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REVIEW ARTICLE

VISFATIN AND CARDIOVASCULAR PROTECTION

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ABSTRACT

In cardiovascular diseases, visfatin was initially proposed as a marker of atherosclerosis, endothelial dysfunction, and vascular damage. **Objectives:** we try to elucidate the relationship between visfatin and cardiovascular diseases as different controversial studies about visfatin role were found.**Data sources:** we summarized the contents of 251 research and review articles from different web sites till 31 January 2013. **Summary of content of the article:** in this review, we summarized the role of visfatin in different cardiovascular diseases and we explain the mechanism of action in different conditions. We discussed the relationship between visfatin, obesity and cardiovascular functions as this triad is considered in different situations. Moreover, we discussed the effect of visfatin on blood pressure and the potential role of visfatin in blood pressure control. We also mentioned briefly the role of visfatin in pre-eclampsia. In addition, we discussed in more details the role of visfatin in cardioprotection and the mechanism of action. Finally we summarized the role of visfatin in renin angiotensin system and its potential usage in clinical pharmacology. **Conclusion:** we found that visfatin has a great beneficial effect in protecting the heart in different situations as well as its relaxing effect on blood vessels is of great value in hypertension. We also concluded that visfatin has a lipid lowering effect in different situations including metabolic syndrome and type 2 diabetes mellitus. The role of visfatin in cardiovascular diseases could be implemented in clinical drug therapy which needs further human studies.

Key words: visfatin- Obesity- Blood pressure- vascular tone- adipokines.

1- INTRODUCTION

Visfatin, also named nicotinamide phosphoribosyl transferase (NAMPT), is an adipokinehas been shown to possess anti-diabetic[1], anti-tumor [2], and pro-inflammatory properties [3].Visfatin expression is increased in animal models of obesity and its plasma concentrations are increased in humans with abdominal obesity or type 2 diabetes mellitus [4,5].Visfatin can regulate immune action and is involved in the NAD+ salvage pathway [6].

It is well established that adipocytes have a more complex physiological role [7] and because blood vessels express receptors for most of the adipocyte-derived factors, adipose tissue seems to play a key role in cardiovascular physiology via the existence of a network of local and systemic signals [8].The relationship between cardiovascular diseases (CVD), obesity and metabolic syndrome was also supported by **Gauvreau et al**[9] who mentioned that metabolic syndrome is characterized by changes in arterial blood pressure, glucose metabolism, lipid and lipoprotein profiles in addition to inflammation. They also reported that intra-abdominal (visceral) adipose tissue in particular, rather than peripheral, appears to be associated with global cardiometabolic risk.

Visfatin may be related to the development of obesity-related diseases such as diabetes mellitus and cardiovascular disease [10]. This suggestion was supported by**De Clercq et al**[11]who reported that adipocytes produce large numbers of hormones, peptides, and other molecules that affect cardiovascular function, not only in an endocrine manner, but also by autocrine and paracrine mechanisms. In this review we summarized the main aspects of visfatin in cardiovascular diseases but first we discussed the relationship between visfatin and serum lipids because of the definite role of lipids in different cardiovascular diseases.

2- VISFATIN AND SERUM LIPIDS:

In our study[12], we found that administration of visfatin, glibenclamide or metformin significantly ($p < 0.05$) decreased the levels of triglycerides(TG) and Very Low Density Lipoproteins (VLDL) in diabetic rats compared to diabetic control rats. Our finding was found to be in agree with**Fukuhara et al** [1]who found that visfatin stimulated the accumulation of triglycerides in pre-adipocytes similarly to cells treated with insulin.Our findings were also in agreement with **Choi et al.,** [13]who corroborates experimental data on the formation and release of visfatin by rosiglitazone**.**They found that the expression of visfatin mRNA in visceral fat deposits was elevated by rosiglitazone or fenofibrate treatments when compared to untreated fatty rats ($P<0.05$).Theysuggestedthat rosiglitazone and fenofibrate may prevent type 2 diabetes by regulating adipocytokines including visfatin, adiponectin and TNF-alpha. Also our findings were supported by **Sun et al**[14] who found that serum visfatin concentrations at baseline were positively correlated with serum triacylglycerols. Our results were also strongly supported by **Hammarstedt et al**[15] who reported a 2-fold increase in plasma visfatin concentrations in individuals with type 2 diabetes mellitus (T2DM) compared with healthy controls.This was also found by other studies in patients with T2DM showed that visfatin plasma levels were significantly increased in T2DM compared with controls [16, 17, 18].However our results in controversy with **Dogru et al**[19]

and Pagano et al[20] who found no correlation between circulating visfatin on one hand and BMI, insulin, glucose and lipid levels on the other hand.However they found that visfatin levels increased significantly in the diabetics compared with controls and this finding support our finding in that visfatin reduced significantly serum levels of VLDL, cholesterol and triglycerides in diabetic rats and visfatin here may act as a counterregulator to serum lipids.

Our results were in controversy with **Pagano et al**[20]in that circulating levels of visfatin were decreased by approx. 50% in obese patients compared with controls and a negative correlation was found between circulating visfatin levels and BMI in obese patients. This controversy can be explained by our suggestion that plasma visfatin is increased in diabetics in a trial to counteract elevated blood glucose as well as serum lipids but the plasma level of visfatin in normal subjects is so small that no effect of visfatin on serum biochemical parameters and this explanation is supported by **Lopez-Bermejo et al,** [18] who found that visfatin levels were significantly increased in patients with long-standing Type 1 diabetes mellitus (T1DM) compared with subjects with T2DM or non-diabetic subjects and in non-diabetic men.

