Role of visfatin in obesity-induced insulin resistance

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**Abstract**

The growing worldwide burden of insulin resistance (IR) emphasizes the importance of early identification for improved management. Obesity, particularly visceral obesity, has been a key contributing factor in the development of IR. The obesity-associated chronic inflammatory state contributes to the development of obesity-related comorbidities, including IR. Adipocytokines, which are released by adipose tissue, have been investigated as possible indicators of IR. Visfatin was one of the adipocytokines that attracted attention due to its insulin-mimetic activity. It is released from a variety of sources, including visceral fat and macrophages, and it influences glucose metabolism and increases inflammation. The relationship between visfatin and IR in obesity is debatable. As a result, the purpose of this review was to better understand the role of visfatin in glucose homeostasis and to review the literature on the association between visfatin levels and IR, cardiovascular diseases, and renal diseases in obesity.

**Key Words:** Homeostatic model assessment for insulin resistance; Insulin resistance; Obesity; Visfatin; pre-B cell colony enhancing factor; Nicotinamide phosphoribosyltransferase enzyme; Diabetes; Adipocytokines

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**Core Tip:** Visfatin is an adipocytokine that is produced by visceral fat and other sources. It has been shown to influence glucose and lipid metabolism, as well as enhance the chronic inflammatory state linked to obesity. The findings on the relationship between visfatin and IR in obese patients are controversial. This review aims to better understand how visfatin contributes to the emergence of IR and to assess the possibility of utilizing visfatin levels as a biomarker for the early detection of IR and IR-related diseases, including cardiovascular and renal diseases.
INTRODUCTION

Accumulation of adipose tissue, particularly visceral adiposity, is the most common contributory factor in the development of insulin resistance (IR). Adipose tissue is an endocrine tissue that secretes many peptides that are adipocytokines including leptin, adiponectin, resistin and visfatin. Adipokines are reported to affect glucose and lipid metabolism as well as food intake[1]. Alterations in the levels of adipokines and genetic polymorphism such as adiponectin SNP + 45 are related to the emergence of IR and its related comorbidities[2]. The serum and salivary levels of these adipokines were extensively assessed as biomarkers for early diagnosis of IR and its consequences for cardiovascular and renal diseases. Visfatin is an adipokine that has attracted the attention of researchers for its role in the pathogenesis of IR and the possibility of using its levels as a biomarker for IR detection[3,4,...].

VISFATIN’S JOURNEY FROM AN INSULIN-MIMETIC TO AN ENZYME KNOWN AS NICOTINAMIDE PHOSPHORIBOSYLTRANSFERASE ENZYME

Visfatin is a 52-kDa molecule, first described in 2004 by Fukuhara et al[7] as an insulin-mimetic adipokine. It was named visfatin because it was thought to be produced exclusively from visceral adipose tissue[6,7], in addition to other sources including subcutaneous adipose tissue[8], skeletal muscle[9], liver[10], immune cells[11], cardiomyocytes[12], brain cells[13] and renal glomeruli[14].

Visfatin’s insulin-like actions were demonstrated by a reduction in plasma glucose concentration 30 min after intravenous infusion of recombinant visfatin into c57BL/6 mice and insulin-resistant obese mice[7]: an outcome that the authors hypothesized was independent of insulin. The insulin-mimetic action of visfatin might be mediated by an increase in peripheral tissue glucose uptake, a decrease in both gluconeogenesis and lipid release, and stimulation of the insulin signaling cascade[7]. The glucose-lowering effect of visfatin attracted researchers’ curiosity about the prospect of visfatin becoming a novel diabetic medication. Extensive research has been conducted to investigate the relationship between visfatin levels, type 2 diabetes mellitus (T2DM), and IR. However, the findings are inconsistent, ranging from a positive correlation between plasma visfatin level and T2DM[15,16] to the existence of an inverse relationship between plasma visfatin level and type 1 diabetes[17].

