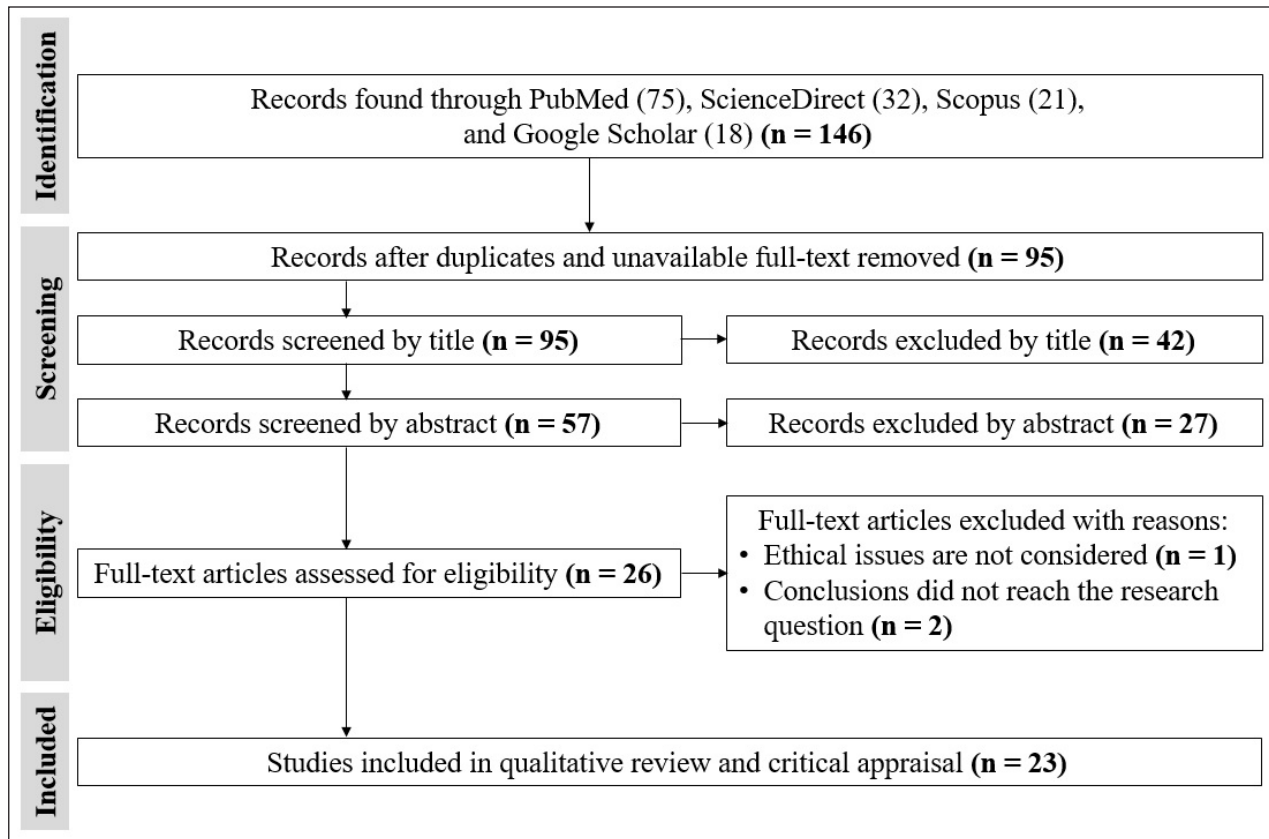


Figure 1. Article selection during the literature search based on the PRISMA flow diagram (Page *et al.*, 2021).

versus normal healthy (MD -0.43 ; 95% CI: -1.35 to 0.50) (Fig. 4) and glucose tolerance disorders versus normal healthy (MD -0.07 ; 95% CI: -0.3 to 0.25) (Fig. 5). Those results indicated that higher vaspin levels in the disease group were preferred.

Mode of action and mechanism of vaspin

Vaspin is an adipokine with targets in kallikrein 7 (KLK) and KLK 14, which are involved in skin desquamation. This VAT-derived serine protease inhibitor has been identified to significantly increase in 30 weeks of OLETF (Hida *et al.*, 2005). Once the circulatory or adipocyte vaspin concentration hits the peak in IR and obesity, the expression of this compound increases significantly. Furthermore, a study showed that KLK 7 co-expressed in rat islets suggests promising relevance of the vaspin-KLK7 mode of inhibition in early insulin secretion (Heiker *et al.*, 2013) (Fig. 6). Meanwhile, the insulin sensitizers of pioglitazone normalize both vaspin serum levels and expression (Wada, 2008).

Vaspin is believed to act as an insulin sensitizer with a compensatory role in white adipose tissue because the favorable effect is involved in the gene expression of IR pathogenesis, including tumor necrosis factor- α (TNF- α), leptin, resistin, glucose transporter-4, and adiponectin (Li *et al.*, 2008). It is considered that vaspin synthesis antagonizes the effect of uninvestigated proteases, which interrupt insulin action (Dwipayana *et al.*, 2019).

It could be compared to other proteins, such as neutrophil elastase and $\alpha 1$ -antitrypsin (D'Souza *et al.*, 2021; Motoyama *et al.*, 2020).

Vaspin and atherosclerosis

In obesity-associated inflammation and cardiovascular diseases, several studies showed the establishment of vaspin anti-atherogenic and anti-inflammatory roles on smooth muscle and vascular endothelial cells. Evidence demonstrates that it protects endothelial cells from apoptosis and inflammation (Fig. 6). Vaspin inhibits TNF- α -induced expression of adhesion molecules in VSMCs and later reduces lymphocyte adhesion by decreasing reactive oxygen species (ROS), protein kinase C, and nuclear factor- κ B (NF- κ B) activation. Additionally, the blockade of ROS production attenuates and reduces cytoskeletal reorganization, platelet-derived growth factor (PDGF), and intercellular adhesion molecule 1 (ICAM1) expression (Li *et al.*, 2013).

According to the critical appraisal in Table 1, seven studies, three cross-sectional, two cohorts, one case-control, and one interventional *in vivo*, suggested that vaspin has a protective and beneficial effect on atherosclerosis progression (Aust *et al.*, 2009; Jung *et al.*, 2011; Kastl *et al.*, 2020; Li *et al.*, 2012; Zhang *et al.*, 2013, 2016, 2020). However, those three cross-sectional studies failed to indicate the cause-effect relationship of vaspin with atherosclerosis. A result showed confounding factors, including 52.5% of patients using angiotensin-converting enzyme

Table 1. Critical appraisal from the review of the association between vaspin serum level and atherosclerosis.

