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VISFATIN AS A PHYSIOLOGICAL MODULATOR AND ITS BIOCHEMICAL ROLE IN THE PATHOPHYSIOLOGY OF TYPE 2 DIABETES MELLITUS: A CURRENT PERSPECTIVE

Jancy Jose[1], Satyendra C Tripathi[2], Vickneshwaran Vinayaga[3*]

[1]PhD Research Scholar, MGMCRI, Sri Balaji Vidyapeeth University, Pillaiyarkuppam, Pondicherry-607402,India / Tutor, Department of Biochemistry, All India Institute of Medical Sciences (AIIMS), Nagpur, Email Id: jancyjose@aiimsnagpur.edu.in, ORCID Id: 0009-0003-4498-2050
[2]Additional Professor, Department of Biochemistry, All India Institute of Medical Sciences (AIIMS), Nagpur,
Email Id: sctripathi@aiimsnagpur.edu.in, ORCID Id: 0000-0003-3917-9645
[3]Associate Professor, MGMCRI, Sri Balaji Vidyapeeth University, Pillaiyarkuppam, Pondicherry-607402, India,
Email Id: vickneshwaranvinayagam@mgmcri.ac.in, ORCID Id: 0000-0002-5374-6880

ABSTRACT
Visfatin is a multifaceted novel adipokine which was initially identified as Pre-B cell Colony Enhancing Factor (PBEF).It functions as a pro-inflammatory cytokine and a key enzyme in the Nicotinamide Adenine Dinucleotide (NAD+) salvage pathway and hence it's also known as Nicotinamide phosphoribosyltransferase(NAMPT). It operates both intracellularly (iNAMPT) to regulate NAD+ biosynthesis where its inhibition yields anti-inflammatory and anti-cancer effects and extracellularly (eNAMPT) in the circulation .Recent studies have highlighted the connecting link between PBEF and the pathophysiology of Type 2 Diabetes Mellitus (T2DM). This review explores visfatin's diverse roles as iNAMPT, eNAMPT, an adipocytokine, and a metabolic regulator, while focusing on its mechanisms in type 2 diabetes mellitus considering its increasing global prevalence. Additionally, future implications as a potential therapeutic target for the prevention, treatment and management of T2DM will also be discussed.

KEYWORDS: Visfatin; PBEF; iNAMPT; eNAMPT; Type 2 Diabetes Mellitus; Adipokines.

INTRODUCTION

Visfatin regarded as a pro-inflammatory cytokine was initially identified as Pre B cell Colony Enhancing Factor (PBEF) due to its first discovered function in B cell development [1].Subsequently, its role as an enzyme in the salvage pathway of Nicotinamide Adenine Dinucleotide(NAD+) was recognised, hence it was also named as Nicotinamide phosphoribosyltransferase (NAMPT). NAMPT is found to exert its actions both intracellularly and extracellularly [2].The function of Intracellular NAMPT (iNAMPT) is to catalyze the rate-limiting step in the NAD+ biosynthesis pathway from nicotinamide. The anti-inflammatory and anti-cancer effects of (iNAMPT) can be attributed to its inhibition which significantly reduces intracellular NAD+ levels [2].In contrast, little is known about Extracellular NAMPT (eNAMPT) which is found in the circulation. However, studies have shown that eNAMPT can influence pathways related to the pathogenesis of certain metabolic disorders such as obesity, Type 2 Diabetes Mellitus (T2DM), atherosclerosis, and cardiovascular complications through its regulatory effect on oxidative stress response, apoptosis, and inflammation [2].Furthermore, it was found that PBEF is expressed in high levels in visceral adipose tissue and hence it's also named as visfatin; an adipokine. A study by Fukuhara et al [3] pinpointed that visfatin exhibits insulin mimetic effects but due to lack of evidence to confirm the same in further analysis the article was later on retracted. However, the insulin mimetic effects of visfatin still remain a controversy and a subject of ongoing scientific research. Consequently, this distinctive protein is known by three different names - visfatin/PBEF/NAMPT used interchangeably with reference to its multiple physiological actions. In this review, we will be exploring the various functions of visfatin as iNAMPT, eNAMPT, adipocytokine and metabolic regulatory effects. The biochemical mechanisms and metabolic derangements associated with type 2 diabetes mellitus and the potential therapeutic opportunities linked to targeting this protein will also be focused in this review.

