Do novel adipokines play a causative or only modulating role in the pathogenesis of obesity and metabolic disorders?

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Submitted: 2011-10-29 Accepted: 2011-12-15 Published online: 2012-03-10

Key words: **adipose tissue; omentin; vaspin; visfatin; obesity**

Neuroendocrinol Lett 2012; **33**(1):11–15 **PMID:** 22467105 NEL330112R01

Abstract

Adipose tissue is an endocrine and paracrine organ that releases a large number of bioactive mediators. Approximately 100 adipokines have been identified including cytokines, chemokines, growth factors and enzymes. The use of adipoproteomic analyses resulted in new findings and, in consequence, the number of new adipokines is rising rapidly. Novel adipokines such as visfatin, vaspin and omentin were discovered about five years ago. Visfatin and vaspin production and secretion take place in adipocytes, but omentin comes from the stromal cells of adipose tissue. Several differences are noticeable between these adipokines especially in correlation with obesity as visfatin and vaspin serum levels increase in obese subjects while omentin serum levels decrease. It has been suggested that these adipokines act as insulin-sensitizers/insulin-mimetics. Increasing number of publications reporting the role of new adipokines does not allow to assess clearly the influence of those adipokines on the pathogenesis of obesity.

INTRODUCTION

Obesity, characterized by excessive accumulation of adipose tissue, is caused by an imbalance between energy intake and expenditure. It is a rapidly growing disease affecting about 300 million people worldwide. Several factors are thought to contribute to fat excess including genetic factors and their interaction with multiple environmental components. Obesity is associated with a wide range of health consequences like insulin resistance, type 2 diabetes mellitus (T2D), hypertension, hyperlipidemia and atherosclerosis.

Adipose tissue consists of white (WAT) and brown adipose tissue (BAT). In general, BAT is responsible for thermogenesis. It makes about 25% of neonate body mass and reduces in adults. WAT creates the greatest part of adipose store being divided into two large depots: subcutaneous and visceral, and many small depots associated with internal organs such as heart, blood vessels, major lymph nodes, pancreas, prostate gland and ovaries. The omental visceral fat in comparison to subcutaneous one is more metabolically active and also contains much more amount of insulin-resistant adipocytes (Johnson *et al.* 2001; Sharma 2002). Body fat distribution is of a great importance because visceral obesity is associated with higher risk of insulin resistance, type 2 diabetes and cardiovascular disease in comparison to subcutaneous type of obesity (Bjorntorp 1991). Growing amount of visceral adiposity enhances an increase of circulating non-esterified fatty acid (NEFA) levels. In result, insulin plasma levels elevate and then inhibit glucose absorption of insulin-sensitive tissue such as liver or muscles. This long-term

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inhibition may contribute to insulin resistance. Moreover, it has been suggested that increased NEFA circulating levels could inhibit activity of glucose transport (Felber *et al.* 2002; Sharma 2002).

Adipose tissue is composed of adipocytes embedded in a matrix of connective tissue, fibroblasts, endothelial cells and immune cells like monocytes and macrophages (Sharma 2002). Adipose tissue has been considered as an active endocrine organ from the time of leptin discovery in 1995 (Trujillo *et al.* 2006). Since then, a large number of bioactive mediators produced by adipose tissue, collectively named adipokines, have been isolated (Renes *et al.* 2009; Poulos *et al.* 2010). These substances such as adiponectin, leptin, resistin, visfatin, vaspin, omentin, tumour necrosis factor (TNF-α) and interleukin-6 (IL-6) have a wide variety of biological functions including modulation of lipid and glucose metabolism, blood pressure or inflammation (Rabe *et al.* 2008).

VISFATIN

Visfatin was isolated in 2005 and described as an adipokine with insulin mimetic effects that directly binds to and then stimulates the insulin receptor (Fukuhara *et al.* 2005). It was named "visfatin" to underline that it is preferentially expressed in abdominal visceral fat (Fukuhara *et al.* 2005, Pagano *et al.* 2006). Visfatin had been originally identified about ten years earlier, as a pre-B cell colony enhancing factor (PBEF), cytokine produced by lymphocytes which enhanced the effect of IL-7. PBEF was then characterized as protein being mainly expressed in bone marrow, liver, and muscle (Samal *et al.* 1994; Kitani *et al.* 2003) and involved in lymphocyte maturation and inflammatory regulation. It has also been described as an enzyme – nicotinamide phosphoribosyltransferase (NAMPT) participating in biosynthesis of nicotinamide adenine dinucleotide (NAD) (Rongvaux *et al.* 2002; Garten *et al.* 2010).

