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Review Article
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Visfatin as a Promising Marker of Cardiometabolic Risk

Mehmet Erten

Adipose tissue is an endocrine organ that produces molecules with important functions in the human body called adipokines. Visfatin can be secreted from various sources, such as macrophages, chondrocytes and amniotic epithelial cells other than adipose tissue. The main effect of visfatin is to promote inflammatory processes. In addition, visfatin has pivotal effects on the entire cardiovascular system, such as endothelial dysfunction, atherosclerosis, plaque rupture and mobilization, myocardial damage, fibrosis and new vessel formation. Vascular pathologies in other tissues also mediate its effects. Visfatin changes in a similar manner to cardiac markers in acute myocardial infarction, and the most cited feature in research studies is that it may be a cardiovascular risk marker. Visfatin is therefore expected to be widely used in cardiovascular pathology in the near future. Visfatin has many target tissues and various effects that occur in relatively complex biological pathways, making it difficult to understand visfatin adequately. In this review, we provide comprehensive information about this promising molecule.

Key Words: Atherosclerosis • Endothelial disfunction • Inflammation • Risk factor • Troponin • Visfatin

INTRODUCTION

Although adipose tissue was previously seen only as a triglyceride reservoir, it is now seen as an endocrine organ that synthesizes and secretes functional molecules called adipokines. Adipokines can act locally in adipose tissue and also participate in the circulation and affect distal organs and tissues. In addition to molecules such as leptin and adiponectin, adipose tissue also synthesizes cytokines such as tumor necrosis factor alpha (TNF-α) and some interleukins (IL). The number of known adipokines including new adipokines such as resistin, apelin and visfatin has significantly increased in recent years.[1-3] Adipokines have many functions such as hunger regulation, insulin sensitivity, immunity, inflammation and vascular homeostasis.[4,5] In patients with obesity and type 2 diabetes mellitus (DM), adipokine imbalances cause chronic systemic inflammation, cardiovascular disorders and endothelial dysfunction.[6] In recent years, adipokines have been proposed to be a potential marker for inflammation and cardiovascular diseases.

VISFATIN

Visfatin was first described by Fukuhara et al.[7] in 2005 as an adipokine with insulinomimetic effects in mice.[5] They observed that glucose levels decreased within 30 minutes following recombinant visfatin administration, but that glucose levels returned to control levels after 60 minutes.[7] However, the article had to be withdrawn because of doubts about the reproducibility of the data.[5] It was later found that visfatin is identical to pre-B cell colony enhancing factor.[6] The nomenclature describing the same molecule is shown in Figure 1. When it was first defined, it was named visfatin because it was thought to mostly be produced in visceral adipose tissue.[7]

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Laboratory of Medical Biochemistry, Public Health Lab., Malatya, Turkey.
Corresponding author: Dr. Mehmet Erten, Laboratory of Medical Biochemistry, Public Health Lab., Malatya, Turkey. E-mail: mehmeter23@gmail.com

