

# The Role of Visfatin in Pregnancy, Complications and Procreation

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## Abstract

Adipose tissue is considered an endocrine organ secreting numerous neuroendocrine and peripheral peptides, also known as “adipokines.” Although, the role of adipokines, precisely visfatin, is still controversial, it was recently discovered their involvement in different mechanisms, including metabolism, inflammation, and endocrine-immunologic system. A literature search of electronic databases was undertaken for the major studies published from 1957 to present. The databases searched were: PubMed, EMBASE, Orphanet, Midline, and Cochrane Library. This review aims to emphasize the molecular and endocrine mechanisms of visfatin and its role in fetal development. This review also reviews the role of adipocytokine in the pathogenesis of inflammatory-endocrine disorders. Further research will bring new insight into linkage between visfatin and humans, during pregnancy and perinatal period.

## Keywords

- ▶ visfatin
- ▶ newborns
- ▶ pregnancy
- ▶ gestational diabetes mellitus
- ▶ preeclampsia
- ▶ breast-feeding

## Introduction

Adipose tissue is considered as an endocrine organ secreting numerous neuroendocrine and peripheral peptides, called adipokines (adiponectin, leptin, resistin,<sup>1</sup> vaspin, apelin, visfatin, tumor necrosis factor- $\alpha$  [TNF- $\alpha$ ], acylation-stimulating protein [ASP], interleukin-6 [IL-6], plasminogen activator inhibitor-1 [PAI-1], and transforming growth factor- $\beta$  [TGF- $\beta$ ]<sup>2,3</sup>). They act as inflammatory molecules, playing a critical role in both short- and long-time energy homeostasis, metabolic processes, and body fat regulation.<sup>4</sup>

Moreover, these peptides are considered as a new link between obesity, insulin resistance,<sup>5</sup> cardiovascular disease, hypertension, as well as hyperlipidemia.<sup>6</sup>

This review aims to emphasize the molecular and endocrine mechanisms of visfatin and its role in fetal development.

## Review

Nicotinamide phosphoribosyltransferase (Nampt) has been identified originally as pre-B-cell colony-enhancing factor (PBEF), capable of promoting the maturation of B-cell precursors together with IL-7 and stem cell factor (SCF).<sup>7</sup> It was rediscovered as an adipocytokine, also known as “visfatin,”

found in visceral adipose tissue, playing a role in glucose homeostasis.<sup>8,9</sup> Nampt has also been identified as nicotinamide adenine dinucleotide (NAD) biosynthetic enzyme. However, some of its functions are controversial and are still being discussed. Nampt exists in two different types: intracellular (iNampt) and extracellular (eNampt) forms.

## iNampt

In 1957,<sup>10</sup> iNampt was identified as NAD biosynthetic enzyme.<sup>11</sup> In mammals, tryptophan, nicotinic acid, and nicotinamide are the major precursors for NAD, but nicotinamide is mainly used to synthesize it.<sup>12</sup>

Nampt promotes the transfer of a phosphoribosyl group from 5-phosphoribosyl-1-pyrophosphate (PRPP) to nicotinamide, forming nicotinamide mononucleotide (NMN) and pyrophosphate (PPi).<sup>13</sup> NMN is then converted to NAD by nicotinamide mononucleotide adenylyltransferase. NAD plays a critical role in cellular redox reactions. Furthermore, NAD is useful for deacetylase activity of proteins and synthesis of transcriptional regulation factor (e.g., silent information regulator [SIR]).<sup>14,15</sup> SIR, NAD-dependent enzymes called *sirtuins*, mediates life span extension cell (mouse fibroblasts, human vascular smooth muscle cells, cardiac myocytes, and pancreatic B cells) caused by variety of stresses as well as

nutritional restriction.<sup>16</sup> In fact, pancreatic B-cell-specific Sirt2-overexpressing (BESTO) mice show strongly enhanced glucose-stimulated insulin secretion (GSIS) and enhanced glucose tolerance. These findings suggest a further Nampt-mediated role in metabolic balance.<sup>17,18</sup>

### eNampt

The molecular mechanism of secretion (through passive and/or active secretory pathway)<sup>18,19</sup> and the role of eNampt are not still clear.<sup>20</sup> Three different functions have been assigned to eNampt: insulin-mimetic hormone (adipocytokine named “visfatin”), cytokine, and aNAD biosynthetic enzyme.<sup>21</sup>