The visfatin gene is located on chromosome 7q22.2 and consists of 11 exons and 10 introns. It encodes 52 KDa protein composed of 491 amino acids. The visfatin amino acid sequence is highly conserved across animal evolution. Its homologues have been found in many different species like bacteria (Martin *et al.* 2001), invertebrate sponges (Muller *et al.* 1999) or fish (Fujiki *et al.* 2001).

At first, visfatin has been considered to be located primarily in the cell nucleus and in the cytoplasm (Kitani *et al.* 2003); however, it could be also secreted extracellularly by an alternative pathway (Rubartelli *et al.* 1990; Andrei *et al.* 1999). These two localizations of visfatin combine different functions: intracellular action is responsible for maintaining the NAD-dependent enzymes activity and the regulation of cellular metabolism, while extracellular one play paracrine or endocrine role due to being released not only by adipocytes but also by many different cell types (Revollo *et al.* 2004; Revollo *et al.* 2007).

Visfatin biological role has not been clarified yet. Initially, studies indicated that visfatin has glucose-lowering and insulin-mimicking/-sensitizing effects by binding insulin receptors (IR). Competitive inhibition test showed that visfatin does not compete with insulin for binding to IR but connects the receptor in different sites (Fukuhara *et al.* 2005). Binding of visfatin to IR induces phosphorylation of IR and IRS-1 and -2 (insulin receptor substrate-1 and -2) which causes stimulation of kinases: protein kinase B (Akt) and mitogen-activated protein kinase (MAPK) (Fukuhara *et al.* 2005). Despite the insulin-sensitizing action of visfatin found *in vitro* and similar to insulin affinity for the IR, low serum visfatin levels under physiological conditions and absence of regulation by fasting and feeding suggest that visfatin may not play a role of the insulin sensitizer *in vivo* (Skop *et al.* 2010).

Visfatin can influence glucose levels directly similarly to insulin, and indirectly by induction the expression of PPAR-γ (peroxisome-proliferator-activated receptor-γ), which may decrease insulin resistance (Fukuhara *et al.* 2005). Another mechanisms by which visfatin can affect glucose levels is stimulation of expression and incorporation of glucose transporter 1 (GLUT1) protein into the plasma membrane of mesangial cells (MCs) (Song *et al.* 2008). Fukuhara *et al.* (2005) in *in vivo* investigation showed that mouse heterozygous with mutations in the visfatin gene have moderately higher levels of plasma glucose. Further research on this mouse model revealed low glucose-stimulated insulin secretion and consequently impaired glucose tolerance (Revollo *et al.* 2007). In this particular study the insulin-mimetic effect was altered by administering nicotinamide mononucleotide (NMN), the visfatin product which is transformed to NAD. This result suggest that glucose-stimulated insulin secretion in pancreatic β-cells are created by NAMPT, an extracellular NAD biosynthetic enzyme (Revollo *et al.* 2007).

Fukuhara *et al.* (2005) in *in vitro* study demonstrated that expression and secretion of visfatin increase during differentiation of adipocytes. The authors also indicated a connection between visfatin secretion from visceral adipose tissue and plasma visfatin level, as well as correlation with human visceral fat mass estimated by computed tomography (Fukuhara *et al.* 2005). Varma *et al.* (2007) questioned relationship of visfatin with visceral fat as they showed that visfatin mRNA is also expressed in high level in subcutaneous adipose tissue in lean, more insulin-sensitive subjects. In other study, Berndt *et al.* (2005) emphasized that plasma visfatin concentration correlates with body mass index (BMI) and percentage of body fat in but there is no difference in visfatin mRNA expression between visceral and subcutaneous adipose tissue in humans. Curat *et al.* (2006) suggested that macrophages of adipose tissue could be the main source of visfatin. Additionally, as demonstrated by Haider *et al.* (2006), a strong relationship is found between obesity and elevated plasma visfatin

concentrations in obese patients in whom visfatin levels decreased after weight loss. However, another studies showed reduced plasma visfatin levels in obese animals and humans (Pagano *et al.* 2006; Mercader *et al.* 2008). The presented data suggest that regulation of visfatin production under conditions of obesity is not entirely clear.