Location (ref.)	Study objective or question	Study design (sample size)	Remarks	Selection issues	Outcome factors	Study factors	Potential confounders	Statistical method used	Main results	Main conclusions	Ethical issues consideration
China (Zhang <i>et al.</i> , 2013)	Determine the relation between plasma vaspin concentration and various states of CAD.	Cross-sectional, single-center (265).	This study presented receiver operating characteristic curves. It confirmed that vaspin plasma concentration significantly differentiated CAD patients.	Simple random sampling, reliability (reproducibility) and validity were reported.	All relevant outcomes were assessed. Measurement error was not detected.	Relevant study factors were included in the study, and they were measured using appropriate tools.	The study did not follow up with the participant, which would cause biases and an inability to establish cause-effect relationship of vaspin with CAD.	Student's <i>t</i> -test (if homogeneity of variances was assumed) or the Mann-Whitney test (if homogeneity of variances was not met).	Serum vaspin levels in AMI were significantly lower than the UAP group (0.21 ± 0.19 vs. 0.40 ± 0.37 µg/l, <i>p</i> = 0.012). Serum vaspin levels in UAP were significantly lower than that in the SAP group (0.40 ± 0.37 vs. 0.92 ± 0.94 µg/l, <i>p</i> = 0.013).	Serum vaspin levels in CAD patients are lower than in normal healthy people.	All subjects gave written consent; the study was approved by the Shanghai Tenth Hospital's Ethics Committee.
China (Zhang <i>et al.</i> , 2020)	Examine the association between vaspin and AIS severity in Chinese patients with AIS.	Case-control; single-center (340).	A follow-up study by Zhang <i>et al.</i> (2013). However, it used AIS patients instead of CAD patients.	Controls were appropriate; records of cases and controls were reviewed blindly; potential recall bias, lead time bias, and detection bias were controlled.	All relevant outcomes were assessed. Measurement error was not detected.	Relevant study factors were included in the study, and they were measured using appropriate tools.	Potential confounders were not found.	Comparisons between groups were conducted by the Mann-Whitney <i>U</i> test, chi-square test, or ANOVA test.	Low serum vaspin concentration (<0.72 [0.48–0.90] ng/ml) was linked with a 2.5-fold increased risk for AIS severity (OR 2.46; 95% CI: 1.75–4.45). Low serum vaspin concentration was linked with a 2.1-fold increased risk of a poor outcome (OR 2.03; 95% CI: 1.42–3.58).	Reduced serum levels of vaspin at admission are significantly related to stroke severity and prognosis.	The study was approved by the Ethics Committee of Xinxiang Medical University Hospital. Written consent was obtained.
Austria (Kastl <i>et al.</i> , 2020)	Determine the vaspin role in the ISR development <i>in vivo</i> and SMC and endothelial cell migration <i>in vitro</i> .	Cohort prospective; single-center (85).	This study demonstrated the role of vaspin within human SMC. Vaspin concentration was also analyzed at a very low concentration (0.004–40 ng/ml).	There was no evidence of volunteer bias; follow-up time was adequate; there was no dropout during the study.	All relevant outcomes were assessed. Measurement error was not detected.	Relevant study factors were included in the study, and they were measured using appropriate tools.	The possibilities of undetected and residual confounding factors were few but cannot be ruled out completely.	Serum vaspin levels were compared by the Mann-Whitney <i>U</i> test; the correlation of vaspin levels with late lumen loss used Spearman's correlation.	The ISR patient group showed significant low vaspin plasma levels compared to non-ISR patients (0.213 vs. 0.382 ng/ml; <i>p</i> = 0.001). Vaspin inhibits human coronary SMC migration <i>in vitro</i> selectively (<i>p</i> < 0.001). Vaspin did not have effect on HUVEC proliferation and migration (<i>p</i> > 0.05), a critical healing course of the stented vessel.	Vaspin selectively inhibits human coronary SMC migration <i>in vitro</i> , but it has no effect on HUVEC migration.	The study was approved by Ethikkommission der Medizinischen Universität Wien.

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Location (ref.)	Study objective or question	Study design (sample size)	Remarks	Selection issues	Outcome factors	Study factors	Potential confounders	Statistical method used	Main results	Main conclusions	Ethical issues consideration
China (Zhang <i>et al.</i> , 2016)	Evaluate the clinical significance of serum vaspin levels in AMI patients.	Cohort prospective; single-center (48).	This study conducted a good follow-up method for 24 ± 2 months to determine vaspin alteration in AMI patients. It is also a follow-up study by Zhang <i>et al.</i> (2013).	There was no evidence of volunteer bias; follow-up time was adequate; there was no dropout during the study.	All relevant outcomes were assessed. Measurement error was not detected.	Relevant study factors were included in the study, and they were measured using appropriate tools.	Approximately 52.5% of patients use ACEI or ARBs and 66.3% receive β-blockers.	Student's <i>t</i> -test (if variances homogeneity was assumed) or Mann-Whitney test (if variances homogeneity was not met).	The serum vaspin levels in the MACE group were lower than the non-MACE group (0.156 ± 0.015 vs. 0.314 ± 0.229 ng/ml, <i>p</i> < 0.001). LVEF recovery in the high serum vaspin level group (>0.259 ng/ml) was significant (54.3% ± 7.6% to 61.2% ± 4.7%, <i>p</i> < 0.001). In the low vaspin group (<0.259 ng/ml), LVEF improvement was not significant (51.3% ± 9.7% to 52.5% ± 10.9%, <i>p</i> = 0.550).	Patients with low vaspin levels have a high risk of MACE; vaspin might have a protective role in post-AMI LVEF improvement.	The study protocol was approved by the Shanghai Tenth Hospital's Ethics Committee.
Korea (Jung <i>et al.</i> , 2011)	Investigate the serum vaspin level effect on the insulin-signaling pathway in cultured endothelial cells and its capability to prevent FFA-induced apoptosis in endothelial cells through vaspin stimulatory effect on PI3-kinase/Akt signaling cascade.	Experimental <i>in vitro</i> study (HAECs).	The first study was to determine the serum vaspin effect on vascular cells through upregulation of the PI3-kinase/Akt signaling pathway.	The HAECs were obtained from Lanza, Inc. (Walkersville, MD). LA was obtained from Sigma Chemical Co. (St. Louis, MO) as the representative FFA.	All relevant outcomes were assessed. Measurement error was not detected.	Relevant study factors were included in the study, and they were measured using appropriate tools.	Potential confounders were not found.	One-way ANOVA followed by a <i>post hoc</i> analysis using Tukey's multiple comparison test.	Dose of serum vaspin 50 ng/ml or more increased Akt phosphorylation (<i>p</i> < 0.05). Vaspin and insulin administration before LA intervention significantly restored Akt phosphorylation compared to control group levels. The increase of LA-induced apoptosis was significantly (<i>p</i> < 0.05) inhibited by 100 ng/ml vaspin in insulin-stimulated-cultured HAECs.	Vaspin protects vascular endothelial from FFA-induced apoptosis; vaspin may have the potential to prevent further atherosclerosis in metabolic syndrome.	The study protocol was approved by the Ethics Committee of the University of Ulsan College of Medicine.

