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The relationship between plasma Visfatin/Nampt and type 2 diabetes, obesity, insulin resistance and cardiovascular disease

Abstract

Context: The adipose tissue is the largest endocrine organ in the body that secretes adipocytokines and molecules that influence the metabolism, insulin resistance, risk for developing type 2 diabetes and cardiovascular disease. Visfatin/Nampt is one of the most recently described adipocytokines that has attracted the attention of researchers due to its link with insulin resistance, obesity type 2 diabetes and cardiovascular disease, and cancer, however, the published data is very conflicting and confusing making it very difficult to draw any solid conclusions about its exact role in the pathophysiology of these metabolic diseases.

Evidence acquisition: PubMed searches were conducted for published work on Visfatin/Nampt all through until September 2016. The search terms included 'Visfatin AND Obesity '; 'Visfatin and Type 2 Diabetes', Visfatin and Insulin Resistance', Visfatin and cardiovascular disease. All articles identified by this search were reviewed if the article text was available in English only and the focus of the manuscript was plasma Visfatin and either obesity; type 2 diabetes, insulin resistance or cardiovascular disease. Subsequent reference searches of retrieved articles resulted in additional articles related to topic and these were included in this review.

Results: Most studies including one meta-analysis showed increased levels of Visfatin/Nampt in subjects with type 2 diabetes, obesity, and cardiovascular disease, however, the association between Visfatin/Nampt and insulin resistance is debated especially when using robust methods for assessment of insulin sensitivity.

Conclusion: There may be an association between elevated levels of plasma Visfatin/Nampt and type 2 diabetes, obesity and cardiovascular disease, however, the exact nature of this relationship is not clear from the current literature. Whether Visfatin/Nampt represents a mediator or a risk factor in cardio metabolic risk will require further clarification in future studies.

Keywords: visfatin, type 2 diabetes, obesity, insulin resistance, cardiovascular disease, nad biosynthesis, chronic atherosclerosis, glucose tolerance

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Abbrevations: PBEF, pre-B cell colony enhancing factor; NAD, nicotinamide adenine dinucleotide; Sir2, silent information regulator 2; NMN, nicotinamide mononucleotide; GLP-1, glucagon like peptide-1; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; FSIGT, frequently sampled intravenous Glucose tolerance; IMCL, intramyocellular lipid; mPTP, mitochondrial permeability transition pore; HCAECs, human coronary artery endothelial cells; NF, nuclear factor

Context

Visfatin is one of the most recently identified adipocytokines and was shown to be predominantly secreted by the visceral adipose tissue and to exert insulin-mimetic effects.[1] Since its discovery in 2005, Visfatin has been a focus of extensive research to further characterize its pathophysiological relevance to visceral obesity, insulin resistance, type 2 diabetes, and cardiovascular disease, however, a great deal of controversy existed with regards to its role and clinical relevance, as reflected by a great deal of inconsistencies in the published work. Visfatin has been described to be increased in insulin resistant states, such as type 2 diabetes and polycystic ovary syndrome.[2] Moreover, Visfatin promoter polymorphism has been shown to be associated with low grade inflammation and type 2 diabetes.[3] Visfatin has also been shown to be associated with proinflammatory markers such as interleukin IL-6.[4] In addition, Visfatin was shown to induce leucocyte adhesion to endothelial cells and aortic endothelium by induction of the cell adhesion molecules, ICAM-1 and VCAM-1.[5] However, the exact role of Visfatin in obesity and its metabolic complications such as insulin resistance and type 2 diabetes as well as cardiovascular disease remains largely unknown. This review will focus on the published literature regarding the relationship between Visfatin and type 2 diabetes, obesity, insulin resistance, and cardiovascular disease.