Visfatin is structurally identical to the pre-B cell colony enhancing factor (PBEF)[18], a cytokine that was isolated in 1994 from a human lymphocyte and was known to accelerate the maturation of B cell precursors[19]. PBEF (visfatin) is regarded as a proinflammatory cytokine that has been shown to have multiple physiological functions related to cell metabolism[20,21], immunomodulation[20,22], and inflammation[23,24]. It has been found in various immune cells other than B cells and has been shown to inhibit apoptosis of macrophages[20]. Extracellular PBEF promotes proinflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-16, transforming growth factor (TGF)-β1, as well as the chemokine receptor CCR3. PBEF also boosts IL-6, TNF-α and IL-1 production in CD14+ monocytes, macrophages, and dendritic cells, improves T cell function, and is required for the development of B and T lymphocytes[20].

In 2001, Martin et al[24] discovered a significant homology between the mammalian PBEF gene and nicotinamide phosphoribosyltransferase (NAMPT); the enzyme that is required for production of NAD, and subsequently, is capable of modulating its intracellular levels[25-27]. NAD is a crucial coenzyme involved in a variety of cellular activities, including the generation of ATP[28] and the synthesis of regulatory proteins such as silent information regulator 2 (Sir2), which has seven types of deacetylase proteins known as sirtuins: SIRT1–SIRT7[29]. Sirtuins are involved in various metabolic functions[30-32]. SIRT1 deacetylases have been demonstrated to regulate many transcription factors required for cell survival, apoptosis and proliferation, including tumor suppressor p53[33-35], a protein forkhead box class O protein[36-38], and peroxisome proliferator-activated receptor-γ coactivator-1α[39,40]. SIRT1 also inhibits the signaling of nuclear factor-κB and suppresses inflammation[41-43]. Visfatin may thus alter metabolic processes involved in glucose and lipid metabolism via its NAMPT enzyme-like activity[3,44,45]. Figure 1 depicts the discovery of visfatin as a structurally similar hormone to the cytokine PBEF, whose gene is homologous to the NAMPT enzyme. As a result, PBEF and NAMPT are synonyms for visfatin.
REGULATION OF VISFATIN

Despite several research published since the discovery of visfatin, the regulation of visfatin (PBEF/NAMPT) appears to be complex. The majority of published research is inconsistent and provides conflicting results. Dexamethasone raised visfatin mRNA expression in 3T3-L1 adipocytes while growth hormone and TNF-α decreased it[18,46,47]. Glucose infusion elevated plasma visfatin levels in healthy participants during clamp testing[48]. However, another study published in 2011 by Bala et al[49] found that 75 g carbohydrate intake following a 2-h oral glucose tolerance test (OGTT) significantly reduced plasma visfatin levels primarily in overweight and female participants, who were more affected than normal healthy glucose-tolerant individuals. The significant inhibitory effect of insulin and glucagon-like peptide (GLP)-1 on visfatin production following oral glucose ingestion might explain the effects of intravenous versus oral glucose consumption[49]. Insulin and GLP-1 dramatically reduced visfatin release from 3T3-L1 adipocytes by nearly 50%, and GLP-1 lowered visfatin production from 3T3-L1 adipocytes by roughly 50%. According to the same study, insulin and GLP-1 under an oral glucose load reduce visfatin levels among those who are healthy, insulin-sensitive and have normal glucose tolerance[49]. The authors concluded that the inhibitory effect of GLP-1 on visfatin production during OGTT may indicate the emergence of a novel incretin-like action described by a GLP-1/visfatin/axis; the significance of which remains unknown. In another investigation, researchers discovered that intravenous glucose, mannitol, and sex hormones (estradiol and testosterone) had no effect on visfatin release[50]. Figure 2 summarizes the control of visfatin secretion in normal, healthy and glucose-tolerant individuals.