2. Protein and Gene Structure

Visfatin is a protein with a molecular weight of 52-kDa which is active as a dimer, with each of its monomer comprising of 491 amino acids [4].It possesses two active sites situated at the interface of the dimeric protein, proving the fact that dimerization is crucial for the enzyme's catalytic activity[5] . The monomer is constituted by 19 β- strands and 13 α-helices each and is arranged into two structural domains (Fig.1) [6]. Fascinatingly, the protein lacks the typical signal peptide for cellular secretion [7], therefore whether it is released from a viable cell or a dead cell is not clearly understood. Human visfatin gene spans a length of 34.7 kb and is situated on the long arm of chromosome 7 between 7q22.1 and 7q31.33 [8]. It contains 11 exons and 10 introns [9]. The gene is highly conserved during evolution.

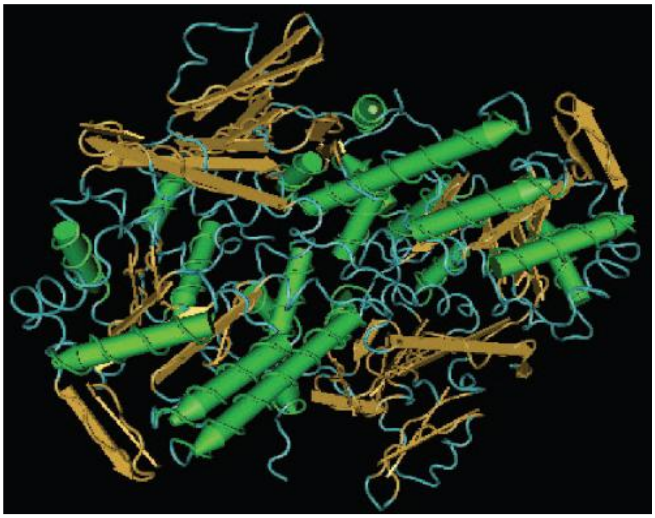

Figure 1: Crystal structure of PBEF/NAMPT/Visfatin. This schematic ribbon illustration highlights that the PBEF dimer is made up of two monomers; each containing 491 amino acid residues. In this diagram the β-strands are represented by orange arrows, and α-helices are depicted by green cylinders. This figure was downloaded from ref [10] and the structure was adapted from NCBI database of molecular modeling [11].

3. Distribution in Tissues and organelles

Evidence reveal that the highest expression of this protein is found in bone marrow, liver and muscle and to a certain extent in other organs like brain, kidney, spleen, heart, lung and immune cells [1].Additionally, visfatin is also released by fetal membrane during gestation. Thus, visfatin expression is no longer confined exclusively to visceral fat and therefore it plays a pivotal role in their physiological actions. Subcellularly, visfatin is found both in the cytoplasm and nucleus of the cells [12].

4. Biochemical Functions

4.1 Intracellular NAMPT (iNAMPT)

Nicotinamide adenine dinucleotides (NAD+ and NADP; phosphorylated form), along with their reduced forms NADH and NADPH respectively, are pyridine-containing cofactors which are involved in several metabolic reactions [13, 14]. The NAD+ biosynthesis has been an integral part of the major metabolic processes inside the cell. Three major pathways for NAD+ biosynthesis have been elucidated which include: (1) the de novo synthesis pathway, which is derived from tryptophan via the kynurenine pathway; (2) the salvage pathway, which produces NAD from nicotinamide (NAM) and finally (3) the Preiss–Handler pathway, which involves the production of NAD from nicotinic acid (NA).The role of iNAMPT in NAD biosynthesis is via the salvage pathway [15, 16]. The salvage pathway entails the transfer of a phosphoribosyl group from 5-phosphoribosyl-1-pyrophosphate to nicotinamide (NAM), or potentially to nicotinamide riboside (NR), leading to the formation of nicotinamide mononucleotide (NMN). This biochemical reaction is catalyzed by the enzyme NAMPT/visfatin [15, 16]. The capability of visfatin to modulate NAD+ synthesis makes it an important regulator of certain cellular components such as sirtuins (SIRTs), poly (ADP-ribose) polymerase (PARPs), CD38, and CD157[17,18]. SIRTs are a group of enzymes that possess NAD-dependent protein deacetylase activity. Post-translational modification of target proteins by transferring an ADP-ribose (ADPr) moiety is mediated by a family of enzymes called as PARPs [19]. Based on their enzymatic activity, they act either as poly (ADP-ribose) polymerases (PARPs) to generate poly (ADP-ribose) (PAR) chains or as mono (ADP-ribose) transferases (MARTs) to produce mono (ADP-ribose) (MAR) [20]. Concurrently, CD38 operates as a membrane-bound protein entrusted with multiple enzyme actions [21–23]. Additionally, CD38 is constitutively expressed within hematopoietic cells specifically in the nucleus [24]. Likewise, CD157 or bone marrow stromal cell antigen-1 (BST-1) is a surface antigen that exhibits both ADP-ribosyl cyclase and cADPR hydrolase activities comparable to those of CD38 [25]. The biochemical purpose of iNAMPT in NAD biosynthesis via these cellular components and its physiological outcomes are mentioned in Fig.2.