History of visfatin

Visfatin as an insulin-mimetic hormone

In their search for adipocytokines that are preferentially produced by abdominal visceral adipose tissue, Fukuhara and colleagues described a 52 kilo Dalton molecule in 2005 that was exclusively secreted by visceral fat and was named 'Visfatin', to indicate that it

is originating from visceral fat.[1] The authors showed that Visfatin, non-competitively, binds to and activates the insulin receptor during *in vivo* and *in vitro* studies, suggesting that Visfatin and insulin bind to different sites.[1] The authors demonstrated that intravenous administration of recombinant Visfatin to c57BL/6J mice, as well as to insulin-resistant obese KKAY mice, resulted in a significant fall in plasma glucose concentration within 30 minutes. The authors suggested that the insulin-mimetic effects of Visfatin on lowering plasma glucose were independent of plasma insulin levels. Visfatin was shown to be effective in activating the insulin signalling cascade, increasing glucose uptake, and inhibiting glucose release.[1] The findings by Fukuhara and colleagues were very interesting and exciting, particularly with regards to the insulin-mimetic effects of Visfatin and its relevance to glucose metabolism and the pathogenesis of insulin resistance and type 2 diabetes. Many research groups took great interest in studying this new adipocytokine, however, this paper was retracted by the authors due to lack of replication of their findings by other authors.[6]

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

Visfatin actually corresponds to a cytokine that has been already known to enhance the maturation of B cells precursors in the presence of Interleukin-7 and a stem cell factor and was already known as pre-B cell colony enhancing factor or 'PBEF'.[7] Samal and colleagues isolated the gene encoding PBEF (Visfatin) from a human peripheral lymphocyte in 1994.[7] In 2004, PBEF gene was shown to be located on the long arm of chromosome 7 between 7q22.1 and 7q31.33.[8] and encoded a polypeptide of 491 amino acids with a molecular weight of 52 kilo Daltons. Samal and colleagues were unable to describe a clear signal sequence in the primary structure of PBEF (Visfatin).[7] The biological function of PBEF (Visfatin) has not yet been fully understood, however, a cytokine-like activity has been reported in several studies.[7-11]

Visfatin as an enzyme (Nampt)

Martin and colleagues showed for the first time in 2001 that there was a significant homology between the mammalian Pre-B-cell colony enhancing factor (PBEF) gene and the gene encoding the bacterial nicotinamide phosphoribosyltransferase enzyme, which was referred to as '*nadV*'.[12] Martin and colleagues showed that '*nadV'* is a plasmid-encoded gene in Haemophilus ducreyi that is essential for the bacteria to grow in nicotinamide adenine dinucleotide (NAD) free media. In 2002, Rongvaux and colleagues demonstrated genetically that the mouse PBEF gene conferred nicotinamide phosphoribosyltransferase (Nampt) enzymatic activity and NAD-independent growth to bacteria lacking *nadV.*[13] In 2004, Revollo and colleagues demonstrated that the mouse PBEF gene product encodes a nicotinamide phosphoribosyltransferase enzyme (Nampt), capable of modulating intracellular NAD levels.[14] Several research groups reported the crystal structure of Nampt/PBEF/Visfatin and all these groups showed that this protein is a dimeric type II phosphoribosyltransferase enzyme involved in NAD biosynthesis.[15,16] NAD and related compounds are very important coenzymes at cellular levels in all living organisms. NAD functions as an electron carrier in the process of generation of ATP in oxidative phosphorylation. Imai and colleagues discovered that the yeast Silent information regulator 2 (Sir2) and its mouse ortholog sirtuin1 (SIRT1) were NAD-dependent deacetylases.[17]

The Mammalian homologues of Sir2 are comprised of a large family of seven proteins named Sirtuins, abbreviated as SIRT1 to SIRT7. Sirtuins are involved in many different metabolic processes and stress resistance.[17-19] SIRT1 (as a deacytylase) has been shown to regulate many important transcription factors in mammals including tumour suppressor p53, forkhead box class O (FOXO) proteins, peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α), and nuclear factor-κB.[20-22] These specific actions may influence many pathways involved in glucose and lipid metabolism and the effects of SIRT1 activation appear to be beneficial, as they trigger metabolic changes similar to those observed in caloric restriction.[18]

All the above studies showed that Visfatin has pleiotropic effects being a cytokine (PBEF), a hormone (Visfatin) and lately, the rate-limiting enzyme (Nampt) in the NAD biosynthesis, however, its physiological role in human beings remains largely unknown.

