DOI: 10.15386/cjmed-591

THE CARDIOVASCULAR IMPACT OF VISFATIN - AN INFLAMMATION PREDICTOR BIOMARKER IN METABOLIC SYNDROME

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Abstract

As it had been already stated by latest research, inflammation is a condition which sits at the very base of atherogenesis, which is the major consequence of the metabolic syndrome. It was stated that adipose tissue impacts all organs by the synthesis of adipokines. Visfatin/NAMPT is a biomarker that was recently discovered in mice (2005). In the beginning it was believed to have insulin-like properties, but afterwards research has found important links between Visfatin and inflammation, endothelial dysfunction and atherosclerosis in coronary artery disease. It was also linked to plaque instability in acute coronary syndromes. More studies are needed though, to clearly state whether Visfatin/NAMPT has a positive or negative role because, up until now, the only sure fact is that its serum levels correlate with the presence of an inflammatory state.

Keywords: visfatin, NAMPT, metabolic syndrome, cardiovascular disease, biomarker

Introduction

Research of the last decade has concluded that obesity is closely linked to systemic inflammation through proinflammatory cytokines such as TNF-alfa, IL-6, as they are being secreted by the adipo-cells. When referring to insulin resistance it has already been stated that these cytokines contribute to the development of T2DM and they also interfere with the immune system. T2DM and insulin resistance are among the most important cardiovascular risk factors, whose prevalence is not foreseen to diminish in the next years.

The definition of the metabolic syndrome is the sum of: low glucose tolerance, high insulin, type 2 diabetes, obesity and arterial hypertension. It is a real health problem worldwide that affects an important proportion of the population and its prevalence is continuously growing. We can almost talk about an epidemic of atherosclerotic disease. In one study [1] regarding the risk factors for the ischemic cardio-vascular disease, patients with metabolic syndrome automatically had a high cardio-vascular risk and increased all cause mortality because it is linked with high prevalence of myocardial infarction and stroke.

Omental adipose tissue also is not an inert organ, but it acts as an endocrine system which sets free in the circulation a various number of adipokines [2]. In particular, individuals with central adipose tissue are at high risk, because these adipocytes synthetize various proinflammatory chemokines (MCP-1, macrophage migration inhibitory factor-MIF-, tumor necrosis factor, interluekine-1, -6, pro-coagulant and proinflammatory mediators such as tissue factor (TF), plasminogen activator inhibitor-1 (PAI-1), vasoactive substances such as angiotensinogen and endothelin-1, molecules involved in the pathogenesis of insulin resistance (TNF and resistin) [3,4,5,6]. Also, Visfatin, which was previously linked to the pre-B cell maturation pathway (also named pre-B cell colony enhacing factor), is abundantly expressed in the visceral adipose tissue and its expression is up-regulated by other cytokines [7]. Visfatin is a protein that can induce the production of IL-1, TNF, and IL-6 by the monocytes [8].

Manuscript received: 22.09.2015
Received in revised form: 05.10.2015
Accepted: 20.10.2015
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The vascular effects of Visfatin are both acute and chronic: if acutely exposed to Visfatin, it acts by increasing the eNOS expression activity in endothelial cells. When administered chronicly it promotes all stages of atherothrombosis (plaque formation, plaque rupture and occlusion) [9].

Inflammation and metabolic syndrome

In all patients, but specially in obese and T2DM patients, at the level of the visceral and subcutaneous adipose fat tissue, there is an intense pro-inflammatory activity which is promoted by the adipose cells together with the inflammatory cells. Therefore the adipose tissue is not only regarded as a fat depot, but a real organ that is capable of synthesizing a wide variety of adipokines. Once these adipokines are released, they can trigger different systemic effects on organs and tissues, many of which have been uncovered by latest research, but as we might assume, are only the "tip of the iceberg". Together with widely known cytokines and chemokines like TNF-alfa, IL-2, (MCP-1), coagulation factors, there are leptines and adiponectin. The latest two are specifically secreted by the adipose tissue. Latest research added a number of adipokines to the above list: resistin, apelin, dypeptidyl-peptidase 4 (DDP-4) and Visfatin/NAMPT nicotinamide-monophosphate-transferase). Samal et.al originally cloned Visfatin and its twin protein was also described in bacteria, intervertebrate sponges and fish.

In a state of chronic arterial wall injury (i.e hypertension, long term exposure to other risk factors) vascular smooth muscle cells (VSMC) respond by intense proliferation. Cytokines and growth factors such as IL-1, IL-6, TGF-1, TNF-alfa, thrombin, bFGF, IGF-1, PDGF, urokinase-plasminogen activator (u-PA), angiotensin-II, VEGF act as stimulators for VSMC through the pathway of MMP-9 [10].