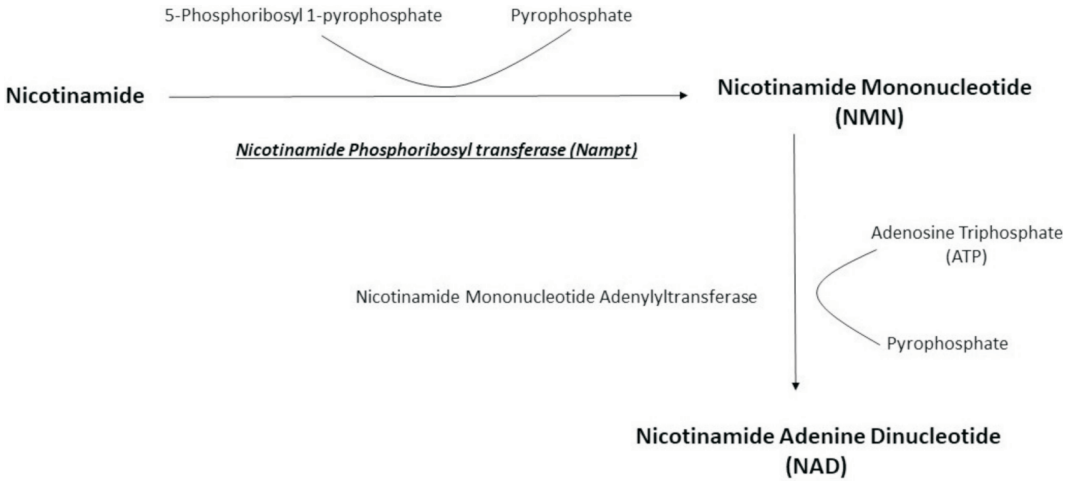

Figure 1. *Nicotinamide phosphoribosyl transferase (Nampt) activity. Nampt catalyzes the key step in the synthesis of nicotinamide adenine dinucleotide (NAD). Nampt converts nicotinamide to nicotinamide mononucleotide (NMN), consequently transformed into NAD$^+$ by nicotinamide mononucleotide adenylyltransferase.*

However, it was later shown to be synthesized equally in subcutaneous adipose tissue and also in epicardial and perivascular adipose tissues.[8-11] Furthermore, visfatin is synthesized and released by inflammatory cells in adipose tissue as well as adipocytes.[12]

Visfatin also shows nicotinamide phosphoribosyl transferase (Nampt) activity.[13] Nampt is the enzyme that catalyzes the key step in the synthesis of nicotinamide adenine dinucleotide (NAD).[14] Nampt converts nicotinamide to nicotinamide mononucleotide (NMN), which is consequently transformed into NAD$^+$ by nicotinamide mononucleotide adenylyltransferase (Nmnat) (Figure 2). In mammals, the Nampt enzyme has two isoforms; the intracellular isoform is called iNampt and has a central role in the activity of NAD-dependent enzymes,[14] and the extracellular isoform is called eNampt and is synthesized by many cells and mediates interactions of organs.[15]

In recent years, visfatin has been shown to be synthesized in many tissues beyond adipose tissue and to have many biological activities[16,17] (Figure 3) in a wide variety of cells, such as immune system tissues, chondrocytes and amniotic epithelial cells.[12,18,19] Samal et al.[20] was the first to demonstrate that visfatin is expressed in the heart, pancreas, liver and skeletal muscle by searching mRNAs. Later, it was found that visfatin is actively synthesized by myoblast and hepatocyte cells.[21,22] Subsequent studies have strengthened the idea that these cells may be the source of circulating visfatin in metabolic events.[23,24]

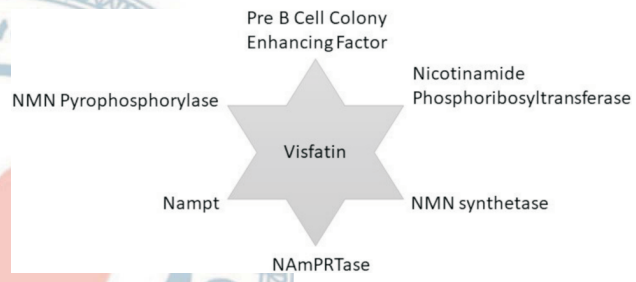

Figure 2. *Visfatin synonyms. nicotinamide phosphoribosyltransferase (NAmPRTase or Nampt) also called according to different locations as pre-B-cell colony-enhancing factor (PBEF) or visfatin and different shapes of enzymatic names.*

METABOLIC SYNDROME, DM, OBESITY AND VISFATIN

There is evidence showing that visfatin levels are higher in patients with type 2 DM, obesity and metabolic syndrome.[25,26] Visfatin expressions have been reported to be high in circulating monocytes in obese patients with type 2 DM, but lower in obese patients without type 2 DM.[27] This shows that visfatin expressions may be related to diabetes rather than obesity. However, Oki et al.[28] concluded that serum visfatin levels are not only associated with inflammatory markers but also independent of insulin resistance. In addition, serum visfatin levels have been found to be high in male patients with infertility associated with obesity and diabetes.[29] The link between metabolic diseases and visfatin levels has not yet been adequately clarified due to