Visfatin (Nampt, PBEF) function

The physiological function of Visfatin/Nampt/PBEF has been debated by many research groups and remains largely unknown. Fukuhara and colleagues described insulin mimetic properties.[1] However, Revollo and colleagues showed that Nampt/PBEF/Visfatin has both intra-and extracellular functions as NAD biosynthetic enzyme [23]. The extracellular form of Nampt 'eNampt', which corresponds to Visfatin (PBEF), is secreted through a non-classical pathway , has both monomeric and diametric iso-forms, and has a higher activity for NAD biosynthesis, compared to the intracellular form of the enzyme 'iNampt'.[23] Nampt-deficient heterozygous (Nampt+/-) female mice had moderate impaired glucose tolerance and reduced glucose-stimulated insulin secretion.[23] Moreover, primary islet cells from Nampt+/- mice showed significant reduction in NAD biosynthesis and a reduced insulin secretion capacity in response to glucose stimulation. Furthermore, wild-type primary islets treated with FK866 (Nampt or Visfatin chemical inhibitor) resulted in the same phenotype as Nampt+/- mice.[23] Revollo and colleagues then demonstrated that the administration of nicotinamide mononucleotide (NMN), which is the product of Nampt reaction, corrected the defects in glucose tolerance and insulin secretion during both in vivo and in vitro studies.[23] However, Revello and many other researchers were unable to replicate the insulin-mimetic findings of Fukuhara and colleagues, namely, the binding of Nampt (Visfatin) to and activation of the insulin receptor.[23]

The current thinking of Visfatin (Nampt, PBEF), is as a secreted enzyme and a source of systemic NAD biosynthesis.[24] Revollo and colleagues showed that Visfatin (Nampt, PBEF)-mediated NAD biosynthesis is essential for B- cell function through regulation of glucose-stimulated insulin secretion.[23,24]

Source of visfatin

Fukuhara and colleagues demonstrated that Visfatin was over-expressed in visceral fat taken from two female volunteers and strongly correlated with obesity.[1] However, Berndt and colleagues found no association between Visfatin expression and BMI in women and were only able to describe a very weak positive association between Visfatin and BMI in men.[25] Therefore, the first observation by Fukuhara and colleagues regarding the over-expression of Visfatin in visceral adipose tissue is debatable. Although Visfatin was originally described to be preferentially produced by visceral adipose tissue and infiltrating macrophages, new evidence by Friebe and colleagues showed that leucocytes, mainly granulocytes, are the main source of circulating Visfatin in human beings, independent of body mass index.[26] Visfatin is also produced by many other cells including skeletal muscle, liver, immune cells, cardiomyocytes and brain cells.[27]