PHYSIOLOGICAL VERSUS PATHOLOGICAL EFFECTS OF VISFATIN

Visfatin (NAMPT), with its two isoforms, the extracellular (eNAMPT) and intracellular (iNAMPT) forms, is crucial for NAD biosynthesis, with the higher activity of the extracellular form. NAD is required for various processes, including metabolic processes, glucose-stimulated insulin secretion, cell survival, cell cycle control, and apoptosis[51]. However, elevated levels of visfatin have been linked to increased levels of inflammatory markers such as IL-6, IL-8, C-reactive protein, and monocyte chemotactic protein-1[52,53], endothelial dysfunction[54], and increase in oxidative stress[55-58]. These findings point to the existence of an average physiological level of visfatin at which it is properly controlled and fulfils its physiological functions, as well as a threshold level at which its pathological consequences occur. Studies have shown that an increased level of visfatin is associated with IR and T2DM[15,59], metabolic syndrome (MetS)[60], polycystic ovary syndrome[61], and T2DM-associated complications such as cardiovascular[62,63], cerebrovascular[64,65], and renal[66-68] diseases. The significance of visfatin in the pathogenesis of IR and its associated consequences reflects the potential utility of visfatin as an early biomarker for IR in high-risk patients, especially obese adults, and as a biomarker for T2DM sequelae.

VISFATIN LEVEL AND IR

The impairment of glucose metabolism and the development of multiorgan IR following the adipose-tissue-specific deletion of visfatin[69] has demonstrated that visfatin is a major target in obesity, diabetes, and dyslipidemia[70]. Visfatin interacts with insulin receptors at locations other than insulin-
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Figure 2 Regulation of visfatin in normal healthy-glucose tolerant individuals. GLP-1: Glucagon-like peptide 1.

binding sites, lowering blood glucose levels via increased muscle and liver cell glucose utilization[5]. It also prompts the action of insulin by inducing phosphorylation of insulin receptors 1 and 2. It also prompts the activation of phosphatidylinositol-3 kinase (PI3K), protein kinase B, and mitogen-activated protein kinase[71]. Visfatin is thought to have endocrine, paracrine and autocrine functions. Visfatin’s autocrine effects in the liver may be important in modifying insulin sensitivity, as indicated by a decrease in glucose-stimulated insulin release linked with decreased visfatin expression and NAD production in the FaO rat hepatocytes[72].

Central visfatin improved glucose homeostasis in diabetic rats by boosting insulin release and sensitivity via the hypothalamus, demonstrating that visfatin is a positive modulator of glucose homeostasis via transmitting hypothalamic signals to the periphery[73]. The increased level of visfatin has been reported in obese patients with T2DM compared with obese patients without T2DM. The high visfatin level in these patients was correlated with an increase in inflammatory markers[59]. The high levels of visfatin found in patients who have uncontrolled glucose levels may represent a regulatory response in an attempt to maintain glucose homeostasis; however, as the insulin secretion/insulin actions are impaired in those patients, there is an imbalance in the regulation of visfatin, with a subsequent marked rise in visfatin level, exceeding the threshold. The increase in visfatin levels promotes the release of inflammatory mediators, as evidenced by the significant association between high visfatin levels with the high levels of inflammatory mediators regardless of the presence of T2DM and MetS[53,54,74] suggesting a role of visfatin in the development of IR and T2DM in a dose-dependent manner. Figure 3 summarizes the role of visfatin in glucose homeostasis and its potential role in the development of IR and IR-related complications.

VISFATIN LEVEL AND CARDIOVASCULAR DISEASES, INCLUDING STROKE

Increased visfatin levels are associated with endothelial dysfunction, smooth muscle cell proliferation in the arterial wall, the formation of atherosclerotic plaques, and acute coronary syndrome[54,73]. The proliferative, proinflammatory and proangiogenic effects of visfatin are mediated via stimulation of PI3K, nuclear factor (NF)-B, signal transducer and activator of transcription (STAT), extracellular signal-regulated kinases (ERKs) and Toll-like receptor 4[54,76,77]. The visfatin-induced cell proliferation is dose-dependent, and it is mediated by increasing the release of vascular endothelial growth factor, fibroblast growth factor-2 (FGF-2), MCP-1, IL-6, and thromboxane A2[77-80]. The increased levels of visfatin in patients with atherosclerosis and acute coronary syndrome are caused by the expression of visfatin by the foam cells and smooth muscle cells of the atherosclerotic plaques, in addition to the increased expression of visfatin by the epicardial and perivascular adipose tissue, in which it is suggested to function in a paracrine fashion on the blood vessels[1,81]. Studies have shown that visfatin stimulates the release of inducible nitric oxide synthase (iNOS), a proinflammatory enzyme associated with vascular complications in diabetic patients[82-84]. The changes in visfatin levels in ST-elevation myocardial infarction (STEMI) followed the same pattern as the troponin levels, suggesting the usefulness of visfatin as a biomarker for STEMI[85]. Visfatin levels are also associated with cardiac fibrosis, as visfatin induces the proliferation of fibroblasts and increases the release of type I and III collagen[86].