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Location (ref.)	Study objective or question	Study design (sample size)	Remarks	Selection issues	Outcome factors	Study factors	Potential confounders	Statistical method used	Main results	Main conclusions	Ethical issues consideration
China (Li <i>et al.</i> , 2012)	Investigate the association between vaspin serum levels and the presence of atherosclerosis or carotid plaque in early T2DM.	Cross-sectional; single-center (61).	This study included T2DM participants based on the WHO criteria for T2DM diagnosis (1999). Thus, it is interesting if the results would give different results from other included studies.	Simple random sampling; reliability (reproducibility) and validity were not reported.	All relevant outcomes were assessed. Measurement error was not detected.	Relevant study factors were included in the study, and they were measured using appropriate tools.	Potential confounders were not found.	Statistical analyses were conducted using the χ^2 -test, Student's <i>t</i> -test, or Pearson's correlation coefficient.	Fasting vaspin serum levels in T2DM patients (with or without carotid plaque) were significantly higher than in the controls ($p < 0.05$). The fasting vaspin serum was higher in T2DM patients without plaque than in controls ($p < 0.01$) but lower in T2DM patients with plaque than in those T2DM patients without plaque ($p < 0.05$). No association between vaspin serum levels and the carotid artery stenosis severity ($r = -0.04, p = 0.7$). A significant negative correlation between vaspin serum levels and symptomatic carotid artery stenosis ($r = -0.3, p = 0.009$). Vaspin serum levels were significantly lower in the symptomatic (0.51 ± 0.06 vs. 0.74 ± 0.09 ng/ml, $p = 0.009$) than asymptomatic carotid artery stenosis patients.	There is a significant association between the serum concentration of vaspin and the presence of carotid plaque in patients with T2DM.	The study was approved by Jinan City Fourth People's Hospital Ethics Committee. Written consent was obtained from participants.
Germany (Aust <i>et al.</i> , 2009)	Investigate whether vaspin serum level elevation contributes to premature and accelerated atherosclerosis.	Cross-sectional; single-center (107)	This study used vaspin measurement assays with a reference range of the assay: 0.016–1 ng/ml, sensitivity: 12 pg/ml.	Simple random sampling; reliability (reproducibility) and validity were reported.	All relevant outcomes were assessed. Measurement error was not detected.	Relevant study factors were included in the study, and they were measured using appropriate tools.	Carotid atherosclerosis severity was only evaluated by one index, the maximum percentage of stenosis. There was no measurement for circulating vaspin in association with plaque burden determined by high-resolution ultrasound.	Paired Student's <i>t</i> -test, chi-square test, and Pearson's correlation.	Serum vaspin level is not related to carotid artery stenosis severity, but low circulating vaspin correlates with recently experienced ischemic events in carotid stenosis patients.	The study was approved by Leipzig University Ethics Committee, and the participants gave written consent.	

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Location (ref.)	Study objective or question	Study design (sample size)	Remarks	Selection issues	Outcome factors	Study factors	Potential confounders	Statistical method used	Main results	Main conclusions	Ethical issues consideration
Turkey (Cura <i>et al.</i> , 2014)	Evaluate whether the serum vaspin concentration can diagnostically predict AIS and its association with carotid stenosis levels in the patient group.	Cross-sectional; single-center (100).	A similar study by Zhang <i>et al.</i> (2013). It used AIS patients instead of CAD patients. However, carotid system color Doppler ultrasonography was performed to evaluate carotid stenosis.	Simple random sampling; reliability (reproducibility) and validity were not reported.	All relevant outcomes were assessed. Measurement error was not detected.	Relevant study factors were included in the study, and they were measured using appropriate tools.	The patients' number of groups other than the 0%–50% stenosis group is quite small; no comparison of vaspin levels in the study population with the infarction area.	Student's <i>t</i> -test for comparing parametric data between the groups; chi-square test for comparing categorical data.	Vaspin concentrations were higher in the AIS than the control group (164.73 ± 153.76 vs. 116.21 ± 34.60 ng/ml, <i>p</i> < 0.05). No significant association between vaspin concentration and the severity of ICA stenosis (<i>p</i> > 0.05).	Serum vaspin levels have been shown to increase in patients with AIS.	Firat University Medical Faculty Clinical Research Ethics Committee approved the study protocol.
Egypt (El-Lebedy <i>et al.</i> , 2018)	Evaluate the vaspin serum levels in T2DM patients with and without CVD to investigate their potential disease risk association.	Cohort retrospective study; single-center (215).	This study included T2DM participants based on the American Diabetes Association (2014). Thus, it is interesting if the results would give different results from other included studies.	There was no evidence of volunteer bias; there was no dropout during the study.	All relevant outcomes were assessed. Measurement error was not detected.	Relevant study factors were included in the study, and they were measured using appropriate tools.	Potential confounders were not found.	Student's <i>t</i> -test for two groups, ANOVA test for more than two groups, and <i>post hoc</i> Bonferroni's multiple comparison test.	T2DM patients with CVD had higher vaspin levels than T2DM patients without CVD (7,417.3 ± 3,507.6 vs. 6,017.3 ± 3,606.4 pg/ml, <i>p</i> = 0.001). In T2DM patients, elevated concentration of serum vaspin was associated with 1.7-fold increased CVD risk (<i>p</i> = 0.001, OR = 1.7, 95% CI = 1.21–2.39).	Serum vaspin level is a potential new risk biomarker of CVD in T2DM patients.	The study was approved by the National Research Center Ethics Committee; written informed consent was obtained from all participants.

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Location (ref.)	Study objective or question	Study design (sample size)	Remarks	Selection issues	Outcome factors	Study factors	Potential confounders	Statistical method used	Main results	Main conclusions	Ethical issues consideration
Korea (Choi <i>et al.</i> , 2011)	Determine whether serum vaspin levels were associated with metabolic syndrome and coronary atherosclerosis.	Cross-sectional, single-center (322).	Coronary atherosclerosis was evaluated by multidetector-row computed tomography because visceral obesity is a cardinal component of metabolic syndrome.	Simple random sampling; reliability (reproducibility) and validity were reported.	All relevant outcomes were assessed. Measurement error was not detected.	Relevant study factors were included in the study, and they were measured using appropriate tools.	Considering the small number of participants with positive findings in MDCT, the study cannot exclude the possibility of false-positive findings in the results.	Statistical analysis was performed using Student's <i>t</i> -test, Mann-Whitney test, Kruskal-Wallis test, linear regression analysis, Pearson's correlation analyses, and multivariate general linear model testing.	<p>Serum vaspin level was higher in men with metabolic syndrome than in men without metabolic syndrome (median 0.60 [IQR 0.40–0.99] vs. 0.40 [0.26–0.66] ng/ml, $p = 0.002$).</p> <p>No significant difference of serum vaspin level between women with and without metabolic syndrome (median 0.51 [IQR 0.30–0.97] vs. 0.53 [0.27–0.99] ng/ml, $p = 0.821$).</p> <p>In men, plasma vaspin concentration was correlated most strongly with %BF ($r = 0.278$, $p < 0.001$), BMI ($r = 0.221$, $p = 0.003$), waist circumference ($r = 0.206$, $p = 0.005$), and TG ($r = 0.159$, $p = 0.031$). Meanwhile, serum vaspin levels did not correlate significantly with these metabolic parameters in women.</p>	In men, high plasma vaspin levels are significantly associated with metabolic syndrome; in women, serum vaspin levels are associated with coronary atherosclerosis.	The study protocol was approved by the Ethical Committee of Seoul National University College of Medicine.

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Location (ref.)	Study objective or question	Study design (sample size)	Remarks	Selection issues	Outcome factors	Study factors	Potential confounders	Statistical method used	Main results	Main conclusions	Ethical issues consideration
Japan (Esaki <i>et al.</i> , 2014)	Determine the association between serum vaspin levels and eGFR, HOMA-IR, and c-IMT.	Cross-sectional; single-center (201).	This study tried to determine the vaspin role in a general population. Furthermore, the progression of atherosclerosis or c-IMT was evaluated by B-mode ultrasonography.	Simple random sampling; reliability (reproducibility) and validity were reported.	All relevant outcomes were assessed. Measurement error was not detected.	Relevant study factors were included in the study, and they were measured using appropriate tools.	Few participants with a relatively homogenous normal profile of BMI, c-IMT, and IR homeostatic model assessment.	Mediation analysis by creating a structural equation model to determine if vaspin was directly associated with c-IMT.	Serum vaspin level was independently and inversely associated with eGFR ($p < 0.01$). Serum vaspin level was independently associated with HOMA-IR ($p < 0.05$) and c-IMT ($p < 0.05$).	Human serum vaspin was positively and independently related to the c-IMT and HOMA-IR index in a general population.	The Kurume University Ethical Committee approved this study. All participants gave written consent.