Also, we found that combination of visfatin with glibenclamide or metforminfurther reduced the levels of TG and VLDL in diabetic rats and significantly decreased total cholesterol in diabetic rats. Our findings were in agree with **Fukuhara et al**[1]who found that circulating visfatin levels were shown to be strongly correlated with the amount of visceral adipose tissue (VAT) but they also found a weak correlation between plasma visfatin concentrations and the amount of abdominal subcutaneous fat.Our findings confirmed that visfatin decreases some serum lipids, so elevated visceral fat secretes more visfatin which in turn decreases serum lipids to prevent hyperlipidemia and this explanation was supported by **Zahorska-Markiewicz et al**[21] who found that serum concentration of visfatin was significantly higher in obese women when compared to controls and they concluded that the observed increase of visfatin in obesity may be a counter regulation preventing further glucose increase. Our explanation was also supported by **Jin et al**[22] who found that serum visfatin levels were significantly higher in obese subjects than in non-obese subjects.Our study was also supported by **Berndt et al**[23] who showed that plasma visfatin concentrations correlated positively and significantly with body mass index and percentage body fat, as well as visfatin mRNA expression in VAT.These findings were supported by **de Luis et al**[24]who found thattotal cholesterol, low-density lipoprotein cholesterol, tumor necrosis factor-α, and resistin levels are elevated in patients with visfatin levels above the median value. Our findings on serum lipids were also supported by **De Luis et al**[25]whofound a positive correlation between visfatin levels and LDL cholesterol ($r=0.194$; $p<0.05$) and C reactive protein ($r=0.266$; $p<0.05$) and a negative correlation with weight ($r=-0.162$; $p<0.05$). We concluded that visfatin has a significant lowering effect on some serum lipids in diabetic rats and we suggested that visfatin act as a counter regulator to elevated serum levels of glucose, cholesterol, VLDL and triglycerides.

3- TRIAD OF VISFATIN, OBESITY AND CARDIOVASCULAR SYSTEM:

Several epidemiological studies have clearly demonstrated that human obesity, a disease in which adipose tissue is largely represented, is a strong cardiovascular risk factor causally involved in the development of cardiovascular disease [26, 27].

Adipokine production and secretion were found by many studies to be increased in central obesity [28, 29, 30]. This fact plays a pivotal role both in the pathogenesis of cardiovascular damage through adverse effects on hemostatic balance and vascular function [31, 32, 29], and in the amplification of inflammatory processes in vascular and nonvascular tissues [29,33,28]. It was also found that adipose tissue from individuals with central obesity synthesizes and releases increased amount of vasoactive substances such as angiotensinogen and endothelin-1 (ET-1) [34, 35].These findings were supported by **Micić and Polovina,** [36]who reported thatobesity is a risk factor for various cardiovascular diseases including hypertension, atherosclerosis, myocardial infarction, heart failure and sudden heart death. **They** suggested that cardiomyopathy in obesity (adipositas cordis) appears due to accumulation of adipose tissue between the heart muscle fibers and degeneration of myocytes. They also reported that obesity is low inflammation state with increased adipokine production from truncal adipose tissue which causes endothelial dysfunction and insulin resistance. These findings and suggestions were also supported by many studies reported that obese subjects are characterized by insulin resistance, metabolic disorders, and vascular abnormalities which cooperate to induce high cardiovascular risk [37,38].

In metabolic syndrome, there is a combination of central obesity, glucose intolerance, atherogenic dyslipidemia, and arterial hypertension [38, 39]. These findings were also supported by **Reaven et al**[31] and**Matsuzawa**[29] who found that adipokines modulate angiogenesis via paracrine mechanisms and exert a role in the control of blood pressure, lipoprotein metabolism, coagulation, immunity and inflammation.

In central obesity, abnormalities in fat mass are associated with a peculiar dysfunction of adipose tissue, responsible for endothelial dysfunction, pro-thrombotic tendency, low-grade chronic inflammation, and oxidative stress [40]. These defects represent the main pathogenetic link between obesity and the increased risk of athero-thrombotic events [31, 32, 41]. These findings were supported by **Dahl et al**[42]who reported thatboth oxidized low-density lipoprotein and tumor necrosis factor-α increased visfatin expression in THP-1 monocytes (THP1 is a human monocytic cell line derived from an acute monocytic leukemia patient) with a particularly enhancing effect when these stimuli were combined. They also found that visfatin increased matrix metalloproteinase-9 activity in THP-1 monocytes and tumor necrosis factor- α and interleukin-8 levels in peripheral blood mononuclear cells

Micić and Polovina[36]reported that adipocytokines act synergistically or competitively with insulin, that explain their impact on insulin resistance. Inflammatory cytokines from adipose tissue could have influence on blood vessels endothelial function without their increase in plasma concentrations. These findings and suggestions were supported by

Nakamura et al[43]who reported thatobesity leads to increased expression of pro-inflammatory adipokines and diminished expression of anti-inflammatory adipokines, resulting in the development of a chronic, low-grade inflammatory state and they suggested that this adipokine imbalance is thought to be a key event in promoting both systemic metabolic dysfunction and cardiovascular disease.

As one of the inflammatory adipokines, visfatin in high circulating levels could be in healthy relations with cardiovascular risk factors, insulin resistance status and adiponectin in diabetic patients [(44)]**.** These findings were supported by**de Luis et al**[45] who found that visfatin was significantly correlated with total cholesterol and C reactive protein in female obese subjects**.** However they found that serum visfatin was not associated with the presence of metabolic syndrome (MS) or the accumulation of MS factors in female obese patients. However, **Guzik et al**[4] reported that visfatin and other adipokines may act on immune cells leading to local and generalized inflammation and may also affect vascular (endothelial) function by modulating vascular nitric oxide and superoxide release and mediating obesity related vascular disorders (including hypertension, diabetes, atherosclerosis, and insulin resistance). They also reported that macrophages and T cells are populating adipose tissue which develops into almost an organized immune organ and these activated T cells further migrate to blood vessels, kidney, brain and other organs surrounded by infiltrated fat leading to their damage, thus providing a link between metabolic syndrome, inflammation and cardiovascular and other associated disorders.This link was also supported by **Fukuhara et al** [1] who reported that several studies showed involvement of visfatin in metabolic and vascular homeostasis.These studies werealso supported by **Dahl et al**[42] who identified visfatin as a gene that was markedly enhanced in carotid plaques from symptomatic compared with plaques from asymptomatic individuals and they showed that visfatin was localized in areas that were rich in lipid-loaded macrophages. The relationship between visfatin and unstable lesions was also found in patients with coronary artery disease, demonstrating a strong visfatin immunostaining in lipid-rich regions within the material obtained at the site of plaque rupture in patients with acute myocardial infarction [42]. They finally suggested that visfatin should be regarded as an inflammatory mediator, localized to foam cell macrophages within unstable atherosclerotic lesions, that potentially plays a role in plaque destabilization.