Stroke is one of the cardiovascular diseases escalating in both developed and developing countries[87]. Diabetes is an established risk factor for stroke because of the cerebrovascular changes induced by
Recent research has found an increase in visfatin levels in stroke patients, indicating that a high visfatin level may be a risk factor for strokes[89,90]. The association observed between high visfatin levels and cerebrovascular strokes can be explained by the endothelial dysfunction induced by high visfatin levels[54,90].

**VISFATIN LEVEL AND KIDNEY DISEASES**

The global prevalence of chronic kidney disease (CKD) among diabetic patients is steadily increasing [91]. An increased visfatin level is associated with the progression of CKD in diabetic and nondiabetic patients[92,93]; an observation that can be explained by endothelial dysfunction associated with high visfatin levels[93], IR[3], inflammation[53,74,94], oxidative stress[57,58], synthesis of profibrotic molecules in the mesangial cells, and increased expression of renin, angiotensinogen, and angiotensin receptors, as well as angiotensin II[95,96], thus increasing the activity of NADPH oxidase. This proinflammatory enzyme causes an increase in glomerular permeability[97]. A decrease in serum visfatin level was noted upon improving endothelial dysfunction following renal transplantation[98]. Overall, these data imply that visfatin has a role in mediating the CKD associated with T2DM. However, more studies are required to elucidate the relative contribution of visfatin compared with other inflammatory biomarkers, and to indicate the threshold level of visfatin at which those complications appear.

**ASSOCIATION BETWEEN VISFATIN LEVEL AND IR IN OBESITY**

To assess the evidence on the relationship between visfatin levels and IR in obesity, PubMed and Google Scholar were searched for articles published between 2015 and March 2022. The search was limited to English-language articles. The references in the discovered texts were further analyzed for other relevant articles. After the search, 15 papers were chosen for evaluation and they are discussed in ascending sequence.

The first research chosen was by Nourbakhsh et al[99] in 2015. The study was conducted among 73 children in Iran; 42 obese patients versus 31 controls. The study involved the measurement of serum visfatin and insulin using ELISA, and IR was assessed using the homeostatic model assessment for IR (HOMA-IR). Fasting plasma glucose (FPG) and lipid profile were also tested, and MetS was defined using the International Diabetes Federation (IDF) criteria. The study revealed that obese children had significantly greater serum visfatin than nonobese children without MetS or IR. In obese individuals, visfatin levels correlated with FPG, insulin, and HOMA-IR[99].

A positive correlation between serum visfatin levels and IR among obese children was further investigated by Salama et al[100] in 2015. The study was conducted among 33 Egyptian children (22 obese and 11 control). Anthropometric measurements such as body mass index (BMI), waist circumference (WC),
The lipid profile and FPG were also measured. The study revealed significantly higher levels of serum visfatin, HOMA-IR, and lipid profile among pregnant women with GDM compared with the control group. Serum visfatin was also shown to be positively correlated with HOMA-IR, hemoglobin A1c, and HOMA-IR in women with GDM than the control group. Correlation analysis showed a negative correlation between serum visfatin with FPG and HOMA-IR among the control group. In contrast, a positive correlation is reported between serum visfatin levels with HOMA-IR, weight gain during pregnancy, and BMI at childbirth. The results of this study were first published in 2015.[102] The increase in serum visfatin levels associated with increased FPG in pregnant women may represent a regulatory response to control blood glucose levels; however, any further increase in visfatin levels may have contributed to IR and GDM.

