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AN OVERVIEW OF ROLE OF VISFATIN IN PREDIABETES

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Abstract

Background: Excess adiposity has been heralded as the most important risk in the development of insulin resistance, pre-diabetes, and type-2 DM. Adipose tissue has been recognized not only a storehouse for energy and lipid storage, but it has emerged as a major endocrine, metabolically active organ producing numerous proteins and enzymes as well as adipocyte derived hormones now globally defined as adipokines. Visfatin acts as nicotinamide phosphoribosyl transferase, catalyzing the rate-limiting step in the biosynthesis of Nicotinamide Adenine Dinucleotide (NAD). Visfatin has anti-apoptotic properties and regulates energy metabolism during stress responses. It also plays arole in immune activation. It has been suggested that increased visceral fat in these patients induces a state of inflammation which may lead to insulin resistance.

Keywords: Visfatin, Prediabetes.

Background

Prediabetes is the term used for individuals whose glucose levels do not meet the criteria for diabetes but are too high to be considered normal. Patients with prediabetes are defined by the presence of IFG and/or IGT and/or A1C 5.7–6.4% (39–47 mmol/mol) (Table 1). Prediabetes should not be viewed as a clinical entity in its own right but rather as an increased risk for diabetes and cardiovascular disease (CVD) **(1).**

Table (1): Criteria defining prediabetes**(1)**

FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)
OR
2-h PG during 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)
OR
A1C 5.7–6.4% (39–47 mmol/mol)

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; 2-h PG, 2-h plasma glucose. *For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at the higher end of the range.

Criteria for testing for diabetes or prediabetes in asymptomatic adults is outlined in Table 2.3. Prediabetes is associated with obesity (especially abdominal or visceral obesity), dyslipidemia with high triglycerides and/or low HDL cholesterol, and hypertension **(2).**

Table (2): Criteria for testing for diabetes or prediabetes in asymptomatic adults**(1).**

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1. Testing should be considered in adults with overweight or obesity (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) who have one or more of the following risk factors:
   - First-degree relative with diabetes
   - High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
   - History of CVD
   - Hypertension (≥140/90 mmHg or on therapy for hypertension)
   - HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
   - Women with polycystic ovary syndrome
   - Physical inactivity
   - Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
2. Patients with prediabetes (A1C ≥5.7% [39 mmol/mol], IGT, or IFG) should be tested yearly.
3. Women who were diagnosed with GDM should have lifelong testing at least every 3 years.
4. For all other patients, testing should begin at age 45 years.
5. If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.
6. HIV

CVD, cardiovascular disease; GDM, gestational diabetes mellitus; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

Visfatin was first described by **Fukuhara et al. (3)**they showed that visfatin is expressed mainly by visceral adipose tissue with insulin-like effects **(3).**

However, the same molecule was previously identified as Pre-B colony Enhancing Factor (PBEF), a growth factor involved in the early development of B lymphocytes. PBEF was previously shown to be synthesized in several tissues including liver, bone marrow, skeletal muscle, neutrophils and fetal membranes **(4).**

Because of the role of visfatin in inflammation and in obesity (a low-grade inflammatory process), it has been postulated that visfatin may play a role in innate immunity. So, visfatin was previously identified as PBEF, its expression in visceral adipose tissue and insulin like effects are novel **(5, 6).**

Role of Visfatin in Prediabetes

Visfatin is believed to exhibit endocrine, paracrine and autocrine activities. The autocrine effects of visfatin may play an important role in regulating insulin sensitivity in the liver **(7, 8).**

In mice, visfatin was found to play an important role in the reduction of the blood glucose concentration. Visfatin displays insulin mimetic effects, which was thought to be mediated through the phosphorylation of signal transduction proteins in the insulin signalling pathway and through binding to the insulin receptor at a site distinct from that of insulin **(9).**

It was also demonstrated that serum visfatin levels were significantly higher in the diabetic compared with the nondiabetic group and found a significant positive correlation of serum visfatin levels with the obesity indicator BMI and waist circumference, even after adjusting for age, sex, smoking status, blood pressure and lipid profile **(10).**

Visfatin is an essential for NAD (nicotinamide adenine di-nucleotide) production, and it exists both in intra and extracellular environments. Mice with heterozygous mutations in the visfatin gene display glucose intolerance mainly due to insulin secretion deficiency, and this insulin secretion defect can be corrected by the administration of nicotinamide mononucleotide (NMN), the product of visfatin in NAD biosynthesis **(7).**

Because the pancreas has very low levels of intracellular visfatin, some have suggested that the maintenance of high NMN circulating levels by extracellular visfatin are critical for normal beta cell function **(7).**