ACEi, angiotensin-converting enzyme inhibitor; AIS, acute ischemic stroke; AMI, acute myocardial infarction; ARBs, angiotensin receptor blockers; BF, body fat; BMI, body mass index; CAD, coronary artery disease; CI, confidence interval; c-IMT, carotid intima-media thickness; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; FFA, free fatty acid; FPG, fasting plasma glucose; HAECs, human aortic endothelial cells; HOMA-IR, homeostatic model assessment of insulin resistance; HUVEC, human umbilical vein endothelial cells; ICA, internal carotid artery; IQR, interquartile range; ISR, in-stent restenosis; LA, linoleic acid; LVEF, left ventricular ejection fraction; MACEs, major adverse cardiac events; MDCT, multidetector-row computed tomography; OR, odds ratio; ROC, receiver operating characteristics; SAP, stable angina pectoris; SMC, smooth muscle cells; T2DM, type 2 diabetes mellitus; TG, triglyceride; UAP, unstable angina pectoris.

inhibitors or angiotensin receptor blockers and 66.3% receiving β -blockers (Zhang *et al.*, 2016).

Meanwhile, four studies, three cross-sectional and one cohort, demonstrated that serum vaspin elevation causes atherosclerosis (Choi *et al.*, 2011; Cura *et al.*, 2014; El-Lebedy *et al.*, 2018; Esaki *et al.*, 2014). Those three cross-sectional types stated no conclusive relationship between vaspin and atherosclerosis. One cross-sectional study had limitations due to small sample size with a relatively homogenous normal profile of body mass index (BMI), carotid intima-media thickness, and IR homeostatic model assessment (Esaki *et al.*, 2014).

Vaspin and glucose tolerance disorders

Several studies showed a positive correlation of serum vaspin levels with waist fat mass, circumference, and BMI, while the higher levels in obese and T2DM patients are possibly the consequence reaction of IR (Jian *et al.*, 2014). Another study explained this pathophysiology that the expression of insulin receptor substrate-2 messenger RNA (mRNA) was increased by administering 80–320 ng/ml vaspin. The VAT-derived serine protease inhibitor stimulated insulin secretion by the insulinoma cell line mediated through kinase Akt activation and the mTOR/p70S6K signaling pathway (Liu *et al.*, 2017). It was also reported to increase β -cell activity by impeding the KLK 7 and KLK 14 inhibitory function (Heiker *et al.*, 2013) (Fig. 6).

Pancreatic cell inflammation was inhibited by vaspin through NF- κ B downregulation (Liu *et al.*, 2017). It is an important fact that T2DM is associated with a chronic inflammatory process mediated by cytokines. Subsequently, high inflammatory cytokine in the pancreatic islets of T2DM patients causes pancreatic β -cell failure and activity impairment (Donath *et al.*, 2009; Nordmann *et al.*, 2017). Hence, high serum vaspin levels improve the β -cell function in patients with glucose tolerance disorders (Jian *et al.*, 2014; Liu *et al.*, 2017).

Based on the critical appraisal in Table 2, this current review indicated that 10 studies, 8 cross-sectional, 1 case-control, and 1 interventional human, demonstrated higher vaspin levels in glucose tolerance disorder patients (Dai *et al.*, 2016; El-Mesallamy *et al.*, 2011; Lal *et al.*, 2018; Liu *et al.*, 2020; Moradi *et al.*, 2016; Yang *et al.*, 2015, 2017a, 2017b; Ye *et al.*, 2009; Youn *et al.*, 2008). As stated in the previous review, all the cross-sectional types did not determine the cause–effect relationship between vaspin and T2DM. Furthermore, one interventional study showed that vaspin plays a role in compensating the insulin physiological and sensitivity function in IR conditions (Youn *et al.*, 2008). The compound is believed to have no significant role in healthy normal subjects and physically active persons (Youn *et al.*, 2008). A case-control study that evaluates the genotype and allele frequency in gestational diabetes mellitus (GDM) showed very little inconsistency in the relationship between vaspin levels and GDM compared with other existing reports. Conversely, the vaspin gene with a predominance of the AA genotype has been said to increase the risk of developing metabolic syndrome more than TT or TA (Lal *et al.*, 2018).

A positive association of serum vaspin level with IR risk has been reported in all adolescents at the pubertal stage and their counterparts with a high percentage of body fat (%BF). Higher

Table 2. Critical appraisal from the review of the association between vaspin serum level and glucose tolerance disorders.

Location (Ref.)	Study objective or question	Study design (sample size)	Remarks	Selection issues	Outcome factors	Study factors	Potential confounders	Statistical method used	Main results	Main conclusions	Ethical issues consideration
Brazil (Pala <i>et al.</i> , 2019)	Determine the association between serum vaspin levels and IR and investigate whether this association is affected by body composition and pubertal stage in adolescents during 300 minutes of physical activity per week for 6 months.	Cross-sectional and case-control; population study (484).	This study used adolescents aged 10–14 years. It is well known that IR becomes more common at a young age.	Simple random sampling; reliability (reproducibility) and validity were reported. Controls were appropriate; records of cases and controls were reviewed blindly; prevalence bias, admission rate bias, and recall bias were controlled; dropout bias was not controlled.	All relevant outcomes were assessed. Measurement error was not detected.	Relevant study factors were included in the study, and they were measured using appropriate tools.	Vaspin affects IR directly because insulin metabolism adjustment is possibly affected by regular physical activity; 180 adolescents did not complete the physical activity protocol; confounding variables included sex, age, BMI, %BF, pubertal stage, and physical activity.	The Mann-Whitney <i>U</i> and Pearson's χ^2 -tests were used to compare continuous and categorical risk variables between %BF groups. (ζ : 0.25–0.46, ζ : 0.36–0.65 μ g/ml, OR = 0.48, [95% CI = 0.27–0.88], $p = 0.017$) and third (ζ : 0.47–0.86, ζ : 0.66–1.49 μ g/ml, OR = 0.48, [95% CI = 0.26–0.87], $p = 0.015$) serum vaspin quartiles had a lower risk of developing IR than in the fourth quartile (ζ : ≥ 0.87 , ζ : ≥ 1.50 μ g/ml).	Vaspin was associated positively with risk factors related to insulin metabolism in adolescents with high %BF; vaspin was related to a reduced risk of IR independently of BMI and pubertal stage; that association was influenced by body fat and physical activity in adolescents.	The Ethics Committee of the Federal University of Ouro Preto, Minas Gerais, Brazil, gave approval (No. 0017.238.000-05) for this study.	
Pakistan (Lal <i>et al.</i> , 2018)	Investigate and associate serum vaspin levels and genotype and allele frequency in GDM.	Case-control; single-center (112).	The glucose tolerance disorders were presented by GDM pregnant women instead of T2DM patients.	Controls were appropriate; records of cases and controls were reviewed blindly; prevalence bias, admission rate bias, lead time bias, and recall bias were controlled.	All relevant outcomes were assessed. Measurement error was not detected.	Relevant study factors were included in the study, and they were measured using appropriate tools.	Potential confounders were not found.	Statistical descriptive analysis of continuous variables was expressed as mean \pm SD. <i>t</i> -test was performed to compare groups.	Serum vaspin levels were lower in the healthy group than in GDM ($p = 0.041$). No significant difference in genotype and allele frequencies regarding serum vaspin levels ($p = 0.330$, $p = 0.327$, respectively).	Higher plasma vaspin concentrations were seen in GDM females.	Approval was obtained from the Aga Khan University Ethics Committee, and participants signed written consent.
China (Yang <i>et al.</i> , 2015)	Determine the changes in serum vaspin concentration in early diagnosed T2DM patients to investigate the relationship between serum vaspin level, BMI, and gender.	Cross-sectional; single-center (66).	This study used vaspin ELISA measurement assays with the lowest measurable concentration of 0.05 mg/L. Moreover, it also determines the vaspin levels in regard to gender.	Simple random sampling; reliability (reproducibility) and validity were not reported.	All relevant outcomes were assessed. Measurement error was not detected.	Relevant study factors were included in the study, and they were measured using appropriate tools.	Potential confounders were not found.	Data are reported as means \pm SD. The <i>t</i> -test, chi-square test, linear correlation analysis, and stepwise multiple regression were performed.	Average serum vaspin levels were significantly higher ($p < 0.001$) in obese patients (1.13 \pm 0.25 mg/l) than in nonobese patients in both the DM group (0.65 \pm 0.13 mg/l) and control group (0.38 \pm 0.18 mg/l). There is significant difference in vaspin level in the T2DM group (ζ : 0.76 \pm 0.22, ζ : 0.92 \pm 0.35 mg/l, $p < 0.001$) and in the control group (ζ : 0.48 \pm 0.14, ζ : 1.05 \pm 0.21 mg/l, $p < 0.001$).	Serum vaspin concentrations were significantly increased in obese people and were independently associated with WHR and gender.	The Ethics Committee of the Affiliated Hospital of Jiangsu University approved this study protocol.