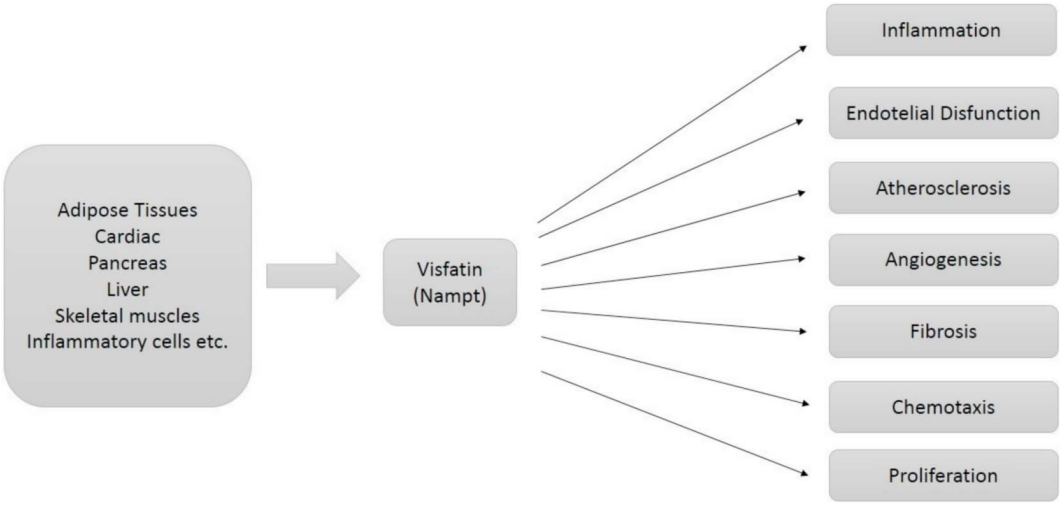

Figure 3. *Visfatin and its effects. Visfatin is secreted from not only adipose tissue but also many other places, especially inflammatory cells. Therefore, visfatin has a wide range of local and systematic effects. Nampt, nicotinamide phosphoribosyl transferase.*

these conflicting findings. However, it is evident that high visfatin levels with or without metabolic disorders are associated with inflammatory conditions, and that the increase in serum visfatin levels is directly related with inflammatory markers. IL-6, C-reactive protein (CRP) and monocyte chemotactic protein-1 (MCP-1) levels support the relationship between visfatin and inflammation.[28,30]

CARDIOVASCULAR SYSTEM AND VISFATIN

The target tissue with which visfatin is most associated and has the most important effects is the entire cardiovascular system, including the peripheral vascular system.

Atherosclerosis and its effects on the vascular system

Initially, the cardiovascular effects of visfatin are in the process of atherosclerosis. Many studies have shown that there is a link between high visfatin levels and atherosclerotic inflammation and plaques.[30-32] Visfatin has been shown to be an important compound for endothelial dysfunction, which is one of the initial stages in the formation of atherosclerosis (Figure 4).[33] Visfatin exerts its proliferative, proinflammatory, proangiogenic effects via stimulating molecular signaling pathways such as phosphatidylinositol 3-kinases (PI3K), nuclear factor-Kb (NF-kB), signal transducer and activator of transcription (STAT3) and extracellular signal-regulated kinases (ERKs).[34-37] Toll-like receptor 4 (TLR4) mediates visfatin to induce endothelial dysfunction.[33] Vascular smooth muscle proliferation is a specific feature of atherosclerotic lesions. While proliferation of endothelial cells (especially progenitor endothelial cells) is beneficial for the vascular system, proliferation of smooth muscle cells contributes to the growth of atherosclerotic plaques. Thus, implications of the proliferative effect depend on the cell type. Visfatin has been shown to act as a growth factor for rat aortic smooth muscle proliferation alongside Nampt activity.[11] Abnormal vessel formation is thought to pose a