Visfatin expression is also upregulated in plaque from the carotid artery of patients with symptoms of stroke and at the sites of plaque rupture in patients with acute myocardial infarction [42].The same study showed that balloon angioplasty, acutely injuring the plaques, caused visfatin levels to peak 4 hours after the procedure, receding back to basal levels after 24 hours. These results were supported by **Curat et al** [46]who demonstrated that visfatin protein is released predominantly by macrophages in visceral adipose tissue.

The relationship between visfatin, obesity and cardiovascular disease was also confirmed by **Garten et al**[47] who reported that visfatin has been implicated in the pathogenesis of several acute or chronic inflammatory conditions such as atherosclerosis and CVD and it may act as a pro-inflammatory cytokine and potentially have a beneficial effect on insulin secretion. This study was supported by **Spiroglou et al**[48] who found that visfatin expression was significantly higher in pericoronary adipose tissue samples compared with periaortic samples (p= 0.008)**.**They also observed that visfatin was expressed in aortic and coronary artery tunica media(in vascular smooth muscle cells).They also detected visfatin in foam cells of atherosclerotic lesions noticeda positive correlation between visfatin expression and aortic atherosclerosis and a significant positive correlation between visfatin foam cell expression and atherosclerosis [48]**.** They concluded that this correlation reflects the role of visfatin in inflammation and plaque destabilization. In a study by **Malavazos et al**[49] found that severely obese (OB) had thicker epicardial fat (EF) and higher visfatin and plasminogen activator inhibitor-1 (PAI-1) antigen concentrations than controls (P<0.0001) and EF thickness, log-visfatin and log-PAI-1 antigen concentrations directly correlated with visceral adipose tissue (VAT) (P<0.0001). They also found that log-visfatin and log-PAI-1 antigen were correlated with EF thickness even after adjusting for indices of fat distribution (P<0.01 and P<0.001 respectively). They suggested that Epicardial fat thickness, an indicator of cardiac adiposity, may be significantly related to inflammatory adipo-cytokines in visceral-obese patients. All these studies confirmed the relationship between visfatin, lipids and cardiovascular diseases.

4- VISFATIN AND HYPERTENSION:

The relationship between visfatin and blood pressure emerged since few years. This relation was found by **Filippatos et al**[50] who found that plasma visfatin concentrations correlated with systolic blood pressure (rho = 0.28, p <0.001) and diastolic BP (rho= 0.27, p<0.001) in 186 Caucasian subjects (90 with Metabolic syndrome and 96 controls). This relation was supported by **Seo et al**[51] who found that plasma visfatin concentrations were independently and positively associated with diastolic BP in 106 non-DM healthy Korean women, but not in 156 men.This relation was also supported by **Ingelsson et al**[52] who observed a correlation between the prevalence of hypertension and visfatin(p = 0.042).

In a study on male albino rats we [53]found that visfatin has insignificant inhibitory effect on blood pressure in normal rats. We found also that visfatin (1 nM) produced insignificant inhibitory effect on systolic and diastolic pressures in DOCA salt treated rats. Our results were in agreement with **Wang et al**[54]who found that no significant changes of circulating visfatin and no association between circulating visfatin levels and blood pressure in normotensive and spontaneously hypertensive rats. However they also found that visfatin expression in visceral fat tissue was slightly lower in stroke-prone spontaneously hypertensive rats (SHR-SP) compared with that in normotensive control Wistar-Kyoto (WKY) rats [54]**.**

We also found significant (P < 0.05) inhibitory effect of visfatin (10 nM) on both systolic and diastolic pressures in DOCA salt induced hypertensive rats. Our findings were in agree with**Eyileten et al**[55]who found thatvisfatin levels were significantly correlated to systolic and diastolic blood pressures and ramipril treatment resulted in a significant decrease in plasma visfatin. Our results werealso supported by the findings of **Kralisch et al**[56]who found a significant downregulation of visfatin expression during isoproterenol (nonselective beta agonist decrease the mean arterial blood pressure) treatment in 3T3-L1 adipocytes (cell line derived from mouse used in biological research on adipose tissue).

However, our findings were in controversy with **Wang et al**[54] in hypertensive rats, but we can explain this controversy by the different animal model, where they used spontaneously hypertensive rats instead of DOCA salt hypertensive rats in our study and we used different doses of visfatin. We also found that visfatin (100 nM) produced highly significant (P < 0.005) inhibitory effect on systolic and diastolic pressures in DOCA salt treated rats. Our results in agreement with **Gunes et al**[57] who found that the mean visfatin level was significantly higher in hypertensive patients and the serum visfatin levels in the pre hypertensive group were also significantly higher than in participants with normal blood pressure. They also found a significant positive correlation between visfatin and blood pressure.We can explain the elevated serum levels of visfatin in hypertensive patients by the suggestion that visfatin act to counteract the elevated blood pressure and as a compensatory mechanism done by visceral adipose tissue to decrease the high blood pressure to its normal value. Our suggestion is supported by the findings of **Mazaheriounet al**[58]who detected high levels of visfatin in patients with acute myocardial infarction. They concluded that pro-inflammatory cytokines such as visfatin may play a role in the development of atherosclerosis as well as destabilization of the atherosclerotic plaque.Our suggestion was also supported by explanation of **Wang et al**[54]who found that serum visfatin levels demonstrated a downward trend without statistical significance in stroke-prone spontaneously hypertensive rats (SHR-SP) in contradiction to a clinical study done by **Lu et al**[59] showing an elevation of plasma visfatin levels in ischemic stroke patients. **Wang et al**[54] explained the contradiction by a big difference in examined time; in their study, serum visfatin was determined long before stroke occurrence, while in the clinical study, serum visfatin was determined after stroke, which perhaps reflects a compensatory reaction in the acute stage of illness.This means that visfatin level was elevated as a beneficial adipokine to counteract complicated hypertension which prove our findings. However, our results were in controversy with**Dogru et al**[19]who found thatvisfatin plasma levels in newly onset hypertensive men andhealthy control men were not significantly different (p = 0.06). The latter study found that visfatin plasma levels did not correlate with the BP, BMI, lipid parameters, glucose, immunoreactive insulin, HOMA index or hsCRP levels either in patients or controls. We can explain this controversy by species differences where our study carried on rats but the latter study was a human study and also the latter study measured visfatin levels in normotensives and newly hypertensive men. In our study we examined the effect of visfatin on DOCA salt hypertensive rats.