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Regulation of visfatin

The regulation of Visfatin (PEBF, Nampt), from the published human and animal studies appears to be very complicated and remains not fully understood despite many publications in the past few years. Most of the reported studies are inconsistent and sometimes describe contradicting results. Kralisch and colleagues showed that both growth hormone and TNF-α down-regulated Visfatin mRNA expression in 3T3-L1 adipocytes, while dexamethasone increased Visfatin expression.[28] Haider and colleagues showed *in vivo* studies that intravenous infusion of glucose during clamp studies increased plasma Visfatin concentrations in healthy volunteers, while infusion of insulin and somatostatin opposed the effect of glucose.[29] Bala and colleagues recently showed that plasma Visfatin levels were rapidly and significantly suppressed after ingestion of 75g of carbohydrates during 2-hour OGTT in healthy, insulin sensitive and normal glucose tolerant subjects.[30] The suppression of plasma Visfatin by oral ingestion of glucose was more pronounced in overweight and female subjects. The authors demonstrated during in vitro experiments that intravenous infusion of glucose, induction of osmotic stress (by mannitol infusion), and administration of sex steroids (estradiol and testosterone), all did not influence Visfatin release in these subjects. Interestingly, infusion of insulin strongly inhibited Visfatin release from 3T3-L1 adipocytes (*in vitro*) by approximately 50%, and this suppression was more pronounced under hyperglycaemic states. The most important finding reported by authors from this study was the fact that glucagon like peptide-1 (GLP-1) inhibited Visfatin release from 3T3-L1 adipocytes by approximately 50%. The authors showed that both insulin and GLP-1 are responsible for the rapid suppression of Visfatin levels during an oral glucose load in healthy, insulin sensitive and normal glucose tolerant subjects. The authors concluded that the inhibitory effect of GLP-1 on Visfatin release from 3T3-L1 adipocytes during OGTT in the absence of any direct effects from intravenous glucose infusion on Visfatin release may indicate the existence of a novel incretin-like effect represented by a GLP-1/ Visfatin/axis the significance of which is yet to be elucidated.3[0]

Evidence acquisition

PubMed searches were conducted for all published work on Visfatin until September 2016. The search terms included 'visfatin AND Obesity/Overweight' where obesity/overweight is defined either by BMI ≥25kg/m^2 for Caucasians, BMI ≥24kg/m^2 for Asians), and/or waist circumference >94cm for men and 80cm for women; 'Visfatin AND Type 2 diabetes' where diabetes is defined as per ADA or WHO diagnostic criteria; ' Visfatin AND Insulin Resistance' where insulin resistance is quantified by either hyperinsulinemic euglycemic clamp, frequently sampled IVGTT, OGIS, and HOMA-IR ; 'Visfatin and Cardiovascular disease' defined as either acute coronary syndromes or chronic atherosclerosis. All articles identified by this search were reviewed if the article text was available in English only and the focus of the manuscript was plasma Visfatin and either obesity, type 2 diabetes, insulin resistance or cardiovascular disease. Subsequent reference searches of retrieved articles resulted in additional articles related to topic and these were included in this review.

Studies involving circulating plasma visfatin and diabetes, insulin resistance, obesity and cardiovascular disease

Visfatin and diabetes

Several studies looked into the relationship between circulating plasma Visfatin and subjects with type 1 diabetes and type 2 diabetes. Lopez-Bermejo and colleagues examined the relationship between serum Visfatin and insulin secretion in subjects with type 2 diabetes.[31] The authors reported higher concentrations of circulating serum Visfatin in type 2 diabetes subjects compared to controls, however, subjects with newly diagnosed type 2 diabetes had similar concentrations of serum Visfatin, compared to healthy controls. There was no association found between serum Visfatin concentration and insulin sensitivity measured by frequently sampled intravenous glucose tolerance tests.[31] The authors did not provide information on dietary intake of the participants or physical activity status which are known potential confounding factors.

Chen and colleagues studied 61 Chinese subjects with type 2 diabetes and 58 age and gender-matched controls without diabetes.[32] This group of authors reported increased circulating plasma Visfatin concentrations in subjects with type 2 diabetes, even after adjustments for, age, gender, fasting insulin, HOMI-IR, Adiponectin, and WHR in simple regression. More interestingly, the researchers showed that plasma Visfatin concentration was independently and significantly associated with type 2 diabetes in logistic regression analysis.[32] However, in multiple linear regression analysis, the WHR was the only factor that was independently associated with plasma Visfatin. Another study by Hammarstedt and colleagues reported increased Visfatin concentration in newly diagnosed type 2 diabetes patients compared to healthy controls without diabetes. The researchers reported no changes in plasma Visfatin concentrations or its mRNA expression level after 4 weeks of treatment with pioglitazone in both study groups.[33] Jian and colleagues studied both circulating Visfatin concentration and Visfatin mRNA expression in 241 subjects with newly diagnosed type 2 diabetes and compared them with subjects with impaired glucose regulation and normal glucose tolerant subjects.[34] The authors reported similar concentrations of plasma in subjects with T2DM patients, impaired glucose regulation and normal glucose tolerant subjects. Plasma Visfatin concentrations were significantly lower in obese than normal-weight subjects.[34] Li and colleagues studied plasma Visfatin and Apelin in subjects with type 2 diabetes (N=30), impaired glucose tolerance (N=26) and normal glucose tolerant controls (N=36). This research group reported significantly reduced both fasting Visfatin and 2-hours post-glucose load Visfatin concentrations in subjects with type 2 diabetes compared with the controls with normal glucose tolerance, even after adjustment for BMI, age and gender.[35]

