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Metabolic Implications of Adiponectin, Visfatin and Resistin After Menopause

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ABSTRACT

After menopause, the risk of obesity increases, and this has effect on health status in women. Adipose tissue, an endocrine organ, is one of the most important sources of sex steroids, because of the aromatization of androgens into estrogens in adipocytes. Adipocytokines are bioactive polypeptides secreted by adipose tissue and regulate physiological and pathological processes, e.g. appetite, insulin sensitivity and resistance, inflammatory processes, immune response, hematopoiesis and angiogenesis. Because menopause is associated with hormonal transition and a higher prevalence of many diseases, adipocytokines have recently been subject to significant interest as they are possible protective or risk factors. These cytokines participate in many metabolic processes and are suggested to be a major link between obesity, inflammation, and cardiovascular diseases; however, the effect of the menopause on their vascular and local (tissue) secretion is still poorly understood. In this review, the role of adipocytokines in the context of metabolic disorders and postmenopausal age have been discussed.

KEYWORDS : adipocytokines, metabolic disorders, postmenopausal age

Introduction

Adipocytokines regulate appetite, inflammatory response and insulin sensitivity [1]. For example, visfatin has some insulin-mimetic properties and plays a regulatory role in inflammation [2, 3]. Resistin stimulates secretion of pro-inflammatory IL-6 and TNF-α and may induce hyperinsulinemia [4, 5, 6, 7]. Adiponectin, in contrast, exerts beneficial effects by suppressing the secretion of inflammatory cytokines, improving metabolic parameters (such as insulin sensitivity or lipid profiles), and inhibiting cell growth and angiogenesis [8].

Adipocytokine levels seem to be associated with estrogens and both determine inflammatory status after menopause [9]. Abnormal levels of adiponectin, visfatin and resistin contribute to systemic low-grade inflammation and promote atherosclerosis and insulin resistance [10-15]. The metabolic changes increase the risk of postmenopausal obesity and influence on cardiometabolic and cancerogenic risks. The present review elucidates recent knowledge about the above-mentioned cytokines, with special consideration being paid to their influence on women's health status post menopause.

Adiponectin

Adiponectin is an insulin-sensitizing protein that is secreted from adipose tissue – mainly by subcutaneous adipocytes. Adiponectin exists in three forms: a low molecular weight trimer (LMW), a hexamer (trimer–dimer) of medium molecular weight (MMW), and a larger multimeric high molecular weight (HMW) form [8]. It is one of the most extensively studied adipocytokines secreted from adipose tissue, which participates in energy homeostasis [16]. Abnormal adiponectin levels are mainly observed in visceral fat deposition characteristic for male and postmenopausal obesity [17]. Plasma adiponectin and adiponectin mRNA are inversely correlated with BMI values [18]. Moreover, the reduction of body weight in obese subjects elevates circulating adiponectin [19], which is associated with increased up-regulation of the adiponectin expression of both subcutaneous and visceral fat depots [20]. Independently of body mass, adiponectin is higher in women than in men. Increased levels of androgens after menopause and low sex hormone binding globulin (SHBG) are associated with decreased production of adiponectin [21, 22].

The distribution of fat seems to have an important influence on adiponectin secretion. Visceral fat is characterized by higher lipolytic activity than subcutaneous adipose tissue and delivers fatty acids directly to the liver via the portal vein. In consequence, the liver becomes insulin resistant, which is often associated with high levels of triglycerides. Adiponectin increases insulin sensitivity by activating insulin-receptor substrate (IRS)-1-associated phosphatidylinositol 3 kinase (PI3-kinase) in muscles [10]. In animal models, the injection of recombinant adiponectin increases fatty acid β-oxidation in skeletal muscle and diminishes serum fatty acid levels [23]. A recent study has confirmed that adiponectin enhances the ability of insulin to stimulate IRS-1 tyrosine phosphorylation and Akt phosphorylation. The activation of the serine/threonine kinase 11/AMP-activated protein kinase (AMPK)/TSC1/2 pathway alleviates the p70S6 kinase-mediated negative regulation of insulin signaling, providing a mechanism by which adiponectin increases insulin sensitivity in cells [10].

A study of animal models has shown that expression of adiponectin in visceral adipose tissue is higher than in subcutaneous tissue in obesity state [24]. In addition, clinical studies have proved that in abdominal adipocytes the synthesis of adiponectin mRNA levels is higher than subcutaneous fat deposition [25]. A study by Sadashiv et al. found significantly lower adiponectin mRNA levels in both visceral and subcutaneous adipose tissue in postmenopausal obese women than in lean postmenopausal women. Besides this, adiponectin mRNA levels are lower in subcutaneous than visceral adipose tissue independently of the fat deposits (lean or obesity state) [26]. Similar data were shown in the study by Fischer et al., who proved significantly lower adiponectin gene expression and protein content in subcutaneous and omental adipose tissue in obese subjects as compared to non-obese ones [27]. Conversely, a study by Yang et al. showed no differences in the adiponectin mRNA levels of visceral adipose tissue in obese and non-obese women [11].