A study that investigated glucose uptake in animal hepatocytes with reduced visfatin expression demonstrated reduced NAD biosynthesis and a significantly decreased incremental uptake of glucose after stimulation with insulin when compared with control hepatocytes with normal visfatin expression **(8).**

A negative correlation of visfatin levels with beta-cell function was demonstrated by studying acute insulin secretion assessed via an intravenous glucose tolerance test **(7).**

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Furthermore, continuous glucose infusion in humans acutely increases visfatin levels. This effect is suppressed by insulin or somatostatin infusion. The relationship between insulin resistance and blood or tissue visfatin concentrations remains unclear. Some studies indicate that blood visfatin concentrations significantly correlate with insulin resistance or type 2 diabetes but not with body fat percentage or body mass index (BMI) **(11).**

Other studies demonstrated that the association between diabetes and blood visfatin concentrations was not significant after adjusting for body mass index (BMI) and waist circumference **(7).**

A study found that visfatin levels were inversely associated with insulin resistance in non-diabetic obese women with energy restricted diet intervention. The natural history of type 2 diabetes (T2D) has been demonstrated to pass through an intermediate stage of impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT), which is designated as impaired glucose regulation (IGR) by the World Health Organization (WHO) or pre-diabetes by the American Diabetic Association (ADA) **(12).**

The role of visfatin as an adipokine:

Visfatin is increased in inflammatory conditions such as acute lung injury, sepsis, and rheumatoid arthritis. Thus, it is considered to be a proinflammatory adipokine via either a compensatory response or an epiphenomenon. Of note, visfatin was recently reported to be expressed almost exclusively in visceral adipose tissue rather than subcutaneous adipose tissue. Adipokines, which are secreted by adipocyte tissue, have been studied in association with insulin resistance and the metabolic syndrome, including obesity, glucose intolerance, and dyslipidemia **(13).**

However, studies of visfatin in human populations have obtained conflicting results. Elevated plasma visfatin levels have been reported in patients with type 2 diabetes mellitus **(14).** On the other hand, other investigative results showed decreased plasma visfatin levels in patients with type 1 diabetes, liver cirrhosis, exercise in type 2 diabetes, and 3rd trimester gestational diabetes **(15).**

The insulin-mimic effect of visfatin:

Despite the insulin-mimic effect of visfatin, controversy exists over its role insulin resistance. The exciting paper of **Fukuhara et al. (3)** which had described the insulin-mimetic effect of visfatin and its naming, has been finally retracted. Several studies failed to show an association of circulating visfatin with insulin sensitivity **(16).**

There has been no report of whether the relation between visfatin and insulin is synergistic. However, it is still interesting whether visfatin binds directly to the insulin receptor at a site distinct from insulin and has hypoglycemic effects by reducing glucose release from hepatocytes and stimulating glucose utilization in peripheral tissue **(15).**

Insulin receptor expression has been ascertained in renal cells such as proximal tubular cells, mesangial cells, and podocytes. However, the affinity of visfatin for the insulin receptor and other receptors such as insulin-like growth factor receptor is unclear. In fact, insulin also binds with low affinity to insulin-like growth factor receptor and insulin-receptor like receptor in kidney. A study reported that insulin receptor expression was shown to be reduced in the kidney of an insulin-resistant rat animal model **(17).**

Despite a high plasma insulin level, decreased insulin receptor expression has been explained to correlate with insulin resistance in various tissues such as liver, skeletal muscle, and adipose tissue. However, this finding in the kidney can be different among renal cells and may be distinct depending on the organ type, i.e., whether liver, skeletal muscle, or adipose tissue. On the other hand, another study suggested that visfatin does not have insulinmimetic actions but rather has a regulatory role in glucose stimulated insulin secretion in pancreatic β-cells in vitro and in vivo. Those authors demonstrated that mice lacking visfatin synthesis develop impaired glucose tolerance and defective insulin secretion, which are restored by administration of visfatin. Taken together, these results suggest that visfatin may act as a multiplayer in either a cell- or tissue-dependent manner **(15).**

Interestingly, in our in vitro study, **(18)** high glucose stimulation upregulated visfatin synthesis and then visfatin stimulated glucose uptake via the glucose transporter (GLUT)-1 in renal mesangial cells. However, angiotensin II stimulation did not induce visfatin synthesis. We found that exogenous visfatin stimulation in renal mesangial cells upregulated the insulin signaling pathway and induced synthesis of its downstream components of profibrotic molecules.