Fasting plasma Visfatin correlated positively and significantly with BMI, WHR, and fasting plasma Resistin, but negatively correlated with both HbA1c and 2 hours postprandial glucose concentration. Using multiple regression analysis, the researchers showed that WHR, HbA1c, 2 hour OGTT glucose were independent predictors of plasma Visfatin concentrations. Another study by Sandeep and colleagues reported higher concentration of circulating plasma Visfatin in 150 Asian subjects with type 2 diabetes (75 males and 75 females) compared to controls without diabetes, even after adjustment for BMI and waist circumference.[36] The only meta-analysis and systemic review in the literature with regards to the association between plasma Visfatin and obesity, type 2 diabetes and cardiovascular disease was published in 2011 by Chang and colleagues.[37] The authors pooled data from 19 different observational studies (N=2405). Visfatin was shown to be significantly increased in subjects with type 2 diabetes compared to controls without diabetes. The authors showed that even after adjusting for the confounding effect of BMI, subjects with type 2 diabetes had significantly higher plasma Visfatin concentrations,

compared to people without diabetes. The authors proposed that the increased concentrations in subjects with type 2 diabetes might represent a physiological protective mechanism to compensate for hyperglycaemia.[37] From all the above studies including one meta-analysis, the evidence indicates that most patients with type 2 diabetes have elevated levels of circulating plasma visfatin, however, the exact relevance and significance of this elevation in the pathophysiology of type 2 diabetes is not clear.

One speculation for Visfatin/eNampt increase in type 2 diabetes might be as compensation by the adipose tissue to increase glucose stimulated insulin secretion by beta cells in response to increasing insulin resistance. In support of this hypothesis is the finding by Revollo and colleagues in a previous study showing that NMN, the product of Namp reaction, corrected the defects in glucose tolerance and insulin secretion during both in vivo and in vitro studies.[23] A very recent study in animal models of diabetes showed that the monomeric iso-form of eNampt (rather than the diameric iso-form) is responsible of diabetes and inflammation in animal models.[38] The authors showed that serum monomeric eNAMPT levels were elevated in HFD-fed mouse models of diabetes, whilst eNAMPT-dimer levels were unchanged. Very interestingly, eNAMPT-monomer neutralisation in HFD-fed mice with anti-monomeric eNampt antibodies resulted in lower blood glucose levels, amelioration of impaired glucose tolerance and whole-body insulin resistance, improved pancreatic islet function, and reduced inflammation.[38] These effects were maintained for at least 3 weeks post-treatment. On the other hand, eNAMPT-monomer administration induced a diabetic phenotype in mice, characterized by elevated blood glucose, IGT, impaired pancreatic insulin secretion and the presence of systemic and tissue inflammation, without changes in NAD levels.