Visfatin has a molecular weight of 52 kDa. The coding region of the gene encodes for 491 amino acids.<sup>22</sup> It is synthesized by the bone marrow, liver, lungs, skeletal muscle, brain, heart, pancreas, and peripheral blood lymphocytes.<sup>23</sup>

In particular, it is mostly expressed in human visceral fat.<sup>24</sup> In a case-control study conducted on prepubertal obese children, it was demonstrated that obese patients have higher concentrations than normal-weight people. Elevated serum visfatin levels were also positively correlated with body fat mass; in fact visfatin concentration decreases when weight loss occurs.<sup>25</sup>

Friebe and colleagues, in an experimental study, revealed that its expression is higher in adipocytes compared with preadipocytes,<sup>9</sup> suggesting that visfatin is a differentiated adipocytes-specific molecule and its production is influenced by serum lipid levels.

The role of visfatin in glucose metabolism is still unclear.

Several case-control studies assessed that visfatin was related to several conditions such as insulin resistance, obesity, dyslipidemia, and metabolic syndrome.<sup>26–29</sup>

In fact, Tascilar and colleagues noted that visfatin is correlated with homeostatic model assessment-insulin resistance (HOMA-IR) in children.<sup>27</sup> However, in comparative study, Berndt and colleagues noted that plasma visfatin correlates significantly with percent body fat, body mass index (BMI), and visfatin messenger RNA (mRNA) level in visceral adipose tissue, but not with visceral fat mass or waist-to-hip ratio.<sup>28</sup> Furthermore, no relationship was observed between serum visfatin levels and fasting plasma insulin, fasting glucose and insulin sensitivity in nondiabetic subjects. In two recent studies, plasma visfatin was higher in patients with type 2 diabetes mellitus (T2DM) than in control group.<sup>29</sup>

Probably, visfatin promotes a glucose uptake (through 3T3L1 on adipocytes and L6 on myocytes and glycolysis, regardless insulin).<sup>30</sup> In fact, visfatin binds the same insulin receptor through a distinct epitope.<sup>24</sup>

Visfatin, stimulated phosphorylation of insulin receptor substrate (IRS)-1/2 and activate phosphatidyl inositol 3-kinase (PI3K), induced glucose uptake, glucose transporter (GLUT)-1 protein expression, production of profibrotic factors (including type 1 collagenase, TGF- $\beta$  1, PAI-1), increased metalloproteinase-9 activity in THP-1 cells (monocyte-like cell line derived from a patient with acute monocytic leukemia), and production of TNF- $\alpha$  and IL-8 in peripheral blood mononuclear cells.<sup>31</sup>

Friebe and colleagues assessed that Nampt influenced leucocyte count and this latter is also correlated to insulin resistance and obesity.<sup>32</sup>

In fact, eNampt, proinflammatory transcription factor nuclear factor- $\kappa$ B (NF- $\kappa$ B) in a reactive oxygen species (ROS)-dependent manner, induces the adhesion of leukocytes to endothelial cells, by activating intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1.

These evidences suggest underlying low-grade vascular inflammation in obesity and T2DM.<sup>33</sup>

### Visfatin and Inflammation

In experimental research, Moschen and colleagues demonstrated inflammatory activities of visfatin. In fact, its serum levels were higher in patients with inflammatory disease than in healthy controls<sup>20,30</sup> (►Table 1). Visfatin seemed to induce human leukocytes and pro- and anti-inflammatory cytokine production: IL-1b, IL-1Ra, IL-6 (in synovial<sup>34</sup> and amniotic epithelial cells), IL-8 (in neutrophils<sup>35</sup>), IL-10, and TNF- $\alpha$  (in monocytes,<sup>31</sup> macrophages,<sup>36</sup> and neutrophils).<sup>20,30</sup> Furthermore, visfatin increased the surface expression of costimulatory molecules CD54, CD40, and CD80 (►Fig. 1). These effects involved p38 as well as MEK1 pathways as determined by inhibition with MAPK inhibitors and activation of NF- $\kappa$ B. In addition, macrophages, dendritic, and epithelial cells might be a source of visfatin. These data confirmed a proinflammatory role of this adipocytokine.<sup>30</sup>

### Visfatin and Pregnancy

During pregnancy, changes in maternal metabolism and redistribution of maternal adipose tissue occur in response to growing and metabolic needs of fetus and placenta. In particular, during fetal development, visfatin is expressed in exocrine and endocrine tissue. iNampt is highly released by fetal membranes, amnion, myometrium, placenta, and adipose tissue.