The high-molecular weight isoform of adiponectin has been shown to be a better predictor of insulin sensitivity and metabolic syndrome than total adiponectin level. Similarly, the ratio of HMV to total adiponectin level is a better indicator of glucose/insulin disorder. In clinical studies, HMW adiponectin levels are significantly higher and the ratio of HMW to total adiponectin has been lower in late post-menopausal women comparing to those in early post-menopause [22]. However, other studies have shown that adiponectin is uncorrelated with age and no differences are observed between pre- and post-menopausal women. The authors summarize that the menopausal transition impacts less on adiponectin levels than the gender or fat deposits [21]. Interesting data are provided by the longitudinal cohort Study of Women's Health Across the Nation, which showed an inverse relation between lower adiponectin and its high-molecular-weight isoform and vasomotor symptoms such as hot flushes during the menopause transition, suggesting some vasoactive properties of this cytokine [19].

Adiponectin correlates not only with insulin sensitivity but also with other metabolic factors. There is also an inverse relationship between adiponectin, triglycerides and LDL levels and a positive relationship with HDL independent of abdominal fat and the degree of insulin resistance [11]. The fact that adiponectin participates in lipid metabolism was also confirmed in the study by Loucif et al., who showed lower plasma adiponectin concentrations in women with loss-of-function lipoprotein lipase gene variants - LPLD (lipoprotein lipase is a key enzyme in the metabolism of triglyceride-rich lipoproteins, which contributes to cardiometabolic homeostasis) [12].

Visfatin

Another adipocytokine that affects metabolic status is visfatin. It is secreted by visceral fat tissue, leucocytes and hepatocytes [2]. Visfatin is also referred to as nicotinamide phosphoribosyl transferase (NAMPT). It is a pleiotropic adipocytokine, which acts as a cytokine, a growth factor and an enzyme. Visfatin plays an essential role in a variety of metabolic and stress responses as well as in the cellular energy metabolism as NAMPT. This cytokine is mainly produced by visceral fat tissue, but in lower amounts it is also secreted by subcutaneous adipocytes.

In women, visfatin has been widely studied in various pathological conditions. Higher levels of visfatin have been reported in premenopausal [28] and postmenopausal women [29] with polycystic ovary syndrome-PCOS when compared to healthy controls, after adjustment for obesity. The higher level of visfatin has been observed in postmenopausal obesity [30]. In contrast, other studies have reported decreased levels of this cytokine [3, 31]. On the other hand, there is evidence that visfatin is not correlated with anthropometric (body mass index, waist circumference) or even metabolic parameters (e.g. insulin resistance) [30, 32]. These facts suggest other mechanisms are involved in visfatin synthesis and secretion, which may depend on adipocyte deposition (subcutaneous or abdominal) or may be unrelated to the amount of body fat. The ratio of visceral to subcutaneous fat may influence visfatin level much more that the content of adiposity itself [2]. A study by Pagano et al. showed lower serum visfatin concentrations and its messenger RNA (mRNA) expression in subcutaneous adipose tissue in obese subjects when compared to lean controls, but obese subjects had increased visfatin mRNA in visceral adipose tissue [3]. These differences may explain the discrepancy of visfatin levels observed in various studies. The changes of visfatin level and its connection with metabolic disorders could also be explained by local intracrine and paracrine adipocyte differentiation effects, which may predominate over visfatin secretion in abdominal obesity. This mechanism is also responsible for insulin resistance in obesity, type 2 diabetes mellitus and PCOS.

An insulin-resistant state co-exists with increased inflammatory processes, in which pro-inflammatory cytokines and insulin may up-regulate visfatin secretion [2, 13]. High levels of this cytokine have been reported in impaired glucose tolerance and type 2 diabetes mellitus [13]. However, studies evaluating the role of visfatin in glucose homeostasis are inconclusive. Some of them show lower fasting and postprandial visfatin levels in patients with type 2 and gestational diabetes mellitus when compared to non-diabetic controls [14]. Nevertheless some authors report no changes in serum visfatin levels in type 2 diabetic patients [31, 33] and in the group of post-menopausal women with and without metabolic syndrome [34].

Questionable data are also reported in studies describing treatment with insulin sensitizers. Management with rosiglitazone (thiazolidinedione) has resulted in an increase in serum visfatin levels [35]; however, the use of other pharmacological insulin-sensitizers has not confirmed this observation [36]. Contrasting observations in diabetic patients and different results from the thiazolidinediones used suggest that other factors influence serum visfatin levels and regulate their relationship with glucose metabolism.