The authors stated that targeting monomeric eNampt represents a therapeutic target for treating type 2 diabetes. Taking the finding by Kieswiah and colleagues together with the findings by Bala and colleagues regarding the suppression of plasma Visfatin/eNampt release from 3T3-L1 adipocytes by approximately 50%, by both GLP-1 and insulin infusions during the OGTT , and the fact that this suppression was more pronounced under hyperglycemic states, it would be reasonable to speculate that high levels of plasma Visfatin could be harmful to beta cells, if we assume that most of this elevation is in the form of monomeric eNampt, however, this will certainly require further mechanistic studies in human beings. Recently, Visfatin gene polymorphism has been shown to influence glucose metabolism and the risk of type 2 diabetes in a study from Spain that included 587 patients with type 2 diabetes and controls with different degrees of obesity.[39] The authors showed that the genotype AA of the rs4730153 SNP on visfatin gene was significantly associated with fasting glucose, fasting insulin and HOMA-IR after adjustment for gender, age, BMI and waist circumference. On the other hand, the obese individuals carrying the CC genotype of the rs11977021 SNP showed higher circulating levels of fasting proinsulin after adjustment for the same variables of glucose metabolism.[39] Therefore, it appears there is an association between Visfatin/Nampt and glucose metabolism but it needs further clarification and consistency in future studies.

Visfatin and insulin resistance

Fukuhara and colleagues described an insulin-mimetic effect to Visfatin when they demonstrated that Visfatin lowered plasma glucose in animal models of insulin resistance (KKAy mice) and improved glucose tolerance.[1]

Pagano and colleagues reported reduced plasma concentrations of Visfatin and its mRNA in subcutaneous adipose tissue (SAT) in obese subjects compared to lean controls. Both plasma Visfatin and SAT Visfatin mRNA expression negatively correlated with BMI, however, no correlation was found between Visfatin and insulin resistance quantified by HOMA-IR. The authors showed no effect to a free fatty acid-induced insulin resistance state on circulating plasma Visfatin concentrations or it's mRNA.[40] Varma and colleagues reported no significant difference in Visfatin mRNA expression between SAT and visceral adipose tissue (VAT) depots. The authors reported a positive correlation between SAT Visfatin and insulin sensitivity measured by frequently sampled intravenous glucose tolerance (FSIGT). However, plasma Visfatin and muscle Visfatin mRNA did not correlate with insulin sensitivity or intramyocellular lipid (IMCL) content. Moreover, the authors reported no change in muscle Visfatin mRNA in response to treatment with both metformin and pioglitazone as insulin sensitizing agents.[41] Dogru and colleagues found no correlation between plasma Visfatin and HOMA-IR, insulin, hs CRP, plasma adiponectin or BMI is subjects with newly diagnosed type 2 diabetes, IGT and NGT.[42] We studied the relationship between circulating plasma visfatin and insulin resistance measured by euglycemic hyperinsulinemic clamp in subjects with early onset type 2 diabetes and severe insulin resistance in comparison with age and BMI-matched, insulin sensitive, obese controls and found no difference in plasma Visfatin concentration between the two groups.[43] Moreover, while we reported a significant reduction in plasma visfatin concentration following 12 weeks of an aerobic exercise intervention programme, insulin sensitivity and weight did not change in that study.[43] From the above studies, it seems that the association between Visfatin and insulin resistance is debatable. Nonetheless, Chang and colleagues published the first meta-analysis and systemic review about the association between Visfatin and insulin resistance.[37] Twenty three population samples were identified from twenty observational studies that assessed the association between Visfatin and insulin resistance, which was assessed by HOMA-IR. The authors reported significant association between Visfatin & HOMA-IR.[37] Despite the acknowledgment by the authors regarding the limitations of the wide heterogeneity among the studies, the authors did not acknowledge the limitations of HOMA-IR as a tool for assessment of insulin resistance. Interestingly, the studies which used hyperinsulinaemic euglycaemic clamp studies (the gold standard for assessment of insulin sensitivity), did not report any correlation between insulin sensitivity and plasma Visfatin.[25,33,43-45] Similarly, other studies which used frequently sampled IVGTT did not report correlation between Visfatin and insulin sensitivity or intramyocellular lipid (IMCL) in skeletal muscle.[41] Therefore, convincing evidence regarding the association between Visfatin and insulin resistance in human beings is currently lacking.