When related to the obese subjects, research has shown that there is impaired vasodilation especially in the arteries involving cerebral, mesenteric, coronary and skeletal muscle areas. This is due to the over-secretion of proinflammatory cytokines , increased release of fatty-acids all of which in turn, alter gene expression and cell signaling at the level of the endothelium, promoting oxidative stress (increased production of super-oxide anion) and vascular insulin resistance which characterizes metabolic syndrome. Also it impairs the balance between vasodilation exerted via the NO/cGMP/PKG pathway and vasoconstriction via ET-1, in favor of the latter [10]. Research made on insulin resistant Zucker fa/fa rats show a reduced response to the NO/cGMP/PKD pathway by a reduced cGMP production, reduced NO and cGMP ability to activate PKG. Also it was demonstrated that Zucker fa/fa rats had high levels of O2 and antioxidants and these work as protectors for the pathway NO/cGMP/PKG, in contrast with oxidative stress products which alter it, therefore promoting detrimental vasoconstriction, which demonstrates the role of the oxidative stress in reducing the endothelium independent relaxation observed by other author in vivo models [11,12].

As mentioned before, the visceral adipose tissue plays a more significant role in the production of proinflammatory factors than the subcutaneous one. Visfatin is a relatively newly identified adipokine - named by joining the two terms; visceral fat - as initially it was thought that it was produced only by the visceral fat. In 2005, Fukuhara et al. described it as an insulin-mimetic adipokine in mice, and then proved that it also existed in the human body, where it was known as the pre-B cell colony enhancing factor [13]. The action of Visfatin is of enzymatic type, similar to that of nicotinamide phosphoribosyl transferase, as demonstrated in 2002 by Rongvaux et al. [14]. Two Nampt isoforms have been described: the intracellular form (iNampt) responsible for the activity of the NAD-dependent enzymes, in relation to cell aging and cell survival, and the extracellular form (eNampt) responsible for transmitting inter-organ signals, an antiapoptotic effect promoting cardiovascular cell survival by delaying mPTP (mitochondrial permeability transition pore) opening due to oxidative stress [15–18]. The latest research studies have shown that in addition to adipocytes there are a variety of cells that secrete Visfatin: chondrocytes, amniotic epithelial cells, heart cells, pancreatic cells, liver cells [19]. The action of Visfatin is of the enzymatic type for nicotinamide adenine dinucleotide synthesis (NAD and Sirt1 [11]). Samal et al. provided significant proof that visfatin is expressed in lysates from human heart, pancreas , liver and skeletal muscle at the level of the mRNA. This finding was completed by recent studies which located visfatin also in human myoblasts and hepatocytes [20] chondrocytes, amniotic epithelial cells, pancreatic cells [21].

The patho-physiological role of Visfatin

Inflammation cells such as monocytes and macrophages induce and regulate immune functions by establishing intimate intercellular contact with T cells. Visfatin was demonstrated to significantly induce the expression of CD-80 and CD40 in monocytes and also of ICAM-1 (CD54), thus resulting in activation of T cells, also being an important chemotactic factor for CD14+ and Cd19+ B cells [12]. Furthermore, Visfatin activates endothelial cells and smooth muscle cells in vessels, and has an immunomodulatory role by increasing the expression of IL8 and TNF-alpha [22]. Stimulation with visfatin on human leukocytes demonstrate a dose dependent induction IL-1 beta, IL-1Ra, IL-10, IL-6. The most significant effects were observed on Il-6 [12]. Same study observed that when treating human monocytes with recombinant visfatin there was an induction dependent on p38 and MEK-1 of Il-1beta, IL-6 and TNFalpha. But when administered to mice, visfatin produced an increase in IL-6, TNF-alpha and Il-1beta were not elevated. The source of IL-6 seems to be the IL-6 mRNA [12]. Il-6 is present and involved in a variety

of immunological processes [12] and is a key factor for the progression of the atherothrombotic disease and plaque destabilization by activating MMPs, promoting oxidation of lipoproteins by phospholipases, stimulating the release of acute phase proteins and proinflammatory cytokines [10]. It is involved in the pathology of insulin resistance associated with visceral obesity [12] and its stimulation is a risk factor for re-stenosis after angioplasty because it is involved in the growth-factor-dependent VSMC migration and proliferation [10].

As demonstrated on HUVEC - Visfatin acts as a growth factor inducing proliferation of vascular smooth muscle cells and of fibroblasts, and plays a part in myocardial fibrosis and cardiac remodeling, in capillary tube neoformation mediated by the vascular endothelial growth factor (VEGF) [23].

Exogenous administration of Visfatin/Nampt promotes the expression of iNOS (inducible NO-synthase), which disrupts the production of nitric oxide and leads to the formation of peroxynitrite, and respectively to endothelial dysfunction.