In contrast, another study published data indicating that life span extension in mice is associated with reduced insulin receptor signaling cascade, which upregulates the expression of SIRT-1 proteins. Therefore, there could be possible crosstalk between the visfatin-mediated and insulin signaling pathways via various physiologic mechanisms **(19).**

Visfatin as a nicotinamide adenine dinucleotide (NAD) biosynthetic enzyme:

A studyhave shown that disturbances in the circadian clock feedback cycle through Nicotinamide phosphoribosyltransferase NAMPT/ visfatin- mediated NAD^+ biosynthesis may cause an imbalance in energy metabolism and homeostasis. Other data showed that this optimizing of SIRT1-mediated p53 degradation by visfatin induces the extension of human cell life span, such as smooth muscle cells, and the resistance to oxidative stress**.** If visfatin is impaired in the aging-dependent circadian cycle and this leads to the decline of pancreatic cell function in type 2 diabetes, visfatin could be an effective target for the treatment and prevention of type 2 diabetes **(20).**

Furthermore, a study suggested that angiotensin II plays a role in the prolongation of the life span in mice **(21).** Agtr1a-/- mice developed a longevity phenotype and upregulation of visfatin expression in the kidney. Although high glucose stimulation induces renal cell visfatin synthesis and intracellular glucose transport, which leads to increased pro-fibrotic

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molecular expression as demonstrated in our previous in vitro study, **(18).** angiotensin II did not induce visfatin synthesis and mice lacking angiotensin receptor expressed visfatin upregulation. Taken together, these data suggest that visfatin may have multiple actions in the kidney, even in the regulation of NAD-consuming enzymes such as sirtuins. In fact, they examined the effect of intraperitoneal visfatin administration on diabetic mice.

Therefore, visfatin has a compensatory effect via both autocrine and paracrine pathways to improve insulin resistance and lipid metabolism. Particularly, one study showed that long-term visfatin infusion does not decrease the abundance of insulin receptors in the kidney of insulin-resistant rats, which is different in other tissues, such as liver, skeletal muscle, and adipose tissue **(17).**

It is also possible that a more physiologic route of intraperitoneal visfatin injection may have benefit compared with vascular infusion, which is directly accumulated in the liver and visceral adipose tissue, which are the main organs regulating lipid and glucose metabolism, before sufficient concentration levels are reached in the systemic circulation of plasma, heart, and kidney. In addition, an unknown receptor for visfatin may exist, which could indirectly affect the insulin signaling pathway. For example, the enzymatic regulatory action of NAMPT/visfatin-mediated NAD synthesis might have a major effect on DM through a different pathway. Nonetheless, it is equally possible that differences in the models of insulin resistance studied may have accounted for this seeming discrepancy **(15).**

Visfatin as Pre-B cell colony Enhancing Factor (PBEF):

Visfatin actually corresponds to a cytokine that has been already known to enhance the maturation of B cells precursors in the presence of Interleukin-7 and a stem cell factor and was already known as pre-B cell colony enhancing factor or 'PBEF' **(22).**

Samal and colleagues (22) isolated the gene encoding PBEF (Visfatin) from a human peripheral lymphocyte in 1994.

The biological function of PBEF (Visfatin) has not yet been fully understood, however, a cytokine-like activity has been reported in several studies **(23).**

Visfatin in clinical studies:

The variations observed in plasma visfatin levels in several metabolic disorders suggests a possible role in the pathogenesis of these disorders and therefore have therapeutic implications. Many research teams have indeed started to investigate visfatin levels in their clinical trials. Several clinical studies targeting metabolic disorders started to include visfatin in their criteria for evaluating therapeutic efficacy. One randomized clinical trial studied the effects of metformin immediate release compared with metformin extended release on glycemic control in type 2 diabetes mellitus (T2DM), the authors observed increased levels of visfatin in patients randomized to metformin extended release **(24).**

Another trial showed a reduction in visfatin serum levels after metformin administration in PCOS women **(25).** In contrast to these studies, one trial reported no variation in serum visfatin levels despite improved glycemic control in response to slow-release and regular-form metformin in T2DM **(26).**

Similarly, one clinical study detected no significant changes in visfatin levels when rosiglitazone or metformin monotherapy was utilized in T2DM patients**.** Similarly, no change in visfatin serum levels was noted when PCOS women were treated with pioglitazone**.**

Additionally, no change in visfatin plasma levels was detected in response to pioglitazone or metformin treatment despite improvement in insulin sensitivity and glycemic regulation in naïve T2DM (newly diagnosed and untreated T2DM) **(27)**

Several human studies are now paying closer attention to visfatin levels when metabolic diseases are investigated. For instance, several studies investigating the effect of L-carnitine supplementation on glucose oxidation and insulin resistance markers in T2DM have considered visfatin levels as an important parameter. Indeed, L-carnitine was found to reduce levels of the adipokine visfatin in many trials when combined with a T2DM regimen. In one study, addition of L-carnitine to glimepiride was found to reduce visfatin levels in T2DM patients **(28).**