Visfatin and obesity

It's known that with expansion of the visceral adipose tissue in obesity, the expression and secretion of pro-inflammatory adipocytokines is increased. Fukuhara and colleagues showed in their original publication in 2005 that visfatin is exclusively secreted from the visceral adipose tissue.[1] Following that study, Berndt and colleagues reported a positive correlation between plasma Visfatin and visceral adipose tissue Visfatin mRNA expression.[25] They also reported a negative correlation between plasma Visfatin and subcutaneous adipose tissue Visfatin expression in 163 subjects with a wide range of age, BMI, and glucose tolerance status.[25] The authors, however, reported no correlation between plasma Visfatin concentrations and

visceral fat mass calculated from computed tomography scans in a subgroup of 73 subjects. Importantly, the authors found no difference in Visfatin gene expression between visceral and subcutaneous adipose tissues in the whole study group and in subgroup analysis.[25] Pagano and colleagues reported significantly reduced concentration of plasma Visfatin and its mRNA expression in subcutaneous adipose tissue in obese subjects, compared with normal-weight controls.[40] The authors reported a negative correlation between circulating Visfatin, subcutaneous Visfatin mRNA and the body mass index. Interestingly, Visfatin mRNA was found to be significantly higher in visceral adipose tissue of obese subjects, compared with lean controls, however, Visfatin mRNA in visceral adipose tissue was positively correlated with BMI and the authors suggested that Visfatin is differentially regulated in visceral and subaqueous adipose tissue in lean and obese subjects.[40] Another study recently published also reported reduced circulating levels of plasma Visfatin in obese subjects compared to controls and, after 52 weeks post endoscopic and surgical weight reduction plasma levels were significantly increased.[46] On the other hands, increased concentrations of plasma Visfatin were reported in obese and overweight Korean women compared to controls and the levels decreased after 12 weeks of an exercise intervention programme.[47] On the contrary to the above mentioned two studies, Shea and colleagues reported no difference in plasma Visfatin concentrations between lean, overweight and obese 53 male subjects.[48] A recent study from Czech Republic looked into the relationship between Visfatin genetic variability with anthropometric parameters and dietary composition in 20 extremely obese subjects with BMI >52kg/m^2 and 605 non-obese subjects the authors found a relationship between one SNP in exon 7 (rs2302559 A/G and serum Visfatin levels.[49] The study showed that the rs2302559 SNP showed significant correlation with Visfatin serum level throughout the entire study cohort and there was a significant tendency toward higher visfatin levels in G allele carriers with the GG homozygotes having the highest serum Visfatin serum.[49]

In the only published meta-analysis and systemic review mentioned above, the authors pooled data from 13 studies (N=644) regarding the association between plasma Visfatin and overweight/Obesity. Chang and colleagues showed in this meta-analysis that plasma Visfatin was increased in overweight and obese subjects.[37] Therefore, most studies described elevation of Visfatin in obesity while some described unchanged or even lower levels, however, whether this elevation is part of the pro-inflammatory milieu of obesity or a compensation to overcome insulin resistance that accompanies obesity is not clear.

Visfatin and cardiovascular disease

The role of Visfatin in cardiovascular disease has been controversial as well since both cardio protective and harmful effects have been reported. Lim and colleagues showed that intravenous administration of Visfatin to atherosclerotic animal models of acute myocardial infarction at the time of myocardial re-perfusion reduced the infarct size.[50] Possible mechanisms suggested by the authors of this study were through the activation of the pro-survival kinases Akt and PI3K pathways and the inhibition of the mitochondrial permeability transition pore (mPTP). The authors speculated that, exogenous Visfatin is likely to exert cardioprotective properties against acute myocardial infarction; however, the role of endogenous Visfatin in cardioprotection is unknown. In a review article it was suggested that the acute cardioprotective effects of Visfatin coupled with its anti-hyperglycaemic effects would provide a novel drug target that would be quite useful to patients with type 2 diabetes with coronary artery disease, presenting with an acute coronary syndrome.[51] However, the same author reviewed the evidence regarding Visfatin and cardiovascular disease and found that Visfatin exerted many diverse effects including endothelial dysfunction, angiogenesis, atherosclerotic plaque instability, besides acute cardioprotection and concluded that the main factors responsible for these diverse effects were shown to be the duration of therapy and cell type being involved.[51]