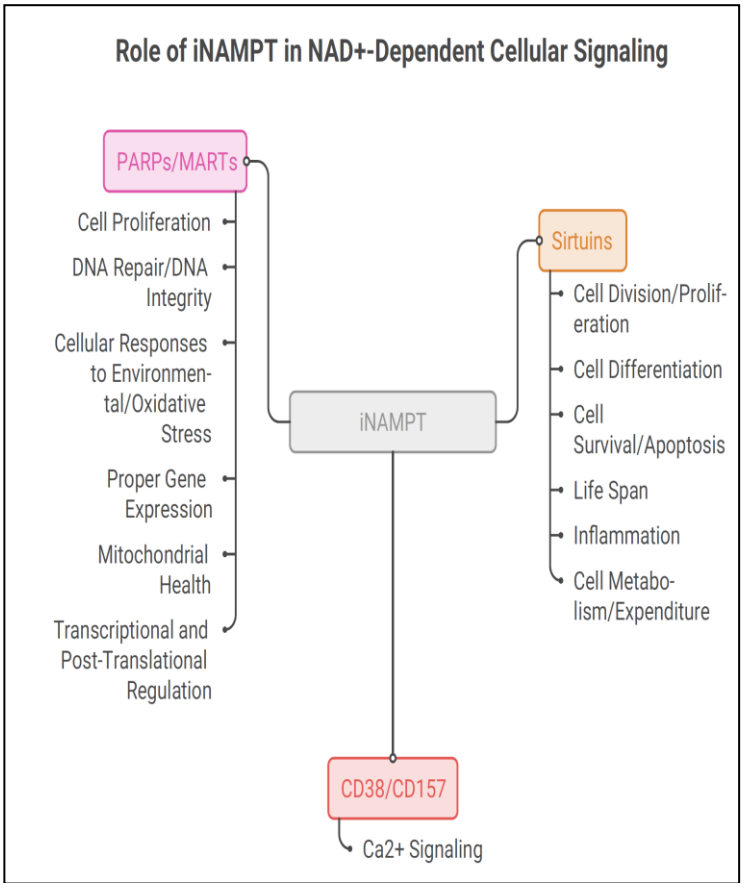

Figure 2: Functional outcomes of iNAMPT through various cellular components via NAD+ dependent cellular signaling.