Similar results were achieved in obese diabetic patients when treated with orlistat and L-carnitine**)** and in diabetic patients when treated with sibutramine and L-carnitine**.** These studies further support the relevance of visfatin in these diseases and warrant further investigations that may present this adipokine as an attractive target in the fight against cardiovasculo-metabolic disease. Visfatin might serve as a biomarker for lipid profile control in metabolic disorders. Its plasma levels may be used to track the therapeutic progress in patients with metabolic diseases. The possibility of visfatin to play a role as a prognostic factor also needs to be investigated.**(29)**

A similar profile of contradictory results has been documented with regards to analyses correlating visfatin and obesity. Whereas some studies have reported positive correlations between visfatin and obesity **(30)**, others have demonstrated low plasma visfatin levels in patients with obesity **(31)**. However, one study has described visfatin to be associated with type 2 diabetes rather than obesity **(32).**

In contrast, visfatin levels were comparable in obese nondiabetics and lean controls but were significantly upregulated in obese type 2 diabetic patients, suggesting that visfatin is related to type 2 diabetes, rather than to obesity. On the other hand, no association between circulating visfatin levels and metabolic disorders, such as diabetes, various types of obesity (generalized, or abdominal and subcutaneous, or visceral), or even dyslipidemia has been documented **(30).**

Despite the contradictory data available regarding visfatin and obesity, some studies reported possible roles of visfatin in obesity-associated injury. Inflammasome activation was shown to be a central player in the pathogenesis of adipose tissue inflammation, insulin resistance (IR), and obesity-associated metabolic diseases **(33).**

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More importantly, inflammasome activation was shown in many instances to be adipokine-driven **(33).** Furthermore, the ability of visfatin to mediate obesity-induced podocyte injury via NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3)-inflammasome activation has also been shown **(5).**

Additionally, visfatin was shown to mediate arterial inflammation and endothelial dysfunction during early stages of obesity, via an NLRP3 inflammasome dependent endothelial inflammatory response **(34).**

Similarly, visfatin-induced vascular dysfunction in mice was shown to involve NLRP3-inflammosome and paracrine IL-1ß via a NAMPT-dependent Toll-like receptor 4 (TLR4)-mediated pathway **(35).** Another study found that visfatin-induced endothelial NLRP3-inflammasomes may result in the production of high mobility group box protein 1 (HMGB1) **(36).**

Consequently, HMGB1 can disrupt inter-endothelial junctions and increase paracellular permeability of the endothelium via paracrine and autocrine signaling, resulting in early-stage endothelial injury during metabolic disorders such as obesity **(36).**

Together, these findings suggest that the NLRP3 inflammasome, HMGB1, TLR4, and possibly some other mediators might serve as promising therapeutic targets to counter visfatin-mediated vascular injury associated to obesity. A very recent paper reported a potentially important new role for visfatin in the context of metabolic disease. The report shows that visfatin upregulates extracellular matrix (ECM) proteins including osteopontin, collagen type VI in pre-adipocytes. Given the documented role of ECM protein in tissue fibrosis, the authors suggested adipose tissue fibrosis as a possible link between visfatin and obesity-associated fibrosis and insulin resistance **(37).**

Visfatin and immune and inflammatory process:

One of the fundamental functions of visfatin/PBEF/ Nampt is the modulation of immune and inflammatory processes. **Moschen et al. (23)** has revealed that human leukocytes can be activated by visfatin to produce several pro and anti-inflammatory cytokines. While stimulation of CD14+ monocytes by visfatin leads to the production of IL-1β, TNF-α and IL-6, on the other hand, anti-inflammatory cytokines such as IL-1Ra and IL-10 might also be produced by stimulation of monocytes by visfatin. Moreover, this adipokine enhanced the surface expression of the co-stimulatory molecules CD54, CD40 and CD80 in CD14+ monocytes. Furthermore, it has been noted that visfatin/PBEF/Nampt was able to activate antigen presenting cells (APCs) and enhance phagocytosis in monocytes. In addition, trafficking CD14+ monocytes and CD19+ B-cells into sites of inflammation is another important function of visfatin which is deemed to be a strong chemotactic factor for these cells. Moreover, it has been reported that visfatin activated nuclear factor-kappa B which has a crucial role in regulating immune responses **(37).**

Indeed, it has been illustrated that serum visfatin levels positively correlated with IL-6 and CRP levels in human serum, which in turn corroborated the significance of visfatin as inflammatory cytokine. Up-regulation of visfatint has been also identified in a variety of pathophysiological conditions of the immune system including rheumatoid arthritis, psoriasis, clinical sepsis and acute lung injury **(23).**

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