Continued

Location (Ref.)	Study objective or question	Study design (sample size)	Remarks	Selection issues	Outcome factors	Study factors	Potential confounders	Statistical method used	Main results	Main conclusions	Ethical issues consideration
China (Liu <i>et al.</i> , 2020)	Evaluate the alteration of serum vaspin in GDM patients after OGTT and investigate the effect of blood glucose levels on serum vaspin secretion.	Cross-sectional, pretest-posttest, single-center (60).	A follow-up study with a relatively similar method by Lal <i>et al.</i> (2018). The glucose tolerance disorders were presented by GDM pregnant women after OGTT exposure.	Simple random sampling, reliability (reproducibility) and validity were not reported.	All relevant outcomes were assessed. Measurement error was not detected.	Relevant study factors were included in the study, and they were measured using appropriate tools.	The glucose levels of OGTT were tested in this study; meanwhile, the insulin levels were not determined at the same time.	Statistical analysis, Pearson's analysis, and linear regression analysis were performed.	The vaspin level alteration after 1 hour OGTT in the GDM group was higher than in the NGT group (0.338 vs. 0.577 mmol/l, respectively, $p < 0.001$). In the GDM group, serum vaspin levels positively correlated with 1 hour PG and TG levels, including the baseline vaspin ($r = 0.494$, $p = 0.006$; $r = 0.385$, $p = 0.036$), 1 hour vaspin ($r = 0.577$, $p = 0.001$; $r = 0.466$, $p = 0.010$), and 2 hours vaspin ($r = 0.557$, $p = 0.001$; $r = 0.488$, $p = 0.006$).	Serum vaspin concentration increased with the OGTT in GDM patients, indicating that vaspin levels in the GDM group might be regulated by the hyperglycemia state.	The Human Ethics Committee of the Hebei General Hospital gave study approval, and all participants gave written consent.
Iran (Moradi <i>et al.</i> , 2016)	Evaluate the effect of serum vaspin levels on RMR in obese people.	Cross-sectional, population study (222).	This study evaluated the vaspin level in regard to gender and RMR in obese people. Furthermore, the RMR was measured by means of calorimetry. It was measured by indirect calorimetry after 10–12 hours of overnight fasting.	Simple random sampling, reliability (reproducibility) and validity were reported.	All relevant outcomes were assessed. Measurement error was not detected.	Relevant study factors were included in the study, and they were measured using appropriate tools.	Potential confounders were not found.	High and low levels of the vaspin group were assessed by the independent t -test. The chi-square test was performed for comparison of the frequencies of variables between different groups in sex analysis.	There was no significant difference of RMR between the low (<0.70 ng/ml) and high (≥ 0.70 ng/ml) vaspin level groups (mean \pm SD, 1,653.50 \pm 352.70 vs. 1,658.02 \pm 352.19, 95% CI: -88.73 to 97.73, $p = 0.920$). Between low and high vaspin level groups, there was significant difference for sex ($p = 0.03$), %BF ($p = 0.008$), RMR per BW ($p < 0.001$), and RMR per FFM ($p = 0.007$).	In obese individuals, serum vaspin level is higher in women than in men; serum vaspin had a mediator effect between visceral fat and fat mass associations with RMR in an obese person.	The Local Ethics Committee of Tehran University of Medical Sciences approved the study protocol (Ethic No.: 91-02-27-18041-69439).
China (Dai <i>et al.</i> , 2016)	Compare serum vaspin levels in recently diagnosed T2DM-obese and T2DM-lean patients.	Cross-sectional, single-center (200).	A follow-up study by a meta-analysis that reported higher serum vaspin concentrations in both obese and T2DM patients.	Simple random sampling, reliability (reproducibility) and validity were reported.	All relevant outcomes were assessed. Measurement error was not detected.	Relevant study factors were included in the study, and they were measured using appropriate tools.	Potential confounders were not found.	Friedman's analysis of variance (ANOVA) with <i>post hoc</i> Dunn's test analysis. Multiple linear regression was conducted in each group.	Vaspin levels of T2DM-obese (0.71 \pm 0.33 ng/ml) is higher than T2DM-lean, nondiabetic obese, and healthy control subjects (0.60 \pm 0.21, $p < 0.05$; 0.59 \pm 0.32, $p < 0.05$; 0.50 \pm 0.28, $p < 0.05$ ng/ml, respectively). This study shows that obesity may further increase vaspin levels even subsequent to diabetes development.	Excessive fat mass-induced inflammation and IR increase serum vaspin levels in obese patients.	Changzhou No. 3 People's Hospital Ethical Committee approved the study protocol.

