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,1 vaspin, apelin, visfatin, tumor necrosis factor-α [TNF-α], acylation-stimulating protein [ASP], interleukin-6 [IL-6], plasminogen activator inhibitor-1 [PAI-1], and transforming growth factor-β [TGF-β]2,3). They act as inflammatory molecules, playing a critical role in both short- and long-time energy homeostasis, metabolic processes, and body fat regulation.4

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

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).7 It was rediscovered as an adipocytokine, also known as “visfatin,” found in visceral adipose tissue, playing a role in glucose homeostasis.8,9 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 1957,10 iNampt was identified as NAD biosynthetic enzyme.11 In mammals, tryptophan, nicotinic acid, and nicotinamide are the major precursors for NAD, but nicotinamide is mainly used to synthesize it.12

Nampt promotes the transfer of a phosphoribosyl group from 5-phosphoribosyl-1-pyrophosphate (PRPP) to nicotinamide, forming nicotinamide mononucleotide (NMN) and pyrophosphate (PPI).13 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]).14,15 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...
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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.17,18

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.20,30 (Table 1). Visfatin seemed to induce human leukocytes and pro- and anti-inflammatory cytokine production: IL-1β, IL-1Ra, IL-6 (in synovia34 and amniotic epithelial cells), IL-8 (in neutrophils35), IL-10, and TNF-α (in monocytes31, macrophages36 and neutrophils).20,30 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-κB. In addition, macrophages, dendritic, and epithelial cells might be a source of visfatin. These data confirmed a proinflammatory role of this adipocytokine.30

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 PBEC mRNA.37 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,38 and it increases with progressive B-cell deterioration, insulin resistance, and maternal weight.29,39

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).40 Nampt seems to confer protection from apoptosis41 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.20 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), procalcin, and IL-6 in neonatal sepsis.42

Friebe and colleagues assessed that Nampt influenced leukocyte count and this latter is also correlated to insulin resistance and obesity.32 In fact, eNampt, proinflammatory transcription factor nuclear factor-κB (NF-κB) 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.33

Visfatin and Newborn: Underlying Mechanisms

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.26–29

In fact, Tasclilar and colleagues noted that visfatin is correlated with homeostatic model assessment–insulin resistance (HOMA-IR) in children.27 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.28 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.29

Probably, visfatin promotes a glucose uptake (through 3T311 on adipocytes and L6 on myocytes and glycolysis, regardless insulin).30 In fact, visfatin binds the same insulin receptor through a distinct epitope.24

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 I collagenase, TGF-β 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-α and IL-8 in peripheral blood mononuclear cells.33

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Visfatin and Gestational Diabetes Mellitus

It has been reported increased serum visfatin levels during pregnancy, in T1DM or T2DM, and in obese patients. 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. 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.

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. It has been hypothesized that visceral adipose tissue is the major source of visfatin, 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. However, Harrington and colleagues did not note differences in fat distribution between newborns with IUGR and control group. 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. 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. In recent years, several studies investigated the relationship between circulating visfatin and risk of development of GDM and fetal size. Mazaki-Tovi and colleagues established the association between visfatin levels and fetal macrosomia. In AGA newborns, visfatin was lower than in LGA newborns. There was a positive correlation between visfatin levels and fetal macrosomia in AGA newborns. In SGA newborns, visfatin levels were lower than in AGA newborns. In cross-sectional study, lower visfatin levels were observed in AGA newborns. In LGA newborns, higher visfatin levels were observed. In SGA newborns, lower visfatin levels were observed. There was a positive correlation between visfatin levels and fetal macrosomia in AGA newborns. In SGA newborns, lower visfatin levels were observed.

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

<table>
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<tr>
<th>Type of study</th>
<th>Authors</th>
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<tbody>
<tr>
<td>Case–control</td>
<td>Tascilar and colleagues 27 Chen and colleagues 29 Cekmez and colleagues 42 Chan and colleagues 35 Pagano and colleagues 56 Yanni and colleagues 61 Giapros and colleagues 62 Cekmez and colleagues 63 Kim and colleagues 72 Demir and colleagues 73</td>
</tr>
<tr>
<td>Experimental</td>
<td>Friebe and colleagues 9 Moschen and colleagues 10 Yonezawa and colleagues 65</td>
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<tr>
<td>Cross-sectional</td>
<td>Mazaki-Tovi and colleagues 51</td>
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<tr>
<td>Comparative</td>
<td>Berndt and colleagues 28 Zhaoxia and colleagues 57</td>
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<tr>
<td>Research support</td>
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<td>Prospective</td>
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<td>Garten A and colleagues 20</td>
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After birth, Nampt expression decreases in exocrine tissue but remains in endocrine cells, predominately β cells. Unlike term newborns, a preterm infant frequently shows glucose homeostasis imbalance. 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. Several studies have confirmed that alterations in circulating adipokines can be associated with adaptations to gestation, as well as in complications of pregnancy. Precisely, hypoadiponectinemia has been shown to be associated with insulin resistance. Leptin may influence the “programming” of satiety, and visfatin can increase in parallel with hyperglycemia for insulin-like effect.

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), and neonates with intrauterine growth restriction (IUGR).
significant differences in adipocytokine levels between the preterm SGA and AGA groups.\textsuperscript{61,62}

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.\textsuperscript{63} It was also noted lower adipocytokine and higher visfatin levels in LGA and SGA than AGA neonates.\textsuperscript{52} 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.\textsuperscript{64} 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.\textsuperscript{65} 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\(^2\). Visfatin seems to limit a weight loss in newborns.\textsuperscript{66}

**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.\textsuperscript{67} 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,\textsuperscript{68} whereas other investigators show similar or even decreased concentrations.\textsuperscript{69} Ferreira and colleagues hypothesized that visfatin develops PE, promoting an impaired placental vascularization, due to increased serum vascular endothelial growth factor (VEGF) levels\textsuperscript{70} (\textbf{Fig. 1}). Conversely, Milovanov and colleagues noted decreased expression of VEGF as well as visfatin in pregnancies complicated by PE.\textsuperscript{71} During the third trimester of pregnancy, in women affected by PE, Kim and colleagues further showed decreased placental visfatin levels.\textsuperscript{72} 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.\textsuperscript{73} However, further studies did not confirm these data.\textsuperscript{51}

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.

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**Fig. 1** Visfatin secretion and function. HDL, high-density lipoprotein; IL-6, interleukin-6; TNF-\(\alpha\), tumor necrosis factor-\(\alpha\).
cytokine/adipokine pro and perinatal period. into linkage between visfatin and humans, during pregnancy 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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