The amnion and deciduae at term contained higher levels of PBEF mRNA.<sup>37</sup>

However, the release and regulatory mechanisms of visfatin in the fetus and the neonate remain unclear. Probably, it may be regulated by glucose and insulin,<sup>38</sup> and it increases with progressive B-cell deterioration, insulin resistance, and maternal weight.<sup>29,39</sup>

Serum visfatin levels fluctuate with advancing gestation. Mastorakos and colleagues recorded that median concentration of visfatin were higher in the second (24–26 weeks) and third trimesters (34–36 weeks).<sup>40</sup>

Nampt seems to confer protection from apoptosis<sup>41</sup> and to increase infection-induced response. It also promotes the release of inflammatory cytokines, such as IL-6 and IL-8, in amnion-like epithelial cells in sepsis patients.<sup>20</sup> Therefore, Cekmez and colleagues, in case-control study (►Table 1), proposed that visfatin could be used as a diagnostic marker similar to C-reactive protein (CRP), procalcitonin, and IL-6 in neonatal sepsis.<sup>42</sup>

**Table 1** Descriptive table of the most important studies conducted on Visfatin function

Type of study	Authors
Case-control	Tascilar and colleagues <sup>27</sup>
	Chen and colleagues <sup>29</sup>
	Cekmez and colleagues <sup>42</sup>
	Chan and colleagues <sup>55</sup>
	Pagano and colleagues <sup>56</sup>
	Yanni and colleagues <sup>61</sup>
	Giapros and colleagues <sup>62</sup>
	Cekmez and colleagues <sup>63</sup>
	Kim and colleagues <sup>72</sup>
	Demir and colleagues <sup>73</sup>
Experimental	Friebe and colleagues <sup>9</sup>
	Moschen and colleagues <sup>30</sup>
	Yonezawa and colleagues <sup>65</sup>
Cross-sectional	Mazaki-Tovi and colleagues <sup>51</sup>
Comparative	Berndt and colleagues <sup>28</sup>
	Zhaoxia and colleagues <sup>57</sup>
Research support	Martos-Moreno and colleagues <sup>25</sup>
	Mu and colleagues <sup>26</sup>
	Ferreira and colleagues <sup>70</sup>
Prospective	Malamitsi-Puchner A and colleagues <sup>52</sup>
Review	Garten A and colleagues <sup>20</sup>
Abstract	Milovanov and colleagues <sup>71</sup>

After birth, Nampt expression decreases in exocrine tissue but remains in endocrine cells, predominately  $\beta$  cells.<sup>23</sup>

Unlike term newborns, a preterm infant frequently shows glucose homeostasis imbalance.<sup>43</sup> After hypoglycemic phase, because of limited glycogen and fat stores, hyperglycemia occurs for a condition of insulin resistance, relative insulin deficiency, and increased ratio of the glucose transporters (Glut)-1/Glut-2 in fetal tissues.<sup>44</sup> Several studies have confirmed that alterations in circulating adipokines can be associated with adaptations to gestation, as well as in complications of pregnancy.<sup>45</sup> Precisely, hypoadiponectinemia has been shown to be associated with insulin resistance,<sup>46</sup> leptin may influence the “programming” of satiety,<sup>47,48</sup> and visfatin can increase in parallel with hyperglycemia for insulin-like effect.<sup>49</sup>

In fact, several studies demonstrated that higher maternal plasma visfatin concentration is associated with insulin resistance, gestational diabetes mellitus (GDM), patients with small-for-gestational-age (SGA),<sup>50,51</sup> and neonates with intrauterine growth restriction (IUGR).<sup>52</sup>