Continued

Location (Ref.)	Study objective or question	Study design (sample size)	Remarks	Selection issues	Outcome factors	Study factors	Potential confounders	Statistical method used	Main results	Main conclusions	Ethical issues consideration
China (Yang <i>et al.</i> , 2017a)	Determine the serum vaspin levels in elderly T2DM patients with and without MC.	Cross-sectional; single-center (230).	This study used elderly patients >60 years old with T2DM. It is well known that T2DM is frequently found in middle age to elderly persons.	Simple random sampling; reliability (reproducibility) and validity were reported.	All relevant outcomes were assessed but residual confounding could be found due to a lack of controlled measurement.	Relevant study factors were included in the study, and they were measured using appropriate tools.	Lifestyle behavior and dietary habits are likely linked with serum vaspin, T2DM, and MC. These factors were not well measured in the study, which may lead to residual confounding.	The chi-square test or Fisher's exact for categorical variables analysis. Logistic regression analysis was performed in the multivariate analysis.	Serum vaspin levels were higher in the T2DM group than in the T2DM + MC group (592.5 ± 45.2 vs. 177.6 ± 54.8 ng/ml, $p < 0.01$).	Serum vaspin appears to play an important role in IR, T2DM, and MC.	Xuanwu Hospital, Capital Medical University Ethics granted the ethics approval.
China (Yang <i>et al.</i> , 2017b)	Investigate the relationship between serum vaspin levels and BMI of elderly patients (>60 years old).	Cross-sectional; single-center (227).	Similar to the study by Yang <i>et al.</i> (2017b), this study used T2DM elderly patients >60 years old with various BMI grades. Moreover, no potential salami publication was found.	Simple random sampling; reliability (reproducibility) and validity were reported.	All relevant outcomes were assessed. Measurement error was not detected.	Relevant study factors were included in the study, and they were measured using appropriate tools.	Potential confounders were not found.	The chi-square test or Fisher's exact test was performed for categorical variables analysis. Multiple stepwise regression analysis was performed in the multivariate analysis.	Serum vaspin levels were higher in the T2DM group (451.9 ± 32.6 vs. 284.2 ± 21.7 ng/ml, $p < 0.01$). In the T2DM, the vaspin levels were higher in the obese than the normal weight group (498.2 ± 17.1 vs. 382.1 ± 21.3 ng/ml, $p < 0.05$). Vaspin levels in the normal weight T2DM group were higher than in the healthy normal weight control group (382.1 ± 21.3 vs. 192.5 ± 45.2 ng/ml, $p < 0.05$).	In middle-aged adults, serum vaspin concentration correlates with adiposity, IR, and DMT2; the higher vaspin levels in IR are a compensatory reaction to poor insulin sensitivity.	The Xuan Wu Hospital Ethics Committee gave Study Approval No. [2013]-001.
Germany (Youn <i>et al.</i> , 2008)	Evaluate vaspin levels before and after an intensive 4-week physical training program in NGT, impaired glucose-tolerant, and T2DM subjects.	Intervention study; single-center (60).	This study explained the regulation of vaspin serum concentrations in human obesity and type 2 diabetes. Its findings were useful for the authors to summarize the mechanisms involving vaspin in the human body (Fig. 6).	Subjects were subsequently divided into groups according to the American Diabetes Association criteria.	All relevant outcomes were assessed. Measurement error was not detected.	Relevant study factors were included in the study, and they were measured using appropriate tools.	Potential confounders were not found.	Paired Student's <i>t</i> -test, chi-square test, and Pearson's simple correlation.	Vaspin levels significantly increased two-fold ($p < 0.05$ in all subgroups) in NGT, impaired glucose-tolerant, and T2DM subjects in response to the intensive 4-week training program compared to each corresponding subgroup vaspin baseline. A significant and positive correlation between vaspin level and change in VO_{2max} ($r = 0.6$, $p = 0.004$) after the training program. Long-term intensive physical training in elite competitive sportsmen was correlated with significantly ($p < 0.05$) lower vaspin serum concentrations.	Vaspin represents a new biomarker for IR and obesity. Elevated serum vaspin during the first weeks of physical training in untrained individuals could recover the IR state in response to exercise.	The study was approved by the University of Leipzig's Ethical Committee. All participants gave written consent.

Continued

Location (Ref)	Study objective or question	Study design (sample size)	Remarks	Selection issues	Outcome factors	Study factors	Potential confounders	Statistical method used	Main results	Main conclusions	Ethical issues consideration
China (Ye <i>et al.</i> , 2009)	Evaluate the association between vaspin concentration and glucose metabolism or obesity in Chinese adults.	Cross-sectional; single-center (123).	This study investigated the association of serum vaspin level with body fat indexes, and the markers of glucose metabolism. It helped the authors to determine the pathophysiological role of vaspin in humans (Fig. 6).	Simple random sampling; reliability (reproducibility) and validity were not reported.	All relevant outcomes were assessed. Measurement error was not detected.	Relevant study factors included in the study, and they were measured using appropriate tools.	Potential confounders were not found.	Student's <i>t</i> -test and ANOVA were performed to compare statistical differences among groups.	In women, vaspin concentration was higher in NGT than T2DM subjects [380 (438–695) vs. 592 (294–517) pg/ml, $p = 0.020$]. In men, there was no significant difference in vaspin levels between T2DM and NGT subjects [476 (320–771) vs. 362 (258–580) pg/ml, $p = 0.162$]. No significant difference in vaspin levels between men and women either in the NGT or T2DM group ($p = 0.320$, $p = 0.295$, respectively).	In women, serum vaspin concentration is significantly higher in DM2 patients than that in NGT subjects.	The Ethics Committee of Shanghai Jiao Tong University Affiliated Sixth People's Hospital approved this study.
Egypt (El-Mesallamy <i>et al.</i> , 2011)	Evaluate the association between vaspin- visfatin/ NAMPT alteration levels and IR, IL-6, and other biochemical parameters in Egyptian T2DM patients.	Cross-sectional; single-center (75).	This study evaluated another yet similar cytokine to vaspin. It showed that vaspin and visfatin/NAMPT are significantly interrelated.	Simple random sampling; reliability (reproducibility) and validity were not reported. The general linear modeling was performed to control for potential confounding factors (e.g., age, sex, and BMI).	All relevant outcomes were assessed. Measurement error was not detected.	Relevant study factors were included in the study, and they were measured using appropriate tools.	Potential confounders were not found.	Groups were compared by ANOVA, and Bonferroni's <i>post hoc</i> was used to compare individual groups. The Kruskal–Wallis and Mann–Whitney <i>U</i> tests for any further skewed data analysis.	Significant increase ($p < 0.01$) of vaspin and visfatin/ NAMPT was found in both nonobese (1.62 ± 0.22 and 25.9 ± 3.44 ng/ml, respectively) and obese T2DM (2.76 ± 0.38 and 45.4 ± 4.60 ng/ml, respectively) compared to control subjects (0.42 ± 0.05 and 9.37 ± 1.98 ng/ml, respectively) at $p < 0.01$. A positive correlation between vaspin and visfatin/ NAMPT levels ($p < 0.0001$). -Vaspin-visfatin/NAMPT were also positively correlated with other biochemical profile parameters, HOMA-IR, TG, TC, LDL-C, IL-6 ($p < 0.001$, $p = 0.001$, $p = 0.003$, $p = 0.034$, and $p < 0.0001$, respectively), but not for HDL-C ($p = 0.604$).	Vaspin is significantly elevated in T2DM patients compared with healthy control subjects; vaspin was found to be significantly correlated with various metabolic parameters; vaspin might play a role in T2DM pathogenesis.	This study was approved by the National Institute of Diabetes and Endocrinology Ethical Committee of Cairo, Egypt, and informed consent was obtained from all participants.

Continued

Location (Ref.)	Study objective or question	Study design (sample size)	Remarks	Selection issues	Outcome factors	Study factors	Potential confounders	Statistical method used	Main results	Main conclusions	Ethical issues consideration
Germany (Von Loeffelholz <i>et al.</i> , 2010)	Investigate whether the induction of IR by lipid infusion affects vaspin levels.	Intervention study; single-center (108).	The only study that stated that vaspin is unrelated to insulin sensitivity in a cohort of nondiabetic humans.	Participants were selected from the Metabolic Syndrome Berlin Potsdam (MeSyBePo) study.	All relevant outcomes were assessed. Measurement error was not detected.	Relevant study factors were included in the study, and they were measured using appropriate tools.	Longer intervention duration caused an insignificant difference between groups.	In subgroup analyses, Student's <i>t</i> -test for independent samples was performed if data were normally distributed. Otherwise, the Mann-Whitney <i>U</i> test was used.	No significant serum vaspin level difference ($p = 0.44$) between the lipid and saline groups after the 4-week intervention.	No major relationship between serum vaspin and insulin sensitivity; at least, this investigated a cohort of nondiabetic persons with widely varying BMI.	The study protocol was approved by the local ethics committee. All subjects gave written consent.