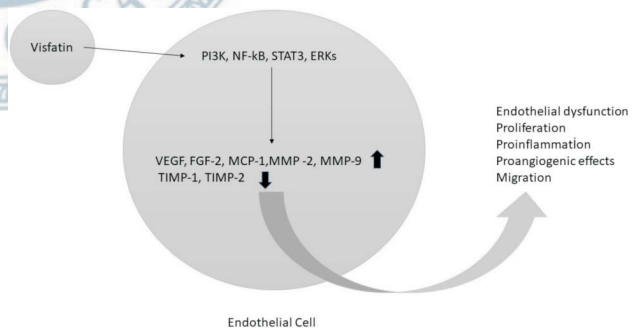

Figure 4. *Visfatin effects on endothelial cell. Visfatin exerts its proliferative, proinflammatory, proangiogenic effects via stimulating molecular signaling pathways such as phosphatidylinositol 3-kinases (PI3K), nuclear factor-Kb (NF-kB), signal transducer and activator of transcription (STAT3) and extracellular signal-regulated kinases (ERKs). Visfatin increases vascular endothelial growth factor (VEGF), fibroblast growth factor-2 (FGF-2), monocyte chemotactic protein (MCP-1), matrix metalloproteinases (MMP-2 and 9) and decrease levels of MMP tissue inhibitors (TIMP-1 and 2).*

risk for coronary atherosclerosis.[38] In a series of endothelial cell culture studies, visfatin was shown to facilitate concentration-dependent cell proliferation, migration and capillary-like tube formation.[39-41] Visfatin exerts these effects by increasing the synthesis of vascular endothelial growth factor (VEGF).[39-42] Besides VEGF, it also induces the release of proangiogenic factors such as fibroblast growth factor-2 (FGF-2), MCP-1 and IL-6.[42-44] The angiogenic effects of visfatin have been proven in animal experiments.[39-41] Kim et al.[45] suggested that thromboxaneA2 (TXA2) mediates the vascular-forming effect of visfatin. Visfatin has also been shown to increase the expressions and activities of matrix metalloproteinases (MMP-2 and 9), which are enzymes that facilitate angiogenesis by extracellular matrix degradation and decrease levels of MMP tissue inhibitors (TIMP-1 and 2).[39]

A study conducted by Uslu et al.[46] in patients with type 2 DM revealed a positive relationship between homocysteine and visfatin levels. However, the same relationship was not found with the levels of asymmetric dimethylarginine (ADMA), the major endogenous blocker of endothelial nitric oxide synthase. Homocysteine is known to be associated with endothelial dysfunction.[47]

In studies where patients with metabolic syndrome and type 2 DM were examined together, visfatin levels were correlated with atherosclerotic carotid thickness in both patient groups.[31,48] Kadoglou et al.[31] suggested that circulating visfatin levels are a marker showing carotid thickness. However, Takebayashi et al.[49] reported that there was no link between visfatin levels and CRP and carotid thickness in patients with type 2 DM. On the other hand, a positive correlation has been reported between epicardial fat thickness as measured by echocardiography in morbidly obese patients and circulating visfatin levels.[50]

Several studies have also reported that visfatin levels reflect systemic inflammation in cardiovascular and kidney pathologies in correlation with CRP levels.[51,52] Furthermore, high visfatin levels have been associated with activated inflammatory molecules such as IL-6 and MCP-1, which are higher in coronary artery disease and especially acute coronary syndrome.[30]

Cardiac effects

A positive relationship between visfatin levels and unstable atherosclerotic lesions have been reported in patients with coronary artery disease and acute myocardial infarction (AMI).[53] Visfatin expressions in AMI patients have been shown to be increased in foam cells as well as smooth muscle cells in atherosclerotic plaque, and the expression of visfatin in lesions has been blamed for atherosclerotic plaque mobilization.[53] Furthermore, the ability to synthesize visfatin in pericardial and periaortic adipose tissue suggests that in addition to circulating visfatin, perivascular visfatin may have a paracrine effect in the formation of coronary artery atherosclerosis.[54] Yu et al.[55] found high visfatin levels in macrophages within ruptured plaques in ST-elevation myocardial infarction (STEMI) patients. This supports the hypothesis that leukocyte-mediated visfatin synthesis may play an important role in the pathogenesis of plaque rupture. Moreover, in another study, the same researchers predicted that high visfatin levels may be related to the degree of myocardial damage and circulating CRP levels.[56] In the light of this information, it can be concluded that there is a relationship between plaque rupture in acute coronary syndrome and high visfatin levels.