Also, our results were found to be in agreement with **Filippatos et al**[50]who found that plasma visfatin levels are increased in patients with metabolic syndrome compared with individuals that do not fulfill the criteria for this syndrome. However our results were in controversy with **Kloting and Kloting** [60]who found that visfatin gene expression in visceral and subcutaneous adipose tissue is similar to that in lean control animals in the Wistar Ottawa rat, a model of polygenic metabolic syndrome with obesity, hypertension, dyslipidemia, hyperinsulinemia, and impaired glucose tolerance**.** However this controversy can be explained by the differences in used animals where we used normal male albino rats where they used a rat model with polygenic metabolic syndrome.

Our results were also supported by **Spiroglou et al**[48]who found astatistically significant higher expression of visfatin in periaortic fat in cases of hypertension compared with normotension.Also, our results were in agreement with **Rotkegel et al**[61]who found that hypertensive patients had significantly higher plasma visfatin level than the control group**.** However, they suggested that increased plasma visfatin concentration may play a significant role in the pathogenesis of hypertension in patients with visceral obesity**.** In controversy, we suggest that increased plasma visfatin level is a result not a cause and we assumed that visfatin secretion is increased to decrease the elevated blood pressure. Our last suggestion is supported by **Yamawaki et al**[62]who found that pretreatment with visfatin (100 ng/ml, 30 min) significantly inhibited noradrenaline-induced contraction in endothelium-intact rat aorta. They also found that visfatin (1-100 ng/ml) directly induced a relaxation in NA (100 nM)-pre-contracted aorta. They reported that the addition of visfatin to an organ bath resulted in a significant endothelium-dependent relaxation in both rat aortas and mesenteric arteries pre-contracted with NA. The vasorelaxant action of visfatin appeared to be independent of the insulin receptor, and was explained by the activation of endothelial nitric oxide synthase (eNOS) through phosphorylation at serine 1177 via Akt and de-phosphorylation at threonine 475 [62]. These findings were also supported by **Lovren et al** [63]who reported the stimulation of both eNOS activity and expression by visfatin, leading to enhanced production of nitric oxide and cyclic GMP formation in cultured human umbilical vein and coronary endothelial cells.Finally we concludedthat visfatin has a direct inhibitory effect on systolic and diastolic blood pressures in DOCA salt hypertensive rats in a dose dependent manner. We suggested that visfatin may have a protective role against hypertension and this role should be further evaluated by human studies.

5- VISFATIN AND PREECLAMPSIA:

Preeclampsia is a multi-system disorder of pregnancy, which is characterized by new onset hypertension (systolic and diastolic blood pressure of ≥ 140 and 90 mm Hg, respectively, on two occasions, at least 6 hours apart) and proteinuria (protein excretion of ≥ 300 mg in a 24 h urine collection, or a dipstick of ≥ 2+), that develop after 20 weeks of gestation in previously normotensive women [64, 65]. Dependent on the systemic involvement, several other symptoms, such as

edema, disturbance of hemostasis, renal or liver failure, and the HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet counts) also complicate the clinical picture [66]. The relationship between visfatin and pre-eclampsia was studied by **Fasshauer et al**[67]who found that mean maternal visfatin serum levels adjusted for maternal age were about 2-fold upregulated in preeclampsia (31.1 ± 23.4 μg/L) compared with controls (15.7 ± 23.1 μg/L). In contrast, in other study **Hu et al**[68] found that plasma visfatin levels were significantly lower in preeclampsia compared with non-pregnant controls ($p = 0.004$) and pregnant controls ($p < 0.001$). They also found that women with severe preeclampsia had a significantly lower serum visfatin level than those with mild preeclampsia ($p = 0.037$). These contradictory results may be attributed to different subject characteristics or to the time of pregnancy when preeclampsia occurred. For example, in the first study gestational age at the time of blood sampling was approximately 30 weeks *vs* 35 weeks in the second study, whereas the BMI was 22.5 kg/m2 in the first study *vs* 27.8 kg/m2 in the second study. Therefore, these studies are not directly comparable. Furthermore, there is evidence that the placenta expresses visfatin [69,70]. Consequently, there may be a decrease in visfatin transfer as placental function worsens [71]. This hypothesis may explain the observation that women with severe preeclampsia had a significantly lower serum visfatin level than those with mild preeclampsia [68]. In a recent study by **Ferreira et al**[72], serum visfatin levels at 11–13 weeks were found increased in women who develop PE by a mechanism unrelated to impaired placental perfusion.However further studies are needed to elucidate the exact relationship between serum visfatin and pre-eclampsia and the exact role of visfatin in development of eclampsia.

6- VISFATIN AND CARDIOPROTECTION:

Increased circulating adipocytokines secreted from visceral fat may have cardioprotective effects.Now, visfatin is well known in the association between obesity and cardiovascular risk and was demonstrated to improve cardiovascular risk factors [73].It was demonstrated that visfatin exhibited direct cardioprotective effects in a murine in vivo (ischemia reperfusion) I/R model, infarct size being reduced by 50% following treatment with a single intravenous bolus dose of visfatin [(74)].These findings were supported by **Yuet al**[75]whodemonstrated that circulating visfatin levels at admission in patients with acute myocardial infarction are associated with thrombotic occlusion of infarct related artery.The latter study was also supported by the findings of **Pala et al**[76]who found that circulating visfatin levels were significantly lower in cases of both CVD (Cerebrovascular Disease) and IHD (Ischemic Heart Disease) with respect to controls ($p= 0.014$ and $p= 0.035$ respectively). They suggested that visfatin has a major effect on the development of cardiovascular disease and they concluded that the measurement of visfatin with other adipokines could be considered for predicting the risk of developing major cardiovascular events.