BF, body fat; BMI, body mass index; BMR, basal metabolic rate; BW, body weight; CI, confidence interval; DM, diabetes mellitus; EHC, euglycemic-hyperinsulinemic clamps; FFM, fat-free mass; FINS, fasting insulin; FPG, fasting plasma glucose; GDM, gestational diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; IL, interleukin; IR, insulin resistance; LDL-C, low-density lipoprotein cholesterol; MC, macrovascular complication; NGT, normal glucose tolerance; OC, oral contraceptives; OGTT, oral glucose tolerance test; OR, odds ratio; PG, plasma glucose; RMR, resting metabolic rate; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglyceride; WHR, waist-to-hip ratio.

serum vaspin level ($\delta: \geq 0.87$, $\eta: \geq 1.50$ $\mu\text{g/ml}$) was linked with a reduced IR risk independently of BMI, %BF, and pubertal stage (Pala *et al.*, 2019). Those results did not conclude whether serum vaspin level affects IR directly because the insulin metabolism adjustment is possibly affected by regular physical activity. Insulin has a propensity to be the factor affecting serum vaspin levels. Nevertheless, the aforementioned study proves that the association between higher serum vaspin levels and lower risk for IR tends to be mediated by physical activity in adolescents. However, there were actual result biases, including 180 adolescents who did not complete the physical activity protocol (Pala *et al.*, 2019). One interventional human study also produced unusual results, which suggested that the longer intervention duration further elucidates the nonsignificant difference between the intervention and control saline groups (Von Loeffelholz *et al.*, 2010).

Vaspin and gender difference

The majority of the studies showed that serum vaspin concentrations were significantly higher in females than in males. Vaspin levels elevated with pubertal stage and age in females, but they were constant in males (Körner *et al.*, 2011). The mechanism between serum vaspin levels and gender differences remains unsettled. Circulating estrogen concentration has been said to elevate serum leptin levels. This tends to also elucidate the elevated vaspin levels in females (Yang *et al.*, 2015). A study reported GRP78 mRNA expression and vaspin levels in porcine oocyte and ovarian follicles (Kurowska *et al.*, 2019). Those vaspin genes and serum depend on the ovarian follicle cycle while serum vaspin increases from the early to the late luteal phase (Kurowska *et al.*, 2020).

A cross-sectional case-control study showed significantly high vaspin levels in females with polycystic ovary syndrome (PCOS). These individuals had stimulated vaspin mRNA expression and its protein product in omental adipose tissue (Dogan *et al.*, 2020). Consequently, PCOS is highly associated with peripheral IR, hyperinsulinemia, and obesity (Kazemi Jaliseh *et al.*, 2017).

Serum vaspin level and its genetic expression

Serum vaspin is regulated and encoded by the SERPINA12 gene consisting of 1,245 nucleotides on the 14q32.1 human chromosome (Hida *et al.*, 2005). This review did not consider vaspin genetic expression aspects; hence, the vaspin expression and serum concentration are indirectly influenced by the gene and single nucleotide polymorphisms (SNPs) role (Fig. 6). Moreover, each type of vaspin gene SNP is strongly influenced by population race.

In the Japanese population, the SNPs restriction site (rs) 77060950 indicated high serum levels by modulating vaspin protein transcription (Teshigawara *et al.*, 2012). Another study on the serum vaspin concentration and T2DM in the Iranian population showed that rs2236242 allele A is protective for T2DM and it indirectly causes a low vaspin level compared to T. According to Hosseini *et al.* (2021), rs2236242 SNPs have no association with IR. Therefore, the population race and its most suitable SNP type need to be considered in every vaspin serological study. Therefore, the population race and its most suitable SNP type need to be considered in every vaspin serological study.

	Zhang <i>et al.</i> , 2013	Zhang <i>et al.</i> , 2020	Kastl <i>et al.</i> , 2020	Zhang <i>et al.</i> , 2016	Jung <i>et al.</i> , 2011	Li <i>et al.</i> , 2012	Aust <i>et al.</i> , 2009	Cura <i>et al.</i> , 2014	El-Lebedy <i>et al.</i> , 2018	Esaki <i>et al.</i> , 2014	De <i>et al.</i> , 2019	Lal <i>et al.</i> , 2018	Yang <i>et al.</i> , 2015	Liu <i>et al.</i> , 2020	Moradi <i>et al.</i> , 2016	Dai <i>et al.</i> , 2016	Yang, Li, and Wang <i>et al.</i> , 2017	Youn <i>et al.</i> , 2008	Ye <i>et al.</i> , 2009	El-Mesallamy <i>et al.</i> , 2011	Von Loeffelholz <i>et al.</i> , 2010		
Random sequence generation (selection bias)	-	-	-	-	?	?	-	-	-	?	-	-	-	-	-	-	?	-	-	?	-	?	
Allocation concealment (selection bias)	?	-	-	-	?	+	?	?	-	+	?	-	-	-	-	-	-	-	+	-	-	-	
Blinding of participants and personnel (performance bias)	-	-	-	-	-	+	?	-	-	+	+	-	-	?	+	-	-	?	-	-	?	?	+
Blinding of outcome assessment (detection bias)	+	-	-	?	?	+	-	-	-	-	-	-	+	-	+	+	-	-	-	-	-	-	
Incomplete outcome data (attrition bias)	-	?	?	+	-	-	-	?	-	+	+	+	+	?	?	-	-	-	-	+	-	-	
Selective reporting (reporting bias)	+	?	-	+	-	-	-	+	?	?	-	?	-	-	-	-	+	+	?	?	+	+	+
Other bias	+	-	-	+	+	+	-	-	-	+	-	-	-	+	+	+	-	+	-	+	-	-	

Figure 2. Risk of bias assessment by the authors' judgments for each reviewed study.

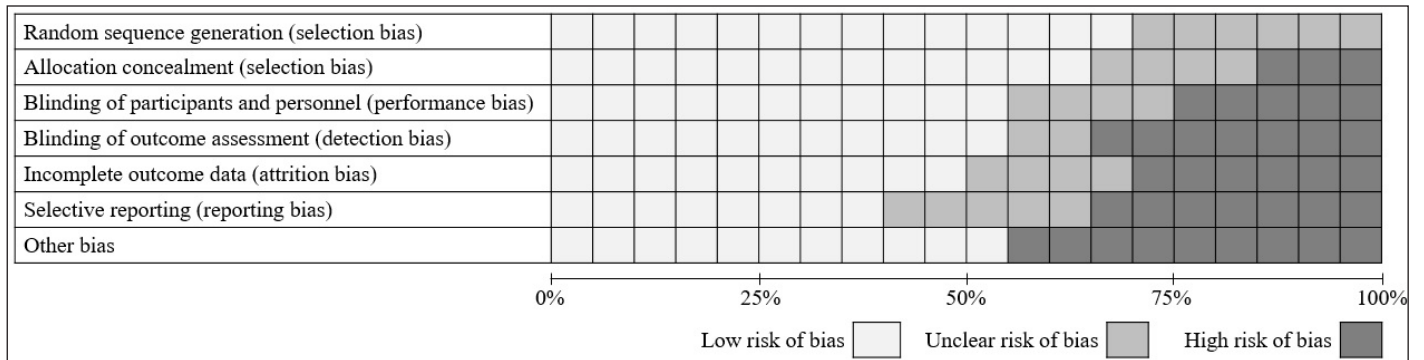


Figure 3. Risk of bias graph by the authors' judgments for each reviewed study.

