Role of visfatin in obesity-induced insulin resistance

Abdalla MMI. Visfatin in obesity-induced IR

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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 drew attention due to its insulin-mimetic activity. It is released from a variety of sources, including visceral fat and macrophages; it influences glucose metabolism and increases inflammation. The relationship between visfatin and IR in obese people is debatable. As a result, the purpose of this work 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 obese people.

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 as well as 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. The current study 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 which 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 on cardiovascular and renal illness. Visfatin is an adipokine that has drawn 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[3-7].

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/6J 

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 glucose 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 II diabetic mellitus (T2DM), and IR. However, the findings are inconsistent, ranging from a positive correlation between plasma visfatin level and T2DM\(^{11,15,16}\) to the existence of an inverse relationship between plasma visfatin level and type I 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 pro-inflammatory cytokine that has been shown to have multiple physiological functions related to cell metabolism\(^{20,21}\), immune modulation\(^{20,22}\), and inflammation\(^{23,24}\). It has been found in various immune cells other than B cells and has been shown to inhibit the apoptosis of macrophages\(^{20}\). Extracellular PBEF promotes pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-\(\alpha\)), interleukin-1 (IL-1), IL-16, transforming growth factor-beta 1 (TGF-\(\beta\)), as well as the chemokine receptor (CCR3). PBEF also boosts IL-6, TNF-\(\alpha\), 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 the nicotinamide phosphoribosyltransferase enzyme (NAMPT), the enzyme which is required for the production of nicotinamide adenine dinucleotide (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\textsuperscript{[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 to SIRT7\textsuperscript{[29]}. Sirtuins are involved in various metabolic functions\textsuperscript{[30-32]}. SIRT1 deacetylases have been demonstrated to regulate many transcription factors required for cell survival, apoptosis, and proliferation, including tumor suppressor p53\textsuperscript{[33-35]}, a protein forkhead box class O protein\textsuperscript{[36-38]}, and peroxisome proliferator-activated receptor-γ coactivator-1α\textsuperscript{[39,40]}. SIRT1 also inhibits the signaling of nuclear factor-κB and suppresses inflammation\textsuperscript{[41-43]}. Visfatin may thus alter metabolic processes involved in glucose and lipid metabolism via its NAMPT enzyme-like activity\textsuperscript{[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\textsuperscript{[46,47]}. Glucose infusion elevated plasma visfatin levels in healthy participants during clamp testing\textsuperscript{[48]}. However, another study published in 2011 by Bala et al\textsuperscript{[49]} found that 75 g of 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 1 (GLP-1) on visfatin production following oral glucose ingestion might explain the effects of intravenous vs oral glucose consumption\textsuperscript{[49]}. Insulin and GLP-1 dramatically decreased visfatin secretion in vitro and in animal experiments. According to Bala et al\textsuperscript{[49]} (2011), insulin infusion 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\textsuperscript{[49]}. The authors concluded that the GLP-1’s inhibitory effect on visfatin production from 3T3-L1 adipocytes 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 in these people\textsuperscript{[50]}. Figure 2 summarizes the control of visfatin secretion in normal, healthy, and glucose-tolerant individuals.

**PHYSIOLOGICAL VS 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\textsuperscript{[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\textsuperscript{[52,53]}, endothelial dysfunction\textsuperscript{[54]}, and increase in oxidative stress\textsuperscript{[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\textsuperscript{[15,59]}, metabolic syndrome (MetS)\textsuperscript{[60]}, polycystic ovary syndrome\textsuperscript{[61]}, and T2DM-associated complications such as cardiovascular\textsuperscript{[62,63]}, cerebrovascular\textsuperscript{[64,65]}, and renal diseases\textsuperscript{[66-68]}. 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\cite{69} has demonstrated that visfatin is a major target in obesity, diabetes, and dyslipidemia\cite{70}. Visfatin interacts with insulin receptors at locations other than insulin binding sites, lowering blood glucose levels \textit{via} increased muscle and liver cell glucose utilization\cite{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, protein kinase B, and mitogen-activated protein kinase\cite{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\cite{72}.

\textbf{Central visfatin improved glucose homeostasis in diabetic rats by boosting insulin release and sensitivity \textit{via} the hypothalamus, demonstrating that visfatin is a positive modulator of glucose homeostasis \textit{via} transmitting hypothalamic signals to the periphery\cite{75}. 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\cite{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 will be 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\cite{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[21,54,75]. The proliferative, proinflammatory and proangiogenic effects of visfatin are mediated via stimulation of phosphatidylinositol 3-kinases (PI3K), nuclear factor-kb (NF-kB), and signal transducer and activator of transcription (STAT), extracellular signal-regulated kinases (ERKs) and Toll-like receptor 4 (TLR4)[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, of which it is suggested to function in a paracrine fashion on the blood vessels[11,81]. 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 were 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 of strokes because of the cerebrovascular changes induced by hyperglycemia[88]. 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 people is steadily increasing\[^91\]. An increased visfatin level was shown to be associated with the progression of CKD in both diabetics and non-diabetics\[^92,93\], an observation that can be explained by endothelial dysfunction associated with high visfatin levels\[^93\], IR\[^3\], inflammation\[^53,74,94\], oxidative stress\[^37,58\], synthesis of profibrotic molecules in the mesangial cells and an increase in the expression of renin, angiotensinogen, and angiotensin receptors (AT-1), as well as angiotensin II\[^85,96\], thus increasing the activity of NADPH oxidase. This pro-inflammatory enzyme causes an increase in glomerular permeability\[^97\]. A decrease in serum visfatin level was noted upon improving endothelial dysfunction following renal transplantation\[^88\]. 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 to other inflammatory biomarkers, and to indicate the threshold level of visfatin at which those complications appear.