The proliferative effects of visfatin are not only limited to the vascular wall, and they also lead to proliferation of cardiac fibroblasts, which causes myocardial fibrosis. Visfatin secretion from rat cardiac cells has shown that local sources can lead to cardiac fibrosis as well as circulation.[57] Increased cardiac fibroblasts and excessive accumulation of the extracellular matrix constitute the basis of myocardial fibrosis. In the article published in 2010 by Yu et al.,[58] the authors showed that visfatin increased cardiac fibrosis depending on the dose and time. In addition, visfatin has been shown to play a role in cardiac fibrosis through a proliferative effect on fibroblasts and increasing type I and III collagen release.[58] Taken together, both local foci such as periadventitial and epicardial adipose tissue and circulating visfatin can be considered to be important factors in the formation of cardiac fibrosis.

Experimental application of visfatin has been shown to increase the expression of inducible nitric oxide synthase (iNOS).[59] iNOS is also a well-known proinflammatory enzyme. Therefore, stimulation of the iNOS enzyme is manifested by vascular pathologies in diabetic patients.[60] Visfatin has also been shown to increase the release of IL-6, IL-8 and MCP-1, which have important roles in the chemotaxis of immune cells.[44,61]

Visfatin levels in the circulation and macrophages have been shown to be higher in patients with MI, and especially STEMI.[62] In a study conducted by Mazaherioun et al.[63] on 83 healthy individuals and 72 patients who applied at 8 hours after AMI, it was found that visfatin levels were significantly higher in the patients with AMI compared to the controls. The authors even suggested that a serum visfatin level above 7.244 ng/mL was the threshold for the diagnosis of AMI. However, appropriate exclusion criteria were not applied while establishing the control and patient groups. Especially in the control group, there was no evidence that the individuals were really healthy. Therefore, it is not certain whether individuals in the control group had coronary artery disease. Nevertheless, in the study of Lu et al.,[56] all individuals were evaluated by coronary angiography. In their study, the changes in visfatin level in STEMI patients from hospital admission until the end of the first month after angiography were examined. The authors showed that visfatin levels changed in a similar manner to cardiac markers. They observed that visfatin levels increased rapidly up to 24 hours, decreased to control levels at the end of the first week, and then did not change for a month. In addition, they observed that the amount of visfatin increased in the immunohistochemical examinations of the left ventricles from rat MI experiments created by coronary artery ligation.[56] In our previous study, we demonstrated that visfatin levels in isoproterenol-induced MI in rats increased from the sixth hour to the end of the first day, and then decreased to the lowest level on the seventh day.[52] We also found a correlation between visfatin and troponin levels that we measured simultaneously. Moreover, we proved the changes in visfatin immunohistochemically. Findings in these and previous studies suggest that visfatin may be a new cardiac marker.

Findings regarding the effects of visfatin on cardiac cell cycle and also apoptosis are contradictory. For example, intracellular visfatin has been shown to be an essential molecule for NAD-dependent enzymes that have important roles in cell metabolism.[14] On the other hand, visfatin has been shown to have antiapoptotic effects on endothelial cells.[64] In cell culture studies with mouse cardiac cells, it has been shown that cell death caused by oxidative stress is prevented by the application of visfatin.[65] It has been suggested that high visfatin levels in mice protect cardiac cells against ischemia-reperfusion injury.[66] In an ischemia-reperfusion experiment on mice, it was observed that the infarct area shrank following the intravenous administration of visfatin.[67] However, Montecucco et al.[68] reported that the administration of APO866, an Nampt inhibitor in mice, narrowed the infarct area, reduced neutrophil infiltration and freed oxygen radicals. In addition, Pillai et al.[57] reported that the administration of external visfatin or high circulating levels of visfatin caused cardiac hypertrophy.