### Visfatin and Gestational Diabetes Mellitus

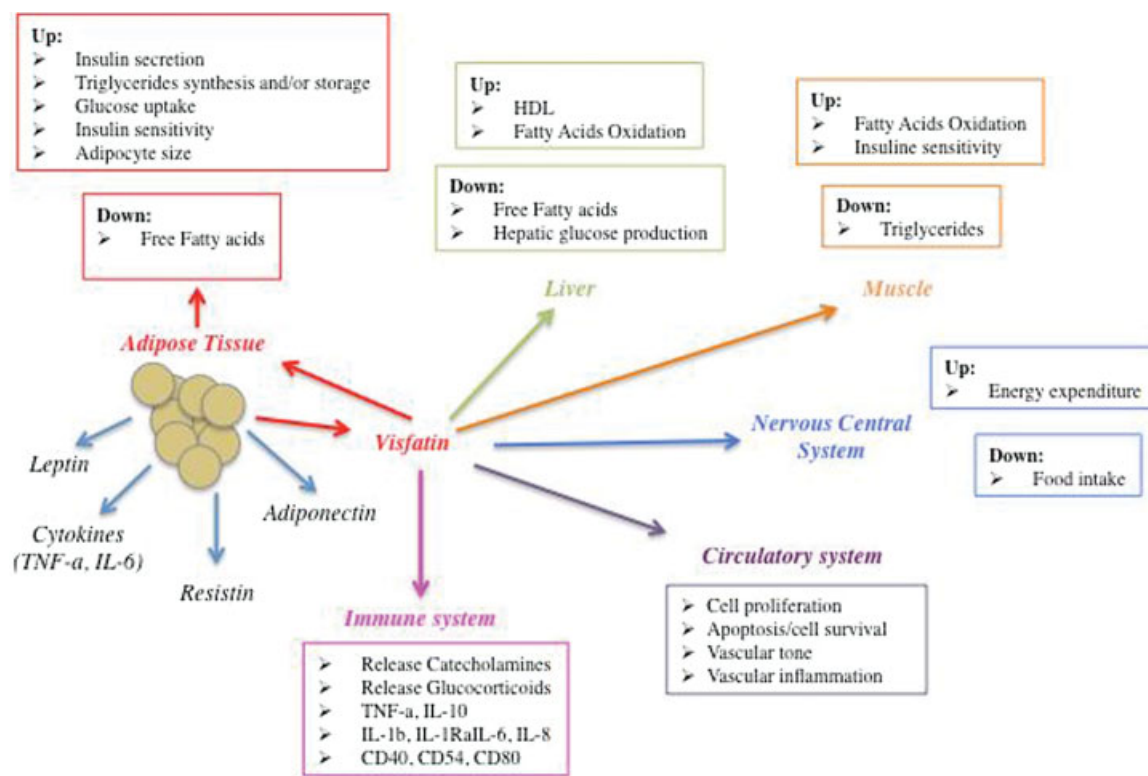
It has been reported increased serum visfatin levels during pregnancy, in T1DM or T2DM, and in obese patients.<sup>39</sup> Insulin

resistance is accompanied by increased visfatin production and/or secretion, it reflect a compensatory mechanism favoring insulin deficiency. In fact, a gradually increasing insulin resistance during 1st and 2nd trimester of pregnancy may be compensated for by a sustained increase of visfatin, an insulinomimetic molecule.<sup>8,53</sup> However, visfatin did not change in a similar way during all 3 trimesters. This condition can be attributable to an increase of visfatin production by an additional source other than adipose tissue, the placenta. Therefore, the increased serum concentration observed in gestational diabetes mellitus (GDM) may result from placental oversecretion.<sup>54</sup> Insulin resistance is physiologic in women with normal pregnancies and it is directly correlated with gestational age. Women affected by GDM showed hyperglycemia and hyperinsulinemia. Insulin response can decrease by up to 40% in late pregnancy.<sup>40</sup> Other studies, however, have revealed opposite effects in gestational diabetes<sup>55</sup> and obesity.<sup>56</sup> Zhaoxia and colleagues evaluated visfatin levels in normal pregnancy and in women with GDM. They found that visfatin levels increased following oral glucose in normal pregnancy, and this directly correlated with glycemia, cholesterol, and insulin resistance. Otherwise, serum visfatin levels were lower in women with GDM<sup>57</sup> (► Fig. 1).

### Visfatin in IUGR and SGA Newborns

Recently, a relationship between circulating maternal visfatin and fetal growth has been proposed. In the third trimester of pregnancy, Fasshauer and colleagues reported that women with fetal growth restriction (FGR) presented higher plasma maternal visfatin than with control group.<sup>58</sup> It has been hypothesized that visceral adipose tissue is the major source of visfatin,<sup>8</sup> and data suggest that low-birth-weight (LBW) and IUGR newborns may have increased visceral fat stores. Therefore, Malamitsi-Puchner and colleagues prospectively considered that visfatin might be considered as biomarker for metabolic syndrome in IUGR.<sup>52</sup> However, Harrington and colleagues did not note differences in fat distribution between newborns with IUGR and control group.<sup>59</sup> Other authors noted that cord blood visfatin concentrations did not differ between SGA and adequate-for-gestational-age (AGA) newborns. Some studies showed that cord serum visfatin is closely associated with indices of fetal size in infants from smoking mothers, but not control group.<sup>60</sup> Otherwise, other authors achieved opposite results finding higher visfatin levels in large-for-gestational-age (LGA) newborns. In cross-sectional study Mazaki-Tovi and colleagues investigated the linkage between visfatin and risk of development of GDM and fetal size, precisely in LGA neonate.<sup>45</sup> In response to maternal hyperglycemia, fetus develops hyperglycemia and hyperinsulinemia due to pancreatic islet cells stimulation. In LGA neonates, hyperinsulinemia in utero leads to fetal macrosomia. LGA, SGA, and LBW newborns have an increased risk for developing metabolic syndrome in adulthood.<sup>49</sup>