Dahl and colleagues showed increased expression of Visfatin in macrophages from subjects with unstable carotid and coronary atherosclerotic lesions and the authors suggested a pro-inflammatory role in plaque destabilization.[52] Both oxidised LDL and TNF-alpha increased Visfatin expression in THP-1 monocytes. Future studies failed to consistently describe the relationship between plasma Visfatin and cardiovascular disease. In the previously published meta-analysis quoted above, Chang and colleagues pooled data from 5 observational studies (N=851) regarding the association between plasma Visfatin and cardiovascular disease. Chang and colleagues showed in this meta-analysis that plasma Visfatin was increased in subjects with cardiovascular disease, compared to those without cardiovascular disease.[37] The authors used different definitions for cardiovascular disease such as acute coronary syndromes, carotid atherosclerosis, stroke, coronary artery disease and carotid plaque. Interestingly, when analyses were adjusted for the BMI, subjects with cardiovascular disease and higher BMI had Visfatin levels similar to that of controls with normal BMI. An important study by Cirillo and colleagues showed that Visfatin induced tissue factor expression in human coronary artery endothelial cells (HCAECs).[53] The authors stimulated HCAECs with Visfatin concentrations that are comparable to levels found in patients with acute coronary syndromes and demonstrated that Visfatin promoted the expression of tissue factor, inducing a procoagulant phenotype in human coronary endothelial cells through the activation of nuclear factor (NF) kB.[53] In an editorial accompanying the same article by Cirillo and colleagues, Halvorsen and colleagues highlighted the complex role of Visfatin in atherosclerosis as it has been shown to mediate both adaptive and maladaptive effects in atherosclerosis, depending on its molecular form.[54] The authors referred to the challenges facing researchers working on Visfatin and raised important research questions with regards to whether extracellular Visfatin/Nampt activity is mediated through a receptor, through enzymatic activity or non-enzymatic. Moreover, it has been shown that the levels of visfatin elevation directly correlated with the number of occluded coronary arteries in subjects presenting with acute myocardial infarction.[55] A recent important study found an association between visfatin genetic variation and the risk for cardiovascular disease.[39] The authors elegantly showed in a population study from Spain including diabetics and controls that the genotype AA of the rs4730153 SNP on Visfatin gene appears to protect against CV-risk in obese and non-obese individuals, estimated by Framingham and SCORE chart.[39] Therefore, although there is a clear signal regarding the association between Visfatin/Nampt and cardiovascular disease, a lot of clarification is needed in future studies.

Conclusion

The current evidence points towards a role for elevated plasma Visfatin concentrations in type 2 diabetes, cardiovascular disease, and obesity and this may be explained by Visfatin's role as a pro-inflammatory adipocytokine, however, this needs further clarification in the future.

Visfatin's role in insulin resistance remains controversial, especially when using robust methods for quantification of insulin sensitivity such as the clamp. The controversies in the published

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literature regarding the association of Visfatin with metabolic diseases may be related to assay detection problems, which have been elegantly described by Korner and colleagues.[56] Also, the presence of different iso-forms for Visfatin/eNampt, as monomeric and diametric eNampt together with lack of known receptor(s) is yet another problem facing researchers and needs careful consideration in interpretation of current and future studies. Whether increased or even reduced levels of plasma Visfatin is a risk factor or a risk mediator in the pathophysiology of metabolic diseases and atherosclerosis will require larger, mechanistic studies using robust assays for Visfatin detection with clear indication of what iso-form that has been measured. There is a potential of drug discovery targeting Visfatin/eNampt for treating metabolic conditions such as type 2 diabetes and coronary artery diseases as evidenced from animal studies, however, a lot of work is required in the next few years to come before we can see studies in human beings.

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Conflicts of interest

The author declares there is no conflict of interest.

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