Fortunately, recent studies based on molecular and clinical evidence have elucidated the role of visfatin in glucose homeostasis (Figure 1). They have shown that NAMPT concentration increases in obese women [37] and is reported in such diseases as type 2 diabetes mellitus, metabolic syndrome, and coronary heart disease [2, 37]. It has been proved that NAMPT plays a significant role in the regulation of glucose-stimulated insulin secretion; and thus, it seems to be an insulin-mimetic molecule [37]. NAMPT changes the enzymatic activation of deacetylase Sirt1 and influences metabolic pathways participating in the regulation of glucose-stimulated insulin secretion in pancreatic β cells [38].

The influence of visfatin on lipid profiles is also equivocal. Some studies suggest an inverse irrelevant relation with total cholesterol and LDL suggesting rather a beneficial influence of visfatin on lipid homoeostasis [32], whereas others have shown no significant correlation between serum visfatin levels and metabolic parameters (e.g. HDL, triglycerides, fasting blood glucose, insulin, HOMA-IR, SHBG, estradiol, testosterone) [32, 34].

Resistin

Obesity is associated with low-grade systemic inflammation that is expressed by changes in the plasma and tissue levels of resistin [5]. In mice, this cytokine was assessed as a link between obesity and insulin resistance. In humans, resistin belongs to a family of cysteine-rich polypeptides, also known as FIZZ 3 - found in inflammatory zone 3 [6]. Circulating resistin, its secretion by local tissues and resistin gene single nucleotide polymorphisms are associated with insulin resistance, inflammation and the development of obesity, diabetes, cancer and coronary heart disease [7].

As mentioned above, resistin has been suggested to be a mediator of insulin resistance and inflammation [4] and both mechanisms may be involved in promoting atherosclerotic processes [39]. This molecule stimulates macrophage infiltration and thus increases the tendency for atherosclerotic plaque formation and rupture [15]. High circulating resistin levels are associated with an increased risk of myocardial infarction [40]. Similarly, the study by Li et al. demonstrated that elevated resistin levels are significantly associated with an increased risk of acute coronary syndrome. Women with higher resistin levels are also predisposed to more major adverse cardiovascular events during seven-year follow-up [41]. Similar data have been presented in other studies showing that resistin concentration is an independent predictor of cardiovascular diseases such as coronary heart disease in postmenopausal women and this association can largely be explained by concomitant inflammatory processes [7, 42].

Resistin levels are even reported to increase with aging and the amount of adipose tissue; however, not all studies confirm such a thesis [43, 44]. Pantsulaia et al. [43] reported non-significant differences in resistin levels between pre- and post-menopausal women. The study by Heilbronn et al. reveled that serum resistin concentrations do not differ between non-obese, obese and obese diabetic subjects and are not significantly correlated to glucose disposal rates during a hyperinsulinemic glucose clamp across groups. Authors have observed only a weak relationship between resistin and insulin sensitivity in non-obese subjects, indicating that resistin is unlikely to be a major link between obesity and insulin resistance in humans. Moreover, serum resistin has not been related to the percentage of body fat, BMI, or fat cell size [44]. Similarly, a study of an obese Indian population revealed no significant independent effect of aging on serum resistin, as well as no associations between resistin levels and markers of obesity state [45]. Interestingly, a study by Sadashiv et al. showed that resistin mRNA expression in visceral adipose tissue of postmenopausal obese women lowered significantly by 20.4% compared with postmenopausal lean subjects and that it was inversely associated with circulating resistin levels and insulin resistance (measured by homeostatic model assessment). In contrast, in postmenopausal non-obese women resistin mRNA expression did not show any association with either insulin resistance or serum resistin [46].

Recently, some studies have highlighted the positive influence of physical activity on resistin concentration. It has been proved that long-term resistance training causes not only a decrease in body mass and body fat content but also diminishes serum resistin concentrations [47]. Not only resistance training, but also aerobic exercise (13-week walking training program) induces significant reductions in body mass and in plasma resistin levels in groups of postmenopausal women [48]. This suggests that physical activity after menopause is effective in decreasing resistin levels and, in consequence, may cause a beneficial reduction in inflammation, and metabolic and cardiovascular disorders in this age.

Conclusion

Recent studies focusing on adipocytokines and etiopathogenesis of metabolic diseases have shown that alterations in adipocytokines may affect metabolic state, energy expenditure and body fat distribution. However, not all the properties of these cytokines are fully confirmed and further prospective and longitudinal studies are needed to evaluate whether adipocytokines such as adiponectin, visfatin and serum resistin could be used as a prognostic tool in metabolic disorders, particularly in postmenopausal age. Elucidating the mechanism of changed levels of the mentioned adipocytokines may be used in the monitoring and management of these pathologies and provide

new therapeutic options.

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