ASSOCIATION BETWEEN VISFATIN LEVEL AND IR IN OBESE INDIVIDUALS
To assess the evidence on the relationship between visfatin levels and IR in obese people, 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; 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 vs 31 control. The study involved the measurement of serum visfatin and insulin using an 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 non-obese children without MetS or IR. In obese individuals, visfatin levels correlated with FPG, insulin, and HOMA-IR\textsuperscript{[99]}. 

A positive correlation between serum visfatin levels and IR among obese children was further evidenced by Salama et al\textsuperscript{[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), hip circumference (HC), and waist-to-hip ratio (WHR) were measured using standardized methods. The serum levels of insulin and visfatin were measured using ELISA. IR was calculated using HOMA-IR. The lipid profile and FPG were also measured. The study revealed significantly higher levels of serum visfatin in obese children (9.18 ± 3.04) compared with control (4.33 ± 3.01). In obese children, Spearman’s correlation analysis revealed a positive correlation between serum visfatin with height, body weight, BMI, WC, HC, and HOMA-IR\textsuperscript{[100]}.

The association between serum visfatin and IR was further evaluated in a study conducted in Turkey, Bursa, in 2015 by Gul et al\textsuperscript{[101]}. The study evaluated the plasma levels of visfatin, insulin, and HOMA-IR in 18 obese vs 19 non-obese premenopausal women with polycystic ovary syndrome (PCOS). The study revealed a significantly higher HOMA-IR among obese patients with PCOS than non-obese PCOS patients and controls with no significant difference between the groups in serum visfatin levels. The study also revealed an absence of correlation between serum visfatin levels and HOMA-IR in the studied groups\textsuperscript{[101]}. The difference between this result and the previous studies’ results can be explained by the difference in the demographics of the studied groups: Age, gender, and associated conditions.

In Poland, Liang and co-researchers evaluated the correlation between serum visfatin with glucose and lipid metabolism among pregnant women with gestational diabetes mellitus (GDM) in a prospective study conducted between 2012 and 2013. The BMI, FPG, serum visfatin, HOMA-IR, and lipid profile were assessed. The study revealed significantly higher levels of serum visfatin, FPG, HbA1c, and HOMA-IR in women with GDM than the control group. Correlation analysis showed a negative correlation between serum visfatin with FBG 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 in women with GDM. The data of this study was 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 studied by Tsiotra et al[103] in Athens, Greece, 2018. Tsiotra et al[103] evaluated the expression of visfatin in the visceral and subcutaneous adipose tissues and placenta in 15 obese and non-obese women with GDM, compared to a control group that consisted of 23 obese and non-obese women with standard glucose tolerance. The study revealed a lower circulating visfatin level in obese women with GDM than non-obese women with normal glucose tolerance. The study reported comparable visfatin mRNA expression in all tissues.

In Egypt, 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, serum levels of visfatin, CRP, IL-6, TNF-α, and HOMA-IR in 80 people with diabetes in comparison to a control group that consisted of 40 healthy control 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 the 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 United States 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 control). 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\textsuperscript{[105]}. Compared to blood sampling, saliva sampling is simple, safe and non-invasive. “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-\(\alpha\), leptin, visfatin, adiponectin, IL-6 and CRP”\textsuperscript{[106]}.

The association between serum levels of visfatin and GDM was further investigated in a study conducted by Souvannavong-Vilivong \textit{et al}\textsuperscript{[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 to 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\textsuperscript{[107]}.

The usefulness of serum visfatin as a biomarker for GDM was further investigated by Bawah \textit{et al}\textsuperscript{[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, leptin, and lipid profile were assessed. The study reported significantly higher serum visfatin levels in patients with GDM compared to the control. 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\textsuperscript{[108]}. 

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Additional evidence of the increased serum visfatin in women with GDM was provided in a study conducted by Manoharan et al\textsuperscript{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\textsuperscript{109}.

The association between serum visfatin and IR among obese children was further evaluated in a study conducted by Yin et al\textsuperscript{110} in China and published in 2019. A total of 244 children (160 obese and 84 Lean) were recruited for this study. The study involved assessing serum levels of visfatin, high-sensitivity CRP (hs-CRP), TNF-\(\alpha\), IL-6, angiotensin-2, vascular cellular adhesion molecule-1 (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 control. The study found a positive correlation between serum visfatin with each of the following: BMI, WC, hs-CRP, TNF-\(\alpha\), 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\textsuperscript{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\textsuperscript{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 a decrease in serum visfatin levels in patients with AD compared to 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 non-obese, non-overweight AD patients\textsuperscript{111}. 