Another study done by **Chang et al**[77]found that visfatin was expressed in cardiomyocytes as well as cardiac fibroblasts. These findings were supported by **Filippatos et al**[78]who found thatthe atherogenic small dense low density lipoprotein subclasses (sdLDL-C) were significantly increased in the top visfatin tertile compared with the lower tertiles.Thesefindings were also supported by **Xiao et al**[79]who demonstrated that visfatin counteracted H_2O_2 -induced apoptotic damage in cardiomyocytes in a time-dependent manner. They demonstrated that visfatin pretreatment attenuated H_2O_2 -induced DNA fragmentation, phosphatidyl serine exposure, and mitochondrial membrane potential depolarization. **Xiao et al**[79]mentioned thatbiochemical studies on cardiomyocytes showed improved cell viability and reduced caspase-3 activation caused by visfatin pretreatment and visfatin specifically suppressed the mitochondria-dependent apoptotic pathways, as characterized by changed levels of p53 and up-regulated the protein levels of phosphorylated AMPK. These findingsproved that visfatin plays a critical role in cardioprotection by suppressing myocardial apoptosis via AMPK activation.These studiessupport our suggestion that visfatin act as a beneficial adipokine protect the heart from myocardial injury and its plasma level can lead to a serious change in cardiovascular system. This suggestion was supported by **Xiao et al**[79] who reported that increased circulating adipocytokines especially visfatin may confer cardioprotective effects, that is, the so called "obesity paradox".

7- MECHANISM OF ACTION OF VISFATIN:

The actions of visfatin have been linked to activation of Akt (protein kinase B)andp44/42 (mitogen-activated protein kinase)signaling pathways that have been linked to cardioprotection [80,81,82]. It was reported that visfatin-induced glucose uptake into kidney mesangial cells via insulin receptor activation and subsequent Akt phosphorylation[83]. In human EC visfatin was shown to induce cellular proliferation through increased VEGF and MMP-2/9 production via PI3K-Akt and p44/42 signaling [84].

It was also reported that visfatin gene is transcribed in response to hypoxia, an effect that is mediated by hypoxia-inducible factor (HIF) [85,86], raising the possibility that visfatin may be upregulated in response to myocardial ischaemia. The upregulation of HIF has recently been established as a major mediator of cardioprotection [87].This means that hypoxia-inducible factor (HIF)-1α, which regulates the transcription of hypoxia-activated genes, may play a pivotal role in cardioprotection [88]. It was reported that hypoxia markedly enhancedvisfatin expression in both 3T3-L1 adipocytes [85] and MCF7 breast cancer cells [86], and that this involved activation of the HIF-1α pathway. These raise thepossibility that visfatin expression may be upregulated as aresult of myocardial ischaemia (and induction by HIF-1α), a scenario that has been invoked previously for leptin [89], apelin[90] and adiponectin[91,92].

Visfatin was also reported to block neutrophil apoptosis in experimental inflammation and clinical sepsis[93].Apoptosis is a key feature of myocardial ischemia reperfusion (I/R) induced injury[80]. Similarly, visfatin was also shown to reduce apoptosis in vascular smooth muscle cells [94] and in human umbilical vein

endothelial cells (HUVECS)[95], in the case of the latter via Akt and Erk1/2 mediated mechanisms. Thus visfatin acts as a growth promoter, enhances Akt and p44/42 signaling, and blocks apoptosis, and may, like leptin and adiponectin, be produced by the heart itself.

Visfatin-induced myocardial protection was also found tobe dependent upon PI3K and MEK 1/2 activation[74]. Furthermore, in murine ventricular cardiomyocytes subjected to hypoxia-reoxygenation, **Lim et al**[74] demonstrated that visfatin administered at reoxygenation reduced cell death substantially and this effect was mediated by the inhibition of the mitochondrial permeability transition pore (MPTP) opening, a non-specific mitochondrial channel, its opening in the first few minutes of myocardial reperfusion being a critical determinant of cardiomyocyte death.These effects could be blocked by the phosphoinositide 3-kinase (PI3K) inhibitor, wortmannin, and theMEK1/2 inhibitor, U0126. These observations were confirmed by **Hsu et al** [96] who showed that the expression of visfatin in the heart is decreased by ischemia/reperfusion and pressure overload.Theyproposed that visfatin may protect against myocardial infarction by regulating autophagy in the cardiomyocytes. These findings were also supported by **Smith and Yellon** [97]who reported that visfatin exerts a powerful direct cardioprotective effect via cellular mechanisms that involve the activation of RISK (Reperfusion Injury Salvage Kinase) pathway components which terminate on the MPTP (mitochondrial permeability transition pore).

Visfatin/Nampt, may also be expected to upregulate NADbiosynthesis thereby enhancing energy metabolism and redox biochemistry, factors that underpin the tolerance of myocardial tissue to ischaemicinjury. This expectation was supported by **Rongvaux et al**[98]whoreported that mice lacking expression of Nampt was found to be more susceptible to genotoxicand oxidative stress, and it has been proposed thatNampt may be required for cell survival in stressfulsituations such as inflammation.These findings were also supported by **Nadtochiy et al**[99]who found thatcardiac-specific overexpression of visfatin in mice had increased the NAD+ content in the heart, prevented downregulation of visfatin and reduced myocardial infarction size and apoptosis upon ischemia and ischemia/reperfusion. They also reported that inhibition of visfatin blocked ischemic preconditioning- induced cardioprotection.