CHRONIC KIDNEY DISEASE AND VISFATIN

DM is the major risk factor for chronic kidney disease (CKD). Levels of vascular, intracellular and melanoma cell adhesion molecules, which are associated with endothelial dysfunction in patients with CKD, have been shown to change with visfatin levels.[69] NADPH oxidase enzyme is a proinflammatory enzyme that forms superoxide anions.[70] Boini et al.[71] showed that visfatin impairs the microtubular function of glomerular endothelial cells by increasing NADPH oxidase activity, which increases glomerular permeability. In hemodialysis patients, visfatin levels have been related to CRP levels, but no relationship has been found with other markers of atherosclerosis such as ADMA levels and abdominal aortic calcification.[72] Visfatin levels decrease with the improvement of endothelial function after renal transplantation.[51]

POLYCYSTIC OVARY SYNDROME AND VISFATIN

Polycystic ovary syndrome (PCOS) is a pathology characterized by obesity, insulin resistance and endothelial dysfunction. Visfatin levels have also been found to be high in patients with PCOS.[9] Moreover, it has been shown to be an early marker of cardiovascular risk in PCOS patients.[73]

CEREBROVASCULAR DISEASES AND VISFATIN

Visfatin has been shown to be effective in the pathogenesis of cerebrovascular diseases.[74,75] Moreover,

several studies have reported that it may be a predictive marker for subarachnoid hemorrhage and aneurysm.[74,75] Lu et al.[76] reported higher visfatin levels in stroke patients, and that this increase was correlated with CRP levels. In addition, intracellular visfatin levels have been shown to be lower in mouse brain tissues depending on age, so that circulating visfatin levels increase, and this causes endothelial dysfunction.[77]

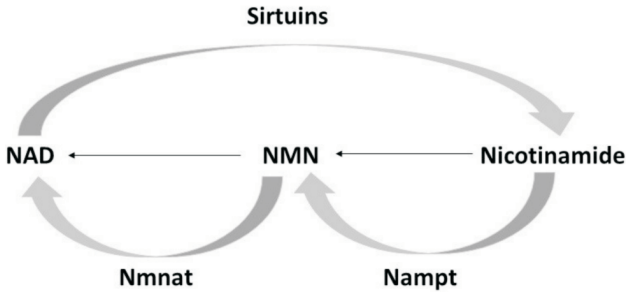

Figure 5. *Sirtuins' mechanism. Nampt, the limiting enzyme that converts nicotinamide to nicotinamide mononucleotide (NMN), followed by transformation of NMN to NAD by Nmnat. Sirtuins needs nicotinamide adenine dinucleotide (NAD) for its activity.*

SIRTUIN AND VISFATIN

Sirtuins are a family of protein deacetylases and adenosine diphosphate ribosyltransferases that need NAD for their activity (Figure 5).[78,79] There are seven types of sirtuins in humans.[80] SIRT 1 is located in the nucleus and cytoplasm and has functions in the regulation of metabolic response due to nutritional change in cells.[78,80] In addition, SIRT 1 has been shown to delay aging and protect against aging-related diseases such as type 2 DM and Alzheimer's.[81] An important relationship has been shown between SIRT 1 and Nampt in cells such as pancreatic β cells, vascular smooth muscle cells and cardiac cells.[82] The Nampt-SIRT 1 linkage has been shown to regulate metabolic responses, cell life cycle, cell differentiation and other important biological events.[83] Systemic NAD biosynthesis decreases with aging. Pancreatic β cells and neurons, especially those containing a small amount of iNampt, are unable to function properly, leading to type 2 DM and dementia, respectively.[84]

CONCLUSION

In conclusion, visfatin can be secreted in many places other than adipose tissue, especially inflammatory cells. It has versatile effects locally or systemically. Its role in inflammation is the most pronounced effect of visfatin. Retrospective studies show that visfatin levels are high in cases where chronic or acute inflammation prevails. Visfatin also has chemotaxis, angiogenesis, fibrosis and proliferative effects. Although these effects are multisystemic, they are mostly reflected clinically as a pathology that occurs in the cardiovascular system. Its effects on the vascular system may be through vascular disorders in other tissues. In addition, several studies claim that visfatin may be a marker of cardiovascular risk and prognosis.[1,73-75,85,86] Moreover, visfatin shows the same changes as cardiac troponins in AMI, supporting these claims.[52,56] Taken together, these data suggest that visfatin will be widely used in cardiovascular pathology in the near future, especially in cardiovascular pathologies. Visfatin has many target tissues and various effects that occur in relatively complex biological pathways. This makes it difficult to understand visfatin adequately. This review provides comprehensive information about this promising molecule.

CONFLICT OF INTERESTS

The author have no conflict of interest to declare.

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