Aside from the fact that visfatin is an adipocyte-specific protein, this protein has been also considered as an inflammatory cytokine being produced and released by the macrophages of adipose tissue (Curat *et al.* 2006). Addition of recombinant visfatin could increase, in the dose-dependent manner, the production of the pro- and anti-inflammatory cytokines such as IL-1, IL-6, IL-10 and TNF-α in human monocytes (Moschen *et al.* 2007). Visfatin association with IL-6 seems to be one of the most significant amongst adipokines (Oki *et al.* 2007). It has been reported that visfatin acts as a mediator of inflammation which induced the production of IL-6 in human monocytes by MAPK and MAPK kinase 1 (MEK1) pathways (Moschen *et al.* 2007). Visfatin produced by neutrophils, macrophages and monocytes remains up-regulated in many acute inflammatory diseases such as acute lung injury (Ye *et al.* 2005), inflammatory bowel disease (Moschen *et al.* 2007) and rheumatoid arthritis (Otero *et al.* 2006).

It has also been reported that visfatin is able to induce oxidative stress by generating reactive oxygen species (ROS). The NFkB pathway is involved in this particular effect (Oita *et al.* 2010).

VASPIN

A novel adipokine vaspin has been identified for the first time in visceral white adipose tissue (WAT) of Otsuka Long-Evans Tokushima Fatty (OLETF) rats (animal model of type 2 diabetes, characterized by abdominal obesity, dyslipidemia, insulin resistance and hypertension) (Hida *et al.* 2005). After identification and characterization as a new member of serpin (serin protease inhibitor) family it was named "vaspin" (visceral adipose tissue-derived serpin). It is worth noticing that although it has reactive site loop and shows structural homology to serpin, its serine protease inhibitor activity has not been observed yet.

Vaspin gene expression increases in 30-week old OLETF rats when obesity and insulin resistance develop, however decreases in 50-week old OLETF rats with worsening of diabetes and body weight loss (Hida *et al.* 2005). Hida *et al.* (2005) demonstrated that vaspin mRNA expression is induced by addition of insulin or thiazolidinedione to this rat, which suggest that vaspin could play a role in compensation for the impairment of glucose metabolism and insulin sensitivity. Moreover, these authors found that administration of recombinant human vaspin to mouse with diet-induced obesity results in significant improvement of both insulin sensitivity and glucose tolerance. In addition, vaspin also influences the expression of genes involved in the pathogenesis of insulin resistance such as genes of resistin, leptin, adiponectin, glucose transporter-4 and TNF-α (Hida *et al.* 2005).

Human vaspin is composed of 395 amino acids and it is homologous in 40% to alpha1-antitrypsin, acute-phase protein originated from the liver, which level increases during inflammation (Gettins 2002). Human vaspin is expressed in visceral and subcutaneous adipose tissue in obese people with normal glucose tolerance (NGT) but it is not detected in WAT of lean subjects with NGT (Klöting *et al.* 2006). It seems that vaspin gene expression is regulated depending on the fat depot. Visceral vaspin expression is found to be significantly correlated with BMI, percentage of body fat and serum glucose levels following 2 hrs oral glucose tolerance test (OGTT). On the other side, subcutaneous expression of vaspin gene is significantly correlated with waist-to-hip ratio (WHR), fasting plasma insulin concentration and glucose infusion rate during steady state of the euglycemic–hyperinsulinemic clamp (Klöting *et al.* 2006). Vaspin serum concentrations are correlated with obesity. Its elevated levels impair insulin sensitivity, however, this correlation is not observed in patients with type 2 diabetes (Youn *et al.* 2008; Handisuraya *et al.* 2010). It is possible that metformin used in the type 2 diabetes treatment decreases serum vaspin levels via glucose-lowering effect by suppression of hepatic glucose production (Johnson *et al.* 1993; Inzucchi *et al.* 1998). Interestingly, low serum vaspin concentrations are found in subjects with long-term physical training activity, although elevated values of this peptide are observed during the first 4 weeks of intensive exercise training (Youn *et al.* 2008). Interpretation of this paradox considers hypothesis that vaspin regulation differs dependently on the resting state and after exercise. Besides, differences in serum vaspin levels are also observed between patients with or without microvascular complications as those with microvascular changes have lower values (Gulcelik *et al.* 2009).