The association between serum visfatin and GDM was further investigated by Tsiotra et al.[103] in Athens, Greece in 2018. Tsiotra et al[103] evaluated the expression of visfatin by the visceral and subcutaneous adipose tissues and placenta in 15 obese and nonobese women with GDM, compared to a control group that consisted of 23 obese and nonobese women with standard glucose tolerance. The study revealed a lower circulating visfatin level in obese women with GDM than in nonobese women with normal glucose tolerance. The study reported comparable visfatin mRNA expression in all tissues.

In Egypt in 2018, the association between serum visfatin with IR and proinflammatory cytokines in patients with T2DM was studied by Hetta and co-researchers[104]. The case-control study involved the assessment of anthropometric measurements, blood pressure, and serum levels of visfatin, CRP, IL-6, TNF-α and HOMA-IR in 80 people with diabetes in comparison to a control group of 40 healthy participants. The study reported significantly higher levels of visfatin, CRP, IL-6 and TNF-α in the diabetic group compared with the healthy control group. Serum visfatin was also shown to be positively correlated with BMI, WC, HOMA-IR and proinflammatory markers[104]. The study results provided evidence of the potential role of serum levels of visfatin in the pathogenesis of IR, an effect that the activation of the proinflammatory cytokines could mediate.

In addition to assessing the association between serum levels of visfatin and IR, the interest in the use of saliva as an alternative tool to serum for the measurement of biomarkers has been developed. The use of salivary levels of visfatin as a biomarker for T2DM was investigated in a study conducted by Srinivasan et al.[105] in the USA and published in 2018. The study involved measuring levels of visfatin, TNF-α, IL-6, resistin and ghrelin in unstimulated fasting saliva samples collected from 40 subjects (20 diabetics and 20 healthy controls). It revealed significantly higher salivary levels of visfatin in patients with T2DM than in the control group, supporting the potential use of salivary visfatin as a biomarker for T2DM.[105]

Compared with blood sampling, saliva sampling is simple, safe and noninvasive. The use of saliva as a diagnostic tool is evolving not only due to the rapid advances that are being made in the fields of nanotechnology and molecular diagnostics but also because saliva contains biomarkers that are ideal for early detection and monitoring of oral as well as systemic diseases including biomarkers for IR such as resistin, TNF-α, leptin, visfatin, adiponectin, IL-6 and CRP.[106]

The association between serum levels of visfatin and GDM was further investigated in a study conducted by Souvannavong-Vilivong et al.[107] in Bangkok, Thailand, and published in 2019. The study involved the measurement of serum visfatin among a sample of pregnant women with GDM class A1 (n = 37) compared with a control group with normal pregnancy (n = 37). The results reported significantly higher levels of serum visfatin and plasma glucose levels in women with GDM class A1. This was associated with a negative correlation between serum levels of visfatin with neonatal weight and length, thus supporting the use of serum visfatin level as a biomarker for GDB and prediction of pregnancy outcomes in patients with GDM.[107]

The usefulness of serum visfatin as a biomarker for GDM was further investigated by Bawah et al.[108] in Ghana and published in 2019. The study examined the alterations of serum levels of visfatin with GDM in a case-control study that included 140 women in their first trimester (70 with GDM and 70 without GDM). In addition to BMI measurement, serum levels of visfatin, resistin and leptin, and lipid
profile were assessed. The study reported significantly higher serum visfatin levels in patients with GDM compared with the controls. It also showed a significant positive correlation between serum levels of visfatin with age, total cholesterol, triglycerides, low-density lipoprotein cholesterol, very low-density lipoprotein cholesterol, and leptin, and a negative correlation with high-density lipoprotein cholesterol [106].

Additional evidence of the increased serum visfatin in women with GDM was provided in a study conducted by Manoharan et al. [109] in India and published in 2019. The study involved measuring cord plasma levels of visfatin, insulin, HOMA-IR, insulin sensitivity, and beta-cell function. The pregnancy outcomes such as birth weight were also assessed. Forty pregnant women were recruited for the study (n = 20 with GDM and n = 20 with normal pregnancy). The results revealed significantly higher cord plasma insulin, visfatin, and HOMA-IR levels in women with GDM than in the control group [109].