4.2 Extracellular NAMPT (eNAMPT)

eNAMPT being an extracellular protein was detected in circulation with its concentration ranging from 10 and 282 ng/ml[26,27]. Moreover, cerebrospinal fluid, synovial fluid and seminal plasma plus supernatants of different cell types such as adipocytes, hepatocytes, leukocytes, cardiomyocytes, neurons, pancreatic β-cells, and mammary epithelial cells also showed detectable levels of eNAMPT [12, 28]. Nonetheless, there is no adequate information regarding the relative concentration of eNAMPT in comparison with iNAMPT. The lack of a signal sequence for secretion of eNAMPT has led scientists to consider the likelihood that eNAMPT could be an intracellular form of visfatin secreted as a result of cell lysis [29, 30, 31]. This could be potentially accounted to its widespread involvement across various pathologies. Subsequently, it was figured out that since human adipocytes produce and actively secrete eNAMPT it may not be indicative of cell lysis [32].A wide array of stimuli have shown to modulate the secretion of eNAMPT both in vivo and in vitro and these are broadly classified into (i) cellular stressors; (ii) nutritional triggers; and (iii) inflammatory signals [2]. Studies have shown significant increase in the release of eNAMPT during Oxygen-glucose deprivation (OGD) and oxidative stress [33, 34]. Additionally, eNAMPT release has been observed in various tumor cell lines [35, 28]. Increased baseline concentration of eNAMPT is closely related to adiposity, and variations in its secretion are generally associated with glucose levels and response of insulin with respect to glucose challenges [36, 37]. Furthermore, inflammation is also another important stimuli for eNAMPT release with notable elevations observed in response to pro-inflammatory agents such as IL-1β, tumor necrosis factor-alpha (TNF-α), and lipopolysaccharide (LPS) through the activation of toll-like receptor 4 [38, 39]. eNAMPT predominantly plays three main biochemical roles namely as PBEF, cytokine and as a metabolic regulator; as summarised in Fig.3. Firstly when discovered as PBEF it was thought to be an immune modulating cytokine which enhances murine pre-B-cell colony formation by working coherently to elevate the activity of stem cell factor (SCF) and IL-7 [1]. Notably, it has been shown to stimulate monocyte chemo attractant protein 1 (MCP-1) production [40] and the expression of matrix metalloproteinases (MMPs) [41]. Additionally it has been implicated in the activation of many inflammatory pathways such as NF- κ B [42], mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3 kinase (PI3) [43]. It also regulates vascular remodelling by up regulating vascular endothelial growth factor (VEGF) [44] and fibroblast growth factor 2 (FGF-2) [45].Finally, as a metabolic modulator it has been found to enhance lipogenesis [3].However, the effect on glucose transport and uptake seems conflicting after the article stating the insulin mimetic effects of visfatin was retracted[3].

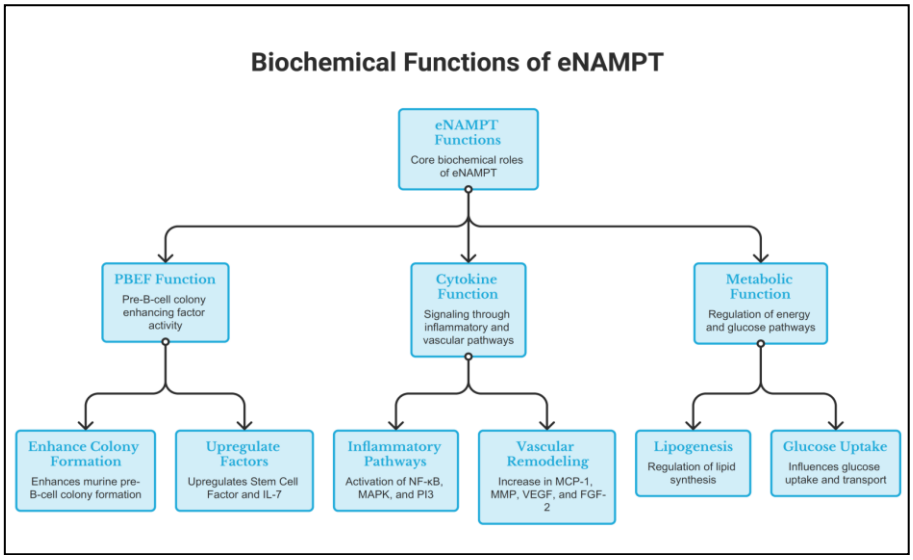

Figure 3: Biochemical functions of eNAMPT as PBEF, cytokine and metabolic regulator.

4.3 PBEF as a cytokine

Visfatin, when initially discovered as PBEF was identified to function as an immunomodulating cytokine. Visfatin displays a predominant role at the convergence between metabolic and immune deregulation. Visfatin is actively involved in visceral adiposity and metabolic diseases by promoting chronic inflammation. It induces the production of cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and monocyte chemoattractant protein-1 (MCP-1), while supporting the survival of pro-inflammatory M1 macrophages and inhibiting the persistence of anti-inflammatory M2 macrophages [46-48]. Scientific data displays the association of circulating levels of visfatin with systemic inflammatory markers such as C-reactive protein (CRP) implying its potential as a biomarker for existing inflammation [46]. Literature suggests that visfatin modulates approximately 50 inflammatory genes in peripheral blood mononuclear cells (PBMCs) [49] and stimulates the release of various inflammatory mediators. Moreover, it has been found out to promote MCP-1 and matrix metalloproteinases (MMPs), which has a significant contribution in tissue remodeling and inflammation [41, 44].