8- VISFATIN AND CORONARY ARTERY DISEASE (CAD):

Visfatin has been shown to be produced by immune cells such as neutrophils and macrophages usually involved in the pathophysiology of acute coronary events [100,101].The pathophysiological basis for the association between NAMPT levels and CAD is still unclear, as both cardioprotection [85,102] and deleterious effects of NAMPT on the cardiovascular system have been reported [42,103]. Also, Visfatin has been suggested to enhance insulin sensitivity, but its potential role in plaque destabilization may counteract this [9].

Chenget al[104] found that tissue level of visfatin was significantly higher in coronary heart disease (CHD) patients relative to control subjects and significantly higher tissue levels of visfatin found in abdominal fat depots compared with those from epicardial fat in CHD patients. These findings were supported by **Liu et al**[105] who demonstrated that patients with coronary artery disease have increased plasma levels of visfatin and that these levels were significantly elevated in patients with acute coronary syndromes. However, the latter study in controversy with **Choi et al**[106]who found that visfatin levels were not significantly different between patients with CHD and control subjects and visfatin levels were not associated with any variables of the metabolic syndrome. Also, **Rho et al**[107]found that visfatin concentrations were associated with insulin resistance but not with coronary calcification. However another study by **Zhong et al**[108] found a positive association between visfatin and metabolic syndrome (MS), mainly among individuals with carotid atherosclerosis. They also found that visfatin was an independent risk factor for augmented carotid intimal-media thickness. The last study was supported by **Fu et al**[109] who found that plasma visfatin level may be related to the pathogenesis of CAD and detection of plasma visfatin might be helpful for early diagnosis of CAD, and patients with higher plasma visfatin level may have more severe coronary lesion. These studies were also supported by **Spiroglou et al**[48]who found thatdecreased coronary VSMC (Vascular Smooth Muscle Cell) visfatin expression was associated with acute coronary occlusion (p= 0.016). The latter study demonstrates that visfatin may act as a beneficial adipokine preventing the occurrence of coronary artery occlusion. However this explanation is not supported by **Maury and Brichard** [110] who suggested that visfatin may work as a pro-inflammatory cytokine being implicated into the pathogenesis of several acute or chronic inflammatory conditions, such as atherosclerosis and CVD. In a recent study, **Saddi-Rosaet al**[111] confirmed that circulating NAMPT levels are associated with CAD in type 2 diabetic patients. Also, **Filippatos et al** [78] observed a positive association between visfatin tertiles with waist circumference and blood pressure, as well as with total cholesterol and triglyceride levels, but not with apolipoprotein C-III. Their results support a role for visfatin in the detection of subjects with many metabolic abnormalities, which result in increased CVD risk.

9- ANGIOGENIC EFFECTS OF CHRONIC VISFATIN THERAPY:

The relationship between adipokine and angiogenesis was reported by **Reaven et al**[31] and**Matsuzawa**[29]who found that adipokines modulate angiogenesis via paracrine mechanisms. The role of visfatin in angiogenesis was supported by **Kimet al**[103] who reported that chronic visfatin therapy has been found to promote angiogenesis in endothelial cells both in vivo and in vitro and this has been suggested to be a potential mechanism for the neovascularisation of atherosclerotic plaques or adipose tissue in the presence of obesity. Subsequent experimental studies suggest that the mechanism underlying this angiogenic effect may relate to increased gene expression and elevated protein levels of vascular endothelial growth factor (VEGF) and matrix metalloproteinase 2/9 (MMP) [84]. Interestingly, the angiogenic

effect induced by visfatin and the associated upregulation of VEGF and MMP2/9 appears to be dependent on the activation of Akt and Erk1/2 [95, 102], protein kinases that have been linked to cardioprotection when activated acutely [112].

10- ROLE OF VISFATIN IN REGULATION OF VASCULAR TONE:

Adipokines secreted by visceral, subcutaneous, and perivascular adipocytes are involved in the regulation of vascular tone by acting as circulatory hormones (leptin, adiponectin, omentin, visfatin, angiotensin II, resistin, tumor necrosis factor-α, interleukin-6, apelin) and/or via local paracrine factors (perivascular adipocyte-derived relaxing and contractile factors) [113].In fact, visfatin/PBEF/Nampt is released by a wide series of cell types, including activated monocytes/macrophages that can directly interact with vascular cells [113].

The conversion of VSMCs (Vascular Smooth Muscle Cell)from a proliferative, noncontractile state to a nonproliferative, contractile state is essential for conferring vasomotor function to developing arteries[94]and promotes VSMC proliferation in perivascular adipose tissue by a paracrine mechanism [115]. Thus, proliferation and differentiation processes in VSMCs under physiological or pathological conditions are important for the understanding of remodeling in diseased arteries. Both exogenous and endogenous visfatin seem to potently regulate the biological functions of VSMCs[116].These findings were supported by **Vanet al**[94]who reported that vascular smoothmuscle maturation from a proliferative non-contractile phenotype to a non-proliferative contractile one has been found to be dependent on the presence of visfatin/ PBEF.

Vascular effects are both chronic and acute: chronic exposure to high visfatin concentrations—such as in obesity and in type 2 diabetes mellitus—promotes endothelial dysfunction, angiogenesis and atherosclerotic plaque instabilization[40], whereas acute visfatin administration stimulates eNOS expression and activity in endothelial cells [62]and directly protects cardiomyocytes against the detrimental effects of acute ischemia-reperfusion injury[117].

Endothelial function improved during the first month after transplantation, and the degree of improvement correlated to reductions in circulating visfatin [118].In a study by **Wang et al**[115]visfatin was found to have a significant relaxingeffect on isolated arteries and stimulates growth of vascular smooth muscle cells.These findings were supported by **Yamawaki et al**[62] who found that visfatin induced relaxation in mesenteric arteries of rats, suggesting that visfatin is effective in resistance vessels.These findings indicate that, besides circulating visfatin/PBEF/Nampt, locally synthesized visfatin/PBEF/Nampt may also exert a relevant paracrine action in regulating the vascular function [119]**.** These findings were also supported by **Maenhaut and Van de Voorde** [120] who found that visfatin can also directly affect vascular contractility and induced endothelium-dependent vasorelaxation in rat isolated aorta through NO production.