HUVEC studies have also shown that Visfatin promotes the expression of cellular adhesion molecules such as ICAM-1, VCAM-1, E-selectin, molecules with a role in leukocyte recruitment and in proatherosclerotic events [24–26].

The current literature on the subject shows high levels of Visfatin/Nampt in patients with type II diabetes and / or obesity which, as it has been reiterated, represent individual risk factors for inflammation and, respectively, atherosclerosis.

Cardiovascular disease and Visfatin

Cardiovascular complications are largely accountable for the highest mortality among patients with diabetes. The atherosclerotic coronary, cerebral and peripheral arteries heart disease accounts for 80% mortality and 75% hospitalization rate in these patients [1].

Studies on the adipokine properties of Visfatin showed its involvement in all syndromes characterized by increased resistance to insulin (type II diabetes, gestational diabetes, polycystic ovary syndrome). Given that deregulated angiogenesis is mentioned as a pathogenetic factor in the atherosclerotic cardiovascular disease, the most recent research focused on demonstrating whether serum Visfatin could be used as a marker and predictor of this disease.

So far it has not been possible to clearly state whether the role of Visfatin is that of a promoter of inflammation or, on the contrary, a protector of the vasculature, or simply that of a biomarker, although there are important studies which stipulate all these variants. For example, some have shown that there is a strong correlation between serum levels of Visfatin and endothelial dysfunction while Uslu et al. claimed that they found no clear connection between Visfatin/Nampt and ADMA (asymmetric dymethylarginina), the main endogenous inhibitor of NO synthase (endothelial nitric oxide synthase) [20]. Taking a step even further, Kadoglou et al. demonstrated a positive connection between serum levels of Visfatin and intima-media thickness (IMT) [27]. Nevertheless, what is clear so far is that Visfatin is found in the plasma of patients with inflammatory syndrome.

The sequence ischemia/reperfusion (I/R) is an event that is an important cause of heart failure. Nicotinamide-phosphoribosyl transferase (NAMPT) is an enzyme that was shown to protect the heart from the IR phenomenon by two possible ways: a) through the positive effect of ischemic preconditioning (IPC) or b) caloric restriction upregulates Nampt and exerts its protective effects through Sirt-1 (a class III histone deacetylase) dependent pathways [24]. During ischemia, in order to survive from in an hypoxia state, cardiomiocytes switch their metabolism from an aerobic one to the anaerobic state. Therefore it goes from fatty acid oxidation to glycolysis, activating autophagy, a mechanism that preserves ATP [28]. If reperfusion rapidly occurs, , it provides fuel for the production of ATP (glucose, fatty acids), washes out the noxious products resulted from necrosis, but at the same time the rapid recovery of extracellular pH and the oxygen supply results in Ca+ overload and oxygen reactive species, which in turn, contribute to reperfusion injury [29]. Studies have shown that endogenous NAMPT/Visfatin is downregulated in response to I/R [24]. More surprisingly is that when administering NMN (nicotinamide-mononucleotide), the product of NAMPT, to NAMPT+/- mice, it caused a partial recovery of insulin secretion from pancreatic B-cells. Takanobu et al. have demonstrated that myocardical infarction after I/R is exacerbated in NAMPT +/- mice, therefore endogenous NAMPT protects the heart from I/R injury [24].

When referring to the acute coronary syndrome, it no longer seems necessary to mention the importance of early detection biomarkers in the prognosis of immediate as well as long-term mortality. In this area it would be interesting to discover if certain markers could predict the risk of plaque rupture. Mazaherioun et al. have demonstrated that serum levels of Visfatin >7.244 ng/ml had a sensitivity of 70% and a specificity of 75% in detecting patients with acute myocardical infarction (AMI) [30]. Also, Yamamoto et al. demonstrated that in mice with an overexpression of NAMPT, infarct size was attenuated and NAMPT seemed to protect the heart from I/R in vivo [31].

What is clear so far is that in acute coronary syndrome plaque instability and serum levels of Il-6 and MCP-1 correlate positively with that of Visfatin / Nampt [30]. An over-expression of it has also been observed in smooth muscle cells in contact with the atherosclerotic plaque, and in the unstable plaque foam cells in patients who have suffered a heart attack. This led to the conclusion that Visfatin could be connected to plaque instability [30].

Another group of researchers has shown that increased levels of Visfatin positively correlate with hs-CRP and artery occlusion, responsible for myocardial infarction [32].

These data allow us to feel confident that probably before long we will be able to predict unstable plaque rupture more accurately, which will result in a decrease of the mortality rate from acute myocardial infarction.

Conclusion

In the current context of knowledge on this new adipokine the following question rises: does Visfatin have a positive or a negative role? Until now, in different clinical contexts its function has not been clearly defined, but research clearly heads towards defining it as a biomarker of inflammation.

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