Recently, however, it has been reported that preterm newborn, whether SGA or AGA, with normal BMI, did not show insulin resistance in childhood. There were no detected



**Fig. 1** Visfatin secretion and function. HDL, high-density lipoprotein; IL-6, interleukin-6; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ .

significant differences in adipocytokine levels between the preterm SGA and AGA groups.<sup>61,62</sup>

However, in a control study, it has been suggested that, independent of being SGA or LBW, visfatin might be an early indicator of insulin resistance.<sup>63</sup> It was also noted lower adiponeptin and higher visfatin levels in LGA and SGA than AGA neonates.<sup>52</sup> Consistently, an increased release of visfatin was demonstrated in the amnion of twins and triplets. It can be assumed maternal plasma visfatin also derived from the stretched fetal membranes of women with LGA fetuses.<sup>64</sup> These data suggest that visfatin is a possible link between maternal and fetal environment.

## Visfatin and Breast-Feeding

In the first 6 months of lactation, Yonezawa and colleagues demonstrated, in animal/experimental study, the presence of mRNA-visfatin in cloned bovine mammary gland and human breast cancer cell line.<sup>65</sup> Moreover, milk visfatin levels are directly related to preconceptional maternal BMI. In fact, it has been found higher breast milk visfatin concentrations for a BMI greater than 28 to 30 kg/m<sup>2</sup>. Visfatin seems to limit a weight loss in newborns.<sup>66</sup>

## Visfatin and Preeclampsia

Preeclampsia (PE) is a multisystemic disorder of pregnancy, characterized by onset hypertension, endothelial dysfunction, and proteinuria that develop after 20 weeks of gestation in previously normotensive women.<sup>67</sup> The precise cause of PE is still unclear, but it is believed to be likely multifactorial. The

role of visfatin in PE was investigated by several studies. Circulating visfatin concentrations are increased in PE in some studies,<sup>68</sup> whereas other investigators show similar<sup>52</sup> or even decreased concentrations.<sup>69</sup> Ferreira and colleagues hypothesized that visfatin develops PE, promoting an impaired placental vascularization, due to increased serum vascular endothelial growth factor (VEGF) levels<sup>70</sup> (→Fig. 1). Conversely, Milovanov and colleagues noted decreased expression of VEGF as well as visfatin in pregnancies complicated by PE.<sup>71</sup> During the third trimester of pregnancy, in women affected by PE, Kim and colleagues further showed decreased placental visfatin levels.<sup>72</sup> Although the severity of PE did not influence serum visfatin values, authors investigated relationship between PE, gestational age (SGA), and maternal circulating visfatin concentrations. These were higher in women who delivered SGA newborns than normal pregnancy and PE groups.<sup>73</sup> However, further studies did not confirm these data.<sup>51</sup>

In conclusions, though the primary purpose of adipose tissue is energy storage, it has been also identified as an active endocrine-immune organ releasing many cytokines (adipocytokines) and hormones. In response to an autocrine and paracrine manner to impair adipocyte function, it has been reported that phenotypic changes of adipocytes occur into inflammatory response and promote a variety of diseases. Here, we have focused on visfatin expression, a recently identified adipocytokine. Although its precise function remains to be established, this review aims to emphasize the molecular and endocrine mechanisms of visfatin and to clarify its role in the pathophysiology of inflammatory-endocrine disorders, also during normal and pathologic pregnancy

(e.g., PE, GDM, and alteration of fetal growth). Moreover, for its potential diagnostic and/or prognostic role in the prediction of any associate disease or condition, visfatin could also be considered as a new biomarker, indicating specific disorders in the neonatal metabolic profile, determining the interconnection of the different processes, and defining disease severity. In addition, several diseases could be treated by normalization and/or regulation of the proinflammatory cytokine/adipokine profile. For these novel concepts, visfatin might be promising candidates for future pharmacologic treatment strategies. Further research will bring new insight into linkage between visfatin and humans, during pregnancy and perinatal period.

#### Authors' Contributions

All authors read and approved the final manuscript.

#### Conflict of Interest

None.

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