11- VISFATIN AND ATHEROSCLEROSIS:

Atherosclerosis is a chronic inflammatory response in the arterial wall, in large part due to the accumulation of macrophages and promoted by low-density lipoproteins [121].Controversial results exist about the expression, circulating levels and the role of visfatin in atherosclerosis-related diseases. Most studies showed increased levels of visfatin in diabetes mellitus, obesity, hypertension, renal and cardiovascular disease. However, other studies reported lower levels of visfatin in these diseases. The discrepancies in clinical studies may be attributed to the multifactorial regulation of visfatin. There is evidence that visfatin expression and circulating levels are influenced by fat area and distribution, inflammatory state, renal function, iron metabolism, hormones as well as several other factors. Furthermore, discrepancies and lack of correlation between commercially available visfatin assays have been reported [71].

Salcedoet al [122] **and Chen and Greene** [123]reported that visfatin dose-dependently stimulate MCP-1 production *via* NF-kappaB and PI3Kinase pathways, but not *via* MEK pathways. Their observations add to visfatin's pro-angiogenic and pro-atherogenic role in human endothelium.Clinical reports have highlighted the relationship existing between visfatin, atherosclerosisand atherogenic plaque instability[42].They found that both oxidized LDL and TNF-alpha increased visfatin expression in THP-1 monocytes, with a particularly enhancing effect when these stimuli were combined. Visfatin also increased MMP-9 activity in THP-1 monocytes andTNF-alpha and IL-8 levels in peripheral blood mononuclear cells. MMP and inflammatory cytokines play an important role in atherogenesis and plaque destabilization. The marked induction of these mediators by visfatin in cells with relevance to atherosclerotic lesions suggests that visfatin, showing enhanced expression in symptomatic plaques, could be an important mediator in these processes[42]. They suggested that visfatin should be regarded as an inflammatory mediator, localized to foam cell macrophages within unstable atherosclerotic lesions, that potentially plays a role in plaque destabilization.

This relationship was supported by **Kim et al**[124] who found that visfatin accelerates monocyte adhesion to endothelial cells by upregulating intercellular (ICAM-1) and vascular (VCAM-1) cell adhesion molecule-1 due to ROS overproduction, suggesting a possible role for visfatin in the development of atherosclerosis.They also reported that visfatin-mediated induction of these molecules was mainly regulated by nuclear factor- kappaB (NF-kappaB). **Xia et al**[125] reported a corresponding mechanism for visfatin-induced endothelial dysfunction in coronary artery endothelial cells, through lysosome-dependent lipid-raft signaling, and subsequent activation of NADPH oxidase and ROS production.These results were also supported by a study involved 139 Chinese patients with metabolic syndrome (40 with carotid plaques and 99 without carotid plaques), serum visfatin levels were found greater in those with carotid plaques ($p < 0.001$)[108]. They also found that visfatin independently correlated with maximum carotid intima media thickness. In another study involved 29 T2DM patients without macroangiopathy, 33 T2DM patients with

macroangiopathy, and 22 non-DM controls,**Alghasham and Barakat** [126] found that serum visfatin was significantly higher in non-complicated T2DM subjects compared with controls and macroangiopathic T2DM patients. They reported that the difference in visfatin levels between macroangiopathic T2DM patients and controls was non-significant. These findings were supported by **Kadoglou et al**[127]who found that high visfatin and low ghrelin serum levels were significantly associated with advanced carotid atherosclerosis in patients with T2DM. They also reported that these adipocytokines were independently associated with carotid intima-media thickness (CIMT), implicating their role as novel atherosclerotic biomarkers and providing another important link between adiposity and atherosclerosis.These results were also supported by **Romachoet al**[128]who found that visfatincan promote vascular smooth muscle inflammation, being associated with a potential role in vascular dysfunction and inflammation associated with some metabolic disorders. So they suggested that visfatin may have a direct role in vascular dysfunction and inflammation through iNOS upregulation.

The mechanism of action of visfatin in atherosclerosis was mentioned by **Adya et al**[95] who found that visfatin significantly increased NF kappaB transcriptional activity ($p < 0.001$) and endothelial cells pre-incubated with visfatin (dose dependently) for 16 h and then subjected to TNF-alpha (10 ng/mL) for 2 h revealed significant inhibition of TNF-alpha-induced NF-kappaB transcriptional activity by visfatin. They also found that in human umbilical vein endothelial cells, visfatin significantly and dose-dependently up-regulated gene expression and protein production of vascular endothelial growth factor (VEGF) and (Matrix metalloproteinases) MMP-2/9 and down-regulated expression of tissue inhibitors of MMPs (TIMP-1 and TIMP-2) [84]. Furthermore, inhibition of NFkappaB inhibitor significantly negated visfatin-induced matrix metalloproteinases (MMP)-2/9 mRNA expression, protein levels and activity ($p < 0.001$) [95].These findings were supported by **Dahl et al** [42]who suggested that visfatin might trigger plaque rupture by accumulating in atherosclerotic plaques where it stimulates monocyte metalloproteinase activity.

Cirillo et al[129]also demonstrated that visfatin induced transcription of mRNA for TF (Tissue Factor) by Real Time PCR and this adipokine promoted surface expression of TF that is functionally active since they measured increased procoagulant activity. These results indicated that visfatin induced a procoagulant phenotype in human coronary endothelial cells by promoting TF expression. Their observations support the hypothesis that this adipokine might play a relevant role as an active partaker in athero-thrombotic disease. These suggestions were supported by studies in different populations suggesting that high levels of circulating NAMPT are positively associated with atherosclerosis-related metabolic phenotypes, as well as with the 10-year CVD Framingham risk score [130,131,78]. These results was also supported by a recent study by **Saddi-Rosa et al**[111]who reported thatvisfatin has emerged in the last few years as a novel adipokine potentially implicated in the pathogenesis of atherosclerosis.