The effect of obesity on serum levels of visfatin in patients with PCOS was further evaluated by Abdul-Maksoud et al.[312] 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 non-obese + 140 with PCOS: 70 non-obese and 70 obese). The results reported an upregulation of visfatin expression in PCOS, thus supporting the use of serum visfatin as a biomarker for PCOS[312].

In addition, 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 to 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].

Another 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 Icli and Bildaci in Turkey. It involved the collection of saliva samples from 91 pregnant women between their 24th through 28th weeks of pregnancy. 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-hour 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.

Figure 1 Visfatin’s journey from an insulin-mimetic to the enzyme (nicotinamide phosphoribosyltransferase enzyme).

Figure 2 Regulation of visfatin in normal healthy- glucose tolerant individuals. GLP-1: Glucagon-like peptide 1.

Figure 3 Role of visfatin in glucose homeostasis in glucose tolerant vs glucose-intolerant individuals.
### PRIMARY SOURCES

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<td>75</td>
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<td>&quot;42nd EASD Annual Meeting of the European Association for the Study of Diabetes&quot;, Diabetologia, 2006</td>
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<tr>
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<td>bmcendocrdisord.biomedcentral.com</td>
<td>36</td>
<td>1%</td>
</tr>
<tr>
<td>7</td>
<td>Ernest Adeghate. &quot;Visfatin: Structure, Function and Relation to Diabetes Mellitus and Other Dysfunctions&quot;, Current Medicinal Chemistry, 2008</td>
<td>34</td>
<td>1%</td>
</tr>
<tr>
<td>8</td>
<td>Zhaoxia Liang, Ying Wu, Jianyun Xu, Qin Fang, Danqing Chen. &quot;Correlations of serum visfatin and</td>
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<td>9</td>
<td>Metabolisms of glucose and lipid in women with gestational diabetes mellitus</td>
<td>Journal of Diabetes Investigation, 2015</td>
<td>bsdwebstorage.blob.core.windows.net</td>
</tr>
<tr>
<td>11</td>
<td>Tania Siahanidou, Alexandra Margeli, Athanasios Kappis, Ioannis Papassotiriou, Helen Mandyla. &quot;Circulating visfatin levels in healthy preterm infants are independently associated with high-density lipoprotein cholesterol levels and dietary long-chain polyunsaturated fatty acids&quot;</td>
<td>Metabolism, 2011</td>
<td><a href="http://www.mdpi.com">www.mdpi.com</a></td>
</tr>
<tr>
<td>13</td>
<td>Da Sol Kim, Suna Kang, Na Rang Moon, Sunmin Park. &quot;Central visfatin potentiates glucose-stimulated insulin secretion and β-cell mass without increasing serum visfatin levels in diabetic rats&quot;</td>
<td>Cytokine, 2014</td>
<td>publish.kne-publishing.com</td>
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<td>15</td>
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<td>ijcrr.com</td>
<td></td>
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J. Tooke. "The association between insulin resistance and endotheliopathy", Diabetes, Obesity and Metabolism, 2002


Brema Imad. "The Relationship between Plasma Visfatin/Nampt and Type 2 Diabetes, Obesity, Insulin Resistance, and Cardiovascular Disease", Endocrinology & Metabolism International Journal, 2016

Chunyan Yin, Wei Hu, Ming Wang, Yanfeng Xiao. "The role of the adipocytokines vaspin and visfatin in vascular endothelial function and insulin resistance in obese children", BMC Endocrine Disorders, 2019

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<td>jamanetwork.com</td>
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<td><a href="http://www.dovepress.com">www.dovepress.com</a></td>
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<td>26</td>
<td>Neda Roshanravan, Mohammad Alizadeh, Mohammad Asghari Jafarabadi, Naimeh Mesri Alamdari et al.</td>
<td>&quot;Effect of prenatal zinc supplementation on adipose tissue-derived hormones and neonatal weight, height and head circumference in women with impaired glucose tolerance test: randomized clinical controlled trial&quot;, International Journal of Diabetes in Developing Countries, 2019</td>
<td>Crossref</td>
<td>2019</td>
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<td>27</td>
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<td>erj.ersjournals.com</td>
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<td>link.springer.com</td>
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<td>lupus.bmj.com</td>
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</table>
Siahanidou, T.. "Circulating visfatin levels in healthy preterm infants are independently associated with high-density lipoprotein cholesterol levels and dietary long-chain polyunsaturated fatty acids", Metabolism, 201103


Dikbas, Oguz, Mehmet Tosun, Cemal Bes, Sukru Burak Tonuk, Ozge Yilmaz Aksehirli, and Mehmet Soy. "Serum levels of visfatin, resistin and adiponectin in