Similarly to other adipokines, leptin and adiponectin, vaspin serum concentrations are gender-dependent and are found to be significantly higher in female than male subjects (Youn *et al.* 2008). This difference might be a result of the amount of adipose tissue and its distribution. Interestingly, in type 2 diabetic patients this gender-dependent dissimilarity is absent. It seems that hyperglycemia or decreased insulin sensitivity could modulate vaspin levels. Besides, the comparison of serum vaspin concentrations between premenopausal and postmenopausal women did not demonstrate significant differences and thus, it could be suggested that estrogens do not participate in the regulation of vaspin (Handisuraya *et al.* 2010).

In addition, the initial studies indicated that vaspin might also reveal anti-inflammatory effects as it is able to suppress leptin, TNF-α and resistin expression (Hida *et al.* 2005).

OMENTIN

In 2005 Yang *et al.* (2006) identified a new adipokine, named omentin, which is highly expressed in visceral omental adipose tissue but barely identifiable in subcutaneous fat depots. Omentin is not secreted by adipocytes but it is primarily expressed in adipose stromal vascular cells (SVCs) in humans (Schäffler *et al.* 2005; Yang *et al.* 2006). Moreover, low expression of omentin is found in other tissues and is named intelectin (Tsuji *et al.* 2001), intestinal lactoferrin receptor (Suzuki *et al.* 2001) and endothelial lectin (Lee *et al.* 2001).

The two omentin genes are localized in adjacent regions of chromosome and encodes 2 highly homolog isoforms. The omentin-1 gene, encodes 34 kDa protein with 313 amino acids. It is located on chromosome 1q21.3 and consists of 8 exons and 7 introns (Schäffler *et al.* 2005). Omentin-1 is the main isoform in human plasma.

Decreased level of omentin-1 is observed in patients with type 1 diabetes mellitus (De Souza Batista *et al.* 2007), type 2 diabetes (Pan *et al.* 2010) and in those with impaired glucose regulation (Pan *et al.* 2010). It has been demonstrated that omentin-1 improves insulin action by increasing insulin-stimulated glucose uptake by subcutaneous and omental adipocytes *in vitro* (Yang *et al.* 2006). Furthermore, omentin-1 induces Akt signaling independently of the absence or presence of insulin (Schäffler *et al.* 2005; De Souza Batista *et al.* 2007). In contrast, in cultured adipocytes omentin-1 expression and its circulating levels are negatively correlated to D-glucose and insulin concentration (De Souza Batista *et al.* 2007). Moreover, decreased plasma levels of omentin and suppressed gene expression are found in visceral adipose tissue in a course of obesity (De Souza Batista *et al.* 2007). In lean women higher circulating level of omentin-1 are found when compared to those in men, whereas less noticeable gender-dependent differences in omentin values are observed in overweight and obesity. Omentin-1 plasma estimation negatively correlates with leptin levels, BMI and homeostasis model assessment (HOMA), and positively with adiponectin and high-density lipoprotein (HDL) levels (De Souza Batista *et al.* 2007; Moreno-Navarrete *et al.* 2010).

CONCLUDING REMARKS

Since the discovery of leptin nearly 15 years ago it has been allowed to consider an adipose tissue as endocrine organ. Recent identification of novel adipokines has broadened the spectrum of research. As the results of the studies are ambiguous, our knowledge of novel adipokines role in obesity and metabolic diseases is also not complete. Further intensive investigations are needed to answer the question whether these adipokines play a causative role in the pathogenesis of obesity or they only reflect the metabolic abnormalities. It seems that adipokines may be used as markers and help to determine the group of patients who will develop obesity and metabolic disorders.

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