12- VISFATIN AND RENIN ANGIOTENSIN SYSTEM:

A study made by **Storka et al**[132]found that the release of visfatin from isolated human adipocytes, skeletal muscle cells and human umbilical vein endothelial cells (HUVEC) was 1.6-fold increased after incubation with lisinopril (ACE inhibitor) and about 2.0-fold increased with telmisartan (Angiotensin II receptor antagonist) and valsartan (Angiotensin II receptor antagonist with more selectivity on AT_1). However in the same study, differences regarding *in vitro* PPARγ (peroxisome proliferator-activated receptor gamma) binding affinity did not affect the release of visfatin into supernatant media from adipocytes or skeletal muscle cells, which was detectable for all ARB (angiotensin receptor blockers) and ACE-I (Angiotensin converting enzyme inhibitors) under study. Thus, the functional metabolic net effect in patients may also differ to some degree from the *in vitro* results obtained. These findings were previously supported by **Takebayashi et al**[133]found that visfatin was also negatively correlated with circulating aldosterone. This finding was supported by **Yilmaz et al** [134]who reported an association betweenelevated plasma visfatin and endothelial dysfunction attributed to chronic renal disease.These findings suggest that visfatin has a specific role in renin angiotensin system. Our suggestion is supported by the findings of**Nüsken et al** [135] who found that loss of renal function is accompanied by increased circulating active visfatin concentrations**.** These results were confirmed by **Huang et al**[136]who found thatvisfatin treatments increasedrenin, angiotensinogen (AGT), AT1 mRNA, and AGT, AT1 protein expression, as well as Ang II levels in a dose-dependent manner but did not affect ACE and AT2 mRNA levels in cultured rat mesangial cells. Our suggestion is also supported by a study done by **Chang et al**[77] who found that Ang II treatment induced the increased expression of visfatin and brain natriuretic peptide in a dose- and time-dependent manner in cardiomyocytes and pretreatment with AT1-R antagonist telmisartan completely blocked Ang II-induced visfatin expression increasement. The increased visfatin expression was also blocked by the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway inhibitor AG490 [77]. They concluded that visfatin expression was increased mainly through the AT1-R-JAK/STAT pathway in the process of Ang II-induced cardiomyocyte hypertrophy. Thus the role of visfatin in renin angiotensin system become well established but due to lack of studies on this aspect, the exact mechanism of action on the elements of this system need further studies.

13- VISFATIN AND HEART FAILURE (HF):

Ina study population consisted of 28 males with systolic HF referred for cardiopulmonary exercise testing and 23 controls**, Straburzyńska-Migaj et al**[137] found that concentrations of visfatin and high-density lipoprotein cholesterol (HDL-cholesterol) in the HF subjects were significantly lower ($p \leq 0.01$) than in controls.They also found significant differences in mean levels of visfatin between controls and heart failure patients. These results were supported byanother study involvingeighty-seven nondiabetic patients under PD (peritoneal dialysis) in which **Karakan et al**[138]found that left ventricular mass index (LVMI) was correlated with body mass index, systolic blood pressureand

serum visfatin levels (r = 0.49, p = 0.03).Theyconcluded that Serum visfatin might be a sensitive marker than HOMA-IR(homeostatic model assessment-insulin resistance)evaluations for cardiac performance in nondiabetic PD patients.

14- VISFATIN AS A CARDIOVASCULAR PROTECTOR:

Drugs as angiotensin converting enzyme inhibitors (ACEI), thiazolidinediones (glitazones) or angiotensin-II receptor antagonists, generally associated with the adequate hypolipidemic (statins, fibrates) or antiobesity (orlistat, sibutramine, rimonabant) medication, would increase those adipocytokines with anti-inflammatory and insulin-sensitizing properties (i.e. adiponectin or visfatin), while reducing pro-inflammatory and thrombogenic cytokines (as leptin, tumor necrosis factor [TNF]-alpha, plasminogen activator inhibitor 1 [PAI-1]). Thus, these pharmacologic therapeutic approaches would have a beneficial effect in order to diminish morbidity-mortality and improve the prognosis of patients with said diseases, all of them related to high cardiovascular risk [139]. These findings were supported by **Nakou et al**[140]who reported that verapamil SR/trandolapril combination together with sibutramine resulted in significant reductions in visfatin plasma levels at the end of a 6-month treatment. They also found that the reduction was correlated with the decrease in body mass index.

Recent evidence suggests that visfatin may be responsible for a number of different cardiovascular effects, depending on the cell type and the duration of therapy, one of which includes the ability to protect the myocardium from the detrimental effects of acute ischaemia-reperfusion injury[117]. As such visfatin may not only provide a potential new target for acute cardioprotection but it may also act as an anti-diabetic agent with a unique mechanism of action, thereby offering a potentially novel drug target for the diabetic patient that experiences an episode of acute myocardial ischaemia-reperfusion injury. These findings were also supported by **Lovren et al**[63]whoreported thatinjection of a plasmid containing visfatin in a mouse model of unilateral limb ischemia results in improved limb perfusion as compared to untreated animals.However a recent study by **Cantarini et al**[141]found thatleptin, adiponectin and visfatin are increased in idiopathic recurrent acute pericarditis (IRAP) patients versus healthy controls and they suggested that these adipokines might be involved in IRAP pathogenesis and that a possible increased cardiovascular risk in these patients, through an early onset atherosclerosis, should be kept in mind.

CONCLUSION:

In this review we concluded that visfatin has a lipid lowering effect as well as a glucose lowering effect. This effect was found to beneficial in diabetic persons who are liable to cardiovascular disease. Visfatin was also proved a protective effect in atherosclerosis which can be utilized as a drug in clinical medicine. A beneficial effect of visfatin was also found as a cardioprotective in case of myocardial infarction which is a serious problem. The valuable effect of visfatin as antihypertensive indicates further studies in human. The role of visfatin renin angiotensin system can explain the beneficial effect of visfatin in regulation of blood pressure. We suggest further studies of visfatin therapy in human for control of hypertension.

CONFLICT OF INTEREST: None.

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