The association between serum visfatin and IR among obese children was evaluated in a study conducted by Yin et al. [110] in China and published in 2019. A total of 244 children (160 obese and 84 lean) were recruited. The study involved assessing serum levels of visfatin, high-sensitivity CRP (hs-CRP), TNF-α, IL-6, angiotensin-2, vascular cellular adhesion molecule (VCAM)-1, E-selectin levels, anthropometric measurements, insulin, glucose, and lipid profile. The study reported significantly higher levels of visfatin in obese children compared with controls. There was a positive correlation between serum visfatin with each of the following: BMI, WC, hs-CRP, TNF-α, IL-6, angiotensin-2, VCAM-1, and E-selectin levels, thus supporting the role of elevated serum visfatin in prompting inflammation and IR in obese children [110].

A more recent study on the association between serum visfatin and IR in patients with Alzheimer’s disease (AD) was conducted by Sharifipour et al. [111] in Iran and published in 2020. The study involved the measurement of serum visfatin, blood glucose levels, HOMA-IR, and BMI among 60 subjects divided into two groups: 34 subjects with AD and 26 normal subjects. The study reported a significant increase in HOMA-IR and decrease in serum visfatin levels in patients with AD compared with the control group, with no significant change in BMI or serum insulin levels among the two groups. The results reported a negative correlation between serum visfatin and HOMA-IR, providing evidence of systemic IR and lower serum visfatin in nonobese, non-overweight AD patients [111].

The effect of obesity on serum levels of visfatin in patients with PCOS was further evaluated by Abdul-Maksoud et al. [112] in a recent study conducted in Egypt and published in 2020. The study involved measuring serum levels of visfatin, insulin and HOMA-IR in 210 women (70 healthy women: 35 obese, and 35 nonobese + 140 with PCOS: 70 nonobese and 70 obese). There was upregulation of visfatin expression in PCOS, thus supporting the use of serum visfatin as a biomarker for PCOS [112].

A recent cross-sectional study was published in 2020 on the correlation between serum visfatin levels and IR in obese women. The study was conducted by Alnowihi et al. [113] in Saudi Arabia, where 83 women were recruited for the study between January 2014 and 2016, divided into three groups according to their BMI (35 obese, 15 overweight and 33 lean). The study involved the evaluation of anthropometric measurements, serum levels of visfatin, insulin, lipid profile, and HOMA-IR. The study reported significantly higher levels of visfatin, insulin, IR, and glucose in the obese group when compared with the lean and overweight groups. The study also reported a positive correlation between serum visfatin levels and BMI, WC, HC, insulin, and HOMA-IR [113].

A study on the use of salivary visfatin as a biomarker for diabetes was published in 2021. This was a case–control study conducted by Eroglu Içli and Bildaci in Turkey. It involved the collection of saliva samples from 91 pregnant women between 24 and 28 weeks’ gestation. Salivary levels of visfatin were measured using ELISA. Classification of the patients was based on their OGTT results into two groups: the GDM group, which consisted of 18 patients, and a control group comprising 73 patients with normal OGTT. The study reported a positive correlation between salivary visfatin levels and 1-h glucose levels in the GDM group, a cut-off value of 13.5 ng/mL for the expected levels of salivary visfatin, a sensitivity of 72% and a specificity of 63% of saliva visfatin as a screening test for GDM [114].

CONCLUSION

Visfatin is important in glucose homeostasis because of its insulin-like actions mediated by NAD biosynthesis. Increased visfatin levels in obesity may indicate a regulatory response to keep blood glucose levels stable. However, exceeding a threshold level appears to be associated with an increase in inflammation, which may contribute to the development of IR, T2DM, and their associated complications, such as cardiovascular and renal diseases. The available evidence supports the potential use of visfatin serum levels as a biomarker for T2DM, including GDM. Salivary visfatin levels appear to be a potential biomarker for IR. However, the number of studies assessing visfatin in saliva in relation to diabetes and related complications is still limited.
FOOTNOTES

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