As mentioned earlier under eNAMPT, visfatin activates multiple inflammatory pathways, such as NF-κB[50], (MAPK), and phosphatidylinositol 3-kinase (PI3K). In addition, the up regulation of growth factors like vascular endothelial growth factor (VEGF) and fibroblast growth factor-2 (FGF-2) has shown to impact vascular remodelling [51]. The cytokine production induced by visfatin in leukocytes involves signaling pathways including p38 MAPK and NF-κB p65 [52]. Apart from immune modulation, visfatin has multiple physiological actions, including the outcome such as enhancing IL-7 and stem-cell factor on pre-B cell colony formation [1]. Furthermore, neutrophils can synthesize and release visfatin in response to inflammatory stimuli, where it acts as an inhibitor of apoptosis triggered by various inflammatory challenges. In the vascular endothelium, visfatin contributes to dysfunction by increasing the activity of adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) [43], thereby promoting leukocyte adhesion. It also enhances oxidative stress, impairs nitric oxide signalling, and activates the NLRP3 inflammasome [53]. Collectively, all these processes foster vascular inflammation, increase permeability, and cause endothelial injury therefore, establishing a mechanistic link to early vascular damage.

4.4 Effects of visfatin on metabolism

Several studies have shown the derangement of visfatin levels in various of metabolic disorders such as T2DM,obesity,Metabolic syndrome(MetS), Polyendocrine metabolic ovarian syndrome(PMOS) previously known as Polycystic ovarian syndrome(PCOS), atheroscelorosis, cardiovascular complications of T2DM,etc. Growing evidence highlights the deregulation of glucose metabolism and the development of multiorgan Insulin Resistance (IR) following the adipose tissue-specific deletion of visfatin [54] has demonstrated that it is a major target in obesity, diabetes, and dyslipidemia[55]. Visfatin exerts its actions through endocrine, paracrine, and autocrine pathways. It interacts with insulin receptors at sites other than standard insulin-binding locations to lower blood glucose via enhanced glucose utilization in muscle and liver cells [12].In addition, it promotes insulin action by stimulating the phosphorylation of insulin receptors 1 and 2, as well as activating phosphatidylinositol-3 kinase (PI3K), protein kinase B, and mitogen-activated protein kinase [56]. Visfatin's autocrine effects in the liver are required for modulating insulin sensitivity, as indicated by reduced glucose-stimulated insulin release paired with reduced visfatin expression and NAD production in

Fao rat hepatocytes [57]. Elevated levels of visfatin are reported in obese patients with type 2 diabetes mellitus (T2DM) compared to those without, and these high levels correlate with increased inflammatory markers [58]. Such elevated visfatin levels in patients with uncontrolled glucose projects a regulatory compensatory response; however, because insulin secretion and actions are impaired, an imbalance occurs, causing a marked rise in visfatin that exceeds the threshold [47, 59]. The excess leads to the release of inflammatory agents along with significant associations between high visfatin and elevated inflammatory mediators regardless of T2DM or MetS suggesting a dose-dependent role for visfatin in the development of insulin resistance (IR) and T2DM [47, 59, 60].The effect of visfatin in glucose homeostasis and its role in IR and IR linked complications are outlined in Fig.4.

As the pivotal hormone regulating glucose homeostasis, insulin's mechanisms of receptor engagement, intracellular signaling, and the alterations leading to insulin resistance has been widely studied [61, 62]. Normal signaling begins with insulin binding to the alpha subunit of the insulin receptor, prompting a conformational change and autophosphorylation on tyrosine residues of the transmembrane beta subunit, which subsequently stimulates the protein tyrosine kinase activity of the insulin receptor [63] to transduce signals via various intracellular substrates. Whether pre-B-cell colony-enhancing factor (PBEF/visfatin) binds to the insulin receptor continues disputed [64]. PBEF exerts insulin-like activity as a growth factor for osteoblasts [65]; like insulin, it has been reported to induce tyrosine phosphorylation of the IR, increase glucose transport into osteoblasts, stimulate osteoblast proliferation, and increase Type 1 collagen expression, with these effects being ablated by an IR inhibitor, hydroxy-2-naphthalenylmethyl phosphonic acid [65]. Studies in diabetic subjects in comparison with healthy controls suggest circulating PBEF levels are maintained by glucose [37].For instance, increasing glucose concentrations in healthy humans raised plasma PBEF levels. While elevated PBEF levels have been reported in patients with Type 1, Type 2, or gestational diabetes [66, 67].Other studies suggest levels may be normal [68] or even decreased [69], and some researchers observed absence of correlation between PBEF and insulin or glucose levels or in response to glucose infusion in obese cohorts [70]. Differences in assay techniques are likely responsible for these discrepancies observed [71].