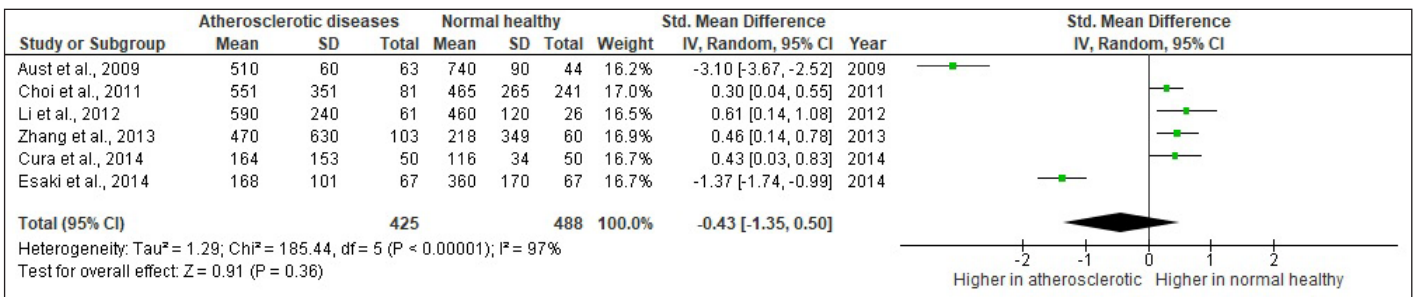


Figure 4. Forest plot of serum vaspin levels (ng/ml) comparison between atherosclerotic diseases and normal healthy. CI, confidence interval and SD, standard deviation.



Figure 5. Forest plot of serum vaspin levels (ng/ml) comparison between glucose tolerance disorders and normal healthy. CI, confidence interval and SD, standard deviation.

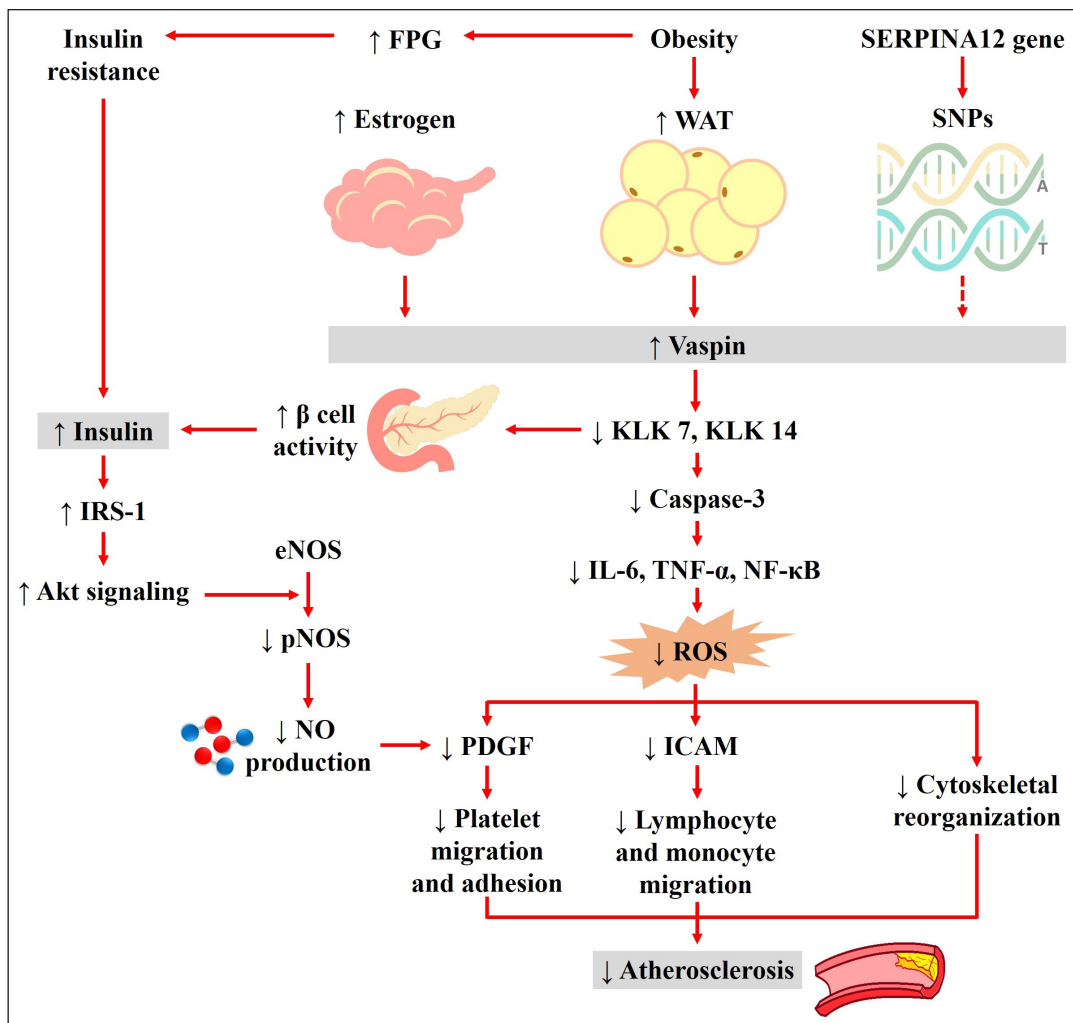


Figure 6. Anti-inflammatory, anti-atherosclerotic, and IR compensatory molecular pathways that are affected by serum vaspin. Vaspin showed a beneficial role in endothelial cells; meanwhile, vaspin increases insulin levels as a compensatory mechanism due to IR. eNOS, endothelial nitric oxide synthase; FPG, fasting plasma glucose; ICAM1, intracellular adhesion molecule 1; IL, interleukin; IRS-1, insulin receptor substrate 1; KLK, kallikrein; NF-κB, nuclear factor-κB; NO, nitric oxide; PDGF, platelet-derived growth factor; pNOS, phosphorylated endothelial nitric oxide synthase; ROS, reactive oxygen species; SNPs, single nucleotide polymorphisms; TNF-α, tumor necrosis factor-alpha; and WAT, white adipose tissue.

CONCLUSION

High serum vaspin levels represent insulin compensatory adipokines during IR conditions in T2DM or obesity. Consequently, the levels of this compound significantly increase in patients with glucose intolerance. In vascular studies, a high serum vaspin level demonstrates a favorable role and beneficial effect in preventing atherosclerosis in either VSMCs or endothelial cells. The main limitation of this review was a failure to consider the effect of population SNP types on serum vaspin levels. Hence, a further review needs to include a detailed discussion of vaspin gene expression, population race, and specific SNP types.

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AUTHOR CONTRIBUTIONS

All authors read and approved the final manuscript. RD, SRT, BP, and DI: Conceptualization, literature search, critical appraisal, discussion, software, and logistics support. FM: Literature search, critical appraisal, data extraction, statistical analyses, writing-original initial draft, and final manuscript. DKM, VW, SNO, SUB, PB, YH, BLH, HRP, EAJH, IR, TT, and RAAT: Reviewing, assessment of the risk of bias, supervision, and validation.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

Available on reasonable request via e-mail at rivan.danuaji@staff.uns.ac.id.

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