Apart from glucose homeostasis, it is well-accepted that insulin exerts actions on fatty acid (FA) metabolism in skeletal muscles. Dyck et al underscores the increasing palmitate esterification into intramuscular lipid pools (like phospholipids, diacylglycerols, and triacylglycerols) while simultaneously decreasing palmitate oxidation in resting, isolated muscle prompted by these established insulin effects. Research findings showed that oxidized LDL increases visfatin expression in cultured monocytes, and visfatin increases the expression of molecules that degrade the extracellular matrix, causing plaque instability. This effect was abolished in the presence of an inhibitor of insulin receptor signaling [72].

Extending beyond lipid and metabolic alterations, visfatin employs significant vascular and angiogenic effects. In a series of endothelial cell culture studies, visfatin facilitated concentration dependent cell proliferation, migration, and capillary-like tube formation [44, 73], doing so primarily by increasing the synthesis of vascular endothelial growth factor (VEGF) [40, 44]. Apart from VEGF, visfatin stimualtes the secretion of proangiogenic factors such as FGF-2, MCP-1, and IL-6 [40, 50].Furthermore, visfatin increases the expression and activities of matrix metalloproteinases MMP-2 and MMP-9 enzymes that facilitate angiogenesis through extracellular matrix degradation, while decreasing the levels of tissue inhibitors of metalloproteinases [44].

These vascular properties link visfatin closely to endothelial dysfunction and atherosclerosis. A study by Uslu et al. [74] in patients with T2DM revealed a positive relationship between homocysteine which is known to associate with endothelial dysfunction [75]. Moreover, in studies examining patients with metabolic syndrome and T2DM together, visfatin levels correlated directly with atherosclerotic carotid thickness in both groups [72,76].Data further suggests that circulating visfatin levels can also serve as a clinical marker of carotid artery thickness.

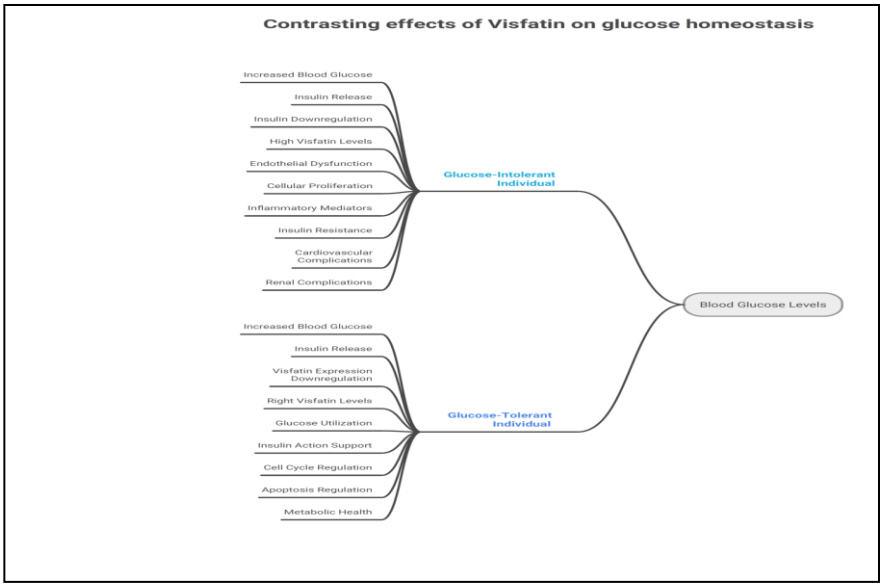

Figure 4: This image highlights the metabolic effects of visfatin on glucose homeostasis in individuals with and without glucose tolerance.

5. Visfatin and T2DM

T2DM is one of the initial metabolic disorders to be linked to visfatin apart from obesity. Research connecting visfatin levels to various types of diabetes presents conflicting results. While several studies have reported positive associations with gestational [77], type 1 [78], and type 2 diabetes [66, 79, 80], alongside elevated circulating visfatin during progressive beta cell deterioration [78], others found no such connection or reported contrasting outcomes. Specifically, low circulating visfatin levels have been observed in gestational [69] and other forms of diabetes [81], while some investigations found no significant difference in type 2 diabetic patients compared to matched healthy controls [82] or noted no association with insulin sensitivity or glucose tolerance [66,68,70,83].Mechanistically, Haider et al. demonstrated that adipocyte visfatin release during hyperglycemia depends on the duration and the magnitude of glucose elevation while being inhibited by insulin [37], though the impact of insulin-sensitizing agents on serum visfatin remains unclear [82,84]. These findings imply that fasting glucose levels rather than insulin resistance may primarily drive elevated visfatin in newly diagnosed T2DM cases. In addition, triglycerides are also directly and independently associated with visfatin [85], suggesting that higher triglyceride levels may partially contribute to its elevation in diabetic patients.

Beyond its metabolic associations, visfatin functions as a key enzyme in NAD+ biosynthesis, potentially maintaining beta cell function in obese and T2DM individuals [32]. In this support, Brown et al. recently showed that incubating clonal mouse pancreatic beta cells with visfatin increased insulin upregulation by ninefold and significantly enhanced insulin secretion by 46% compared to low glucose conditions [86]. Moreover, acute visfatin injections in KKAy obese type 2 diabetic mice significantly reduced plasma glucose levels [64]; collectively suggesting that elevated visfatin concentrations in T2DM may serve as a physiological protective response against hyperglycemia. On the contrary, certain other studies have shown elevated visfatin levels in T2DM is not dependent on obesity and insulin resistance and is predominantly on the basis of fasting glucose and triglycerides levels [87]. To summarise, visfatin may be used as promising predictor of insulin resistance, diabetes status, obesity metabolic syndrome, and resultant cardiovascular disease [88].

6. Future perspective

Identifying potential ligands for visfatin could open new avenues for diabetes therapeutic management by promoting β-cell proliferation and enhancing insulin sensitivity. Development of new pharmacological interventions in this field would facilitate in depth understanding of the mechanisms underscoring NAMPT-mediated disease pathophysiology. A major breakthrough in this area of work was the characterization of (E)-N-(4-(1-benzoylpiperidin-4-yl) butyl)-3-(pyridine-3-yl) acrylamide, known as FK866 or APO866 [89]. FK866 exhibits a high affinity for NAMPT, inhibiting its activity by competing with NAD for the same binding site (90). While FK866-mediated cytotoxicity was initially attributed to apoptosis induction, autophagy has also been recognized as a key factor in this form of cell death (91). Additionally, inhibition of NAMPT causes a time-dependent depletion of NAD+ and ATP, suggesting the involvement of multiple pathways (92). Myriads of research groups both in industrial side and academia are involved in investigating novel NAMPT inhibitors derived from chemical modifications of FK866. However, alternative approaches should be explored to address the limitations of current strategies. For example, existing enzyme inhibitors lack selectivity for extracellular NAMPT, which prevents the avoidance of detrimental side effects caused by inhibiting intracellular NAMPT (93). Conversely, developing a soluble receptor for eNAMPT could provide a selective pharmacological intervention, limiting inhibition to eNAMPT, as has been demonstrated for VEGF and TNF-α. Unfortunately, the structure of such a receptor remains unclear. Lastly, neutralizing antibodies against eNAMPT may represent a promising approach; indeed, a humanized form of an eNAMPT antibody P-BEFizumab has been developed and is presently undergoing preclinical investigation for the treatment of acute lung injury (94). Further research, particularly in the field of autoimmune diseases, malignancies, and T2DM linked to elevated eNAMPT levels, is warranted for validating the therapeutic applications.

7. Conclusion

To conclude, visfatin can be a promosing predictor for obesity, T2DM, metabolic syndrome, insulin resistance and cardiovascular disease. In view of the literature, the elevated levels of visfatin in patients with T2DM regardless of their degree of adiposity suggest a compensatory mechanism responding to heightened insulin resistance and insufficient insulin action. Therefore, this represents the need for a potential novel target for future management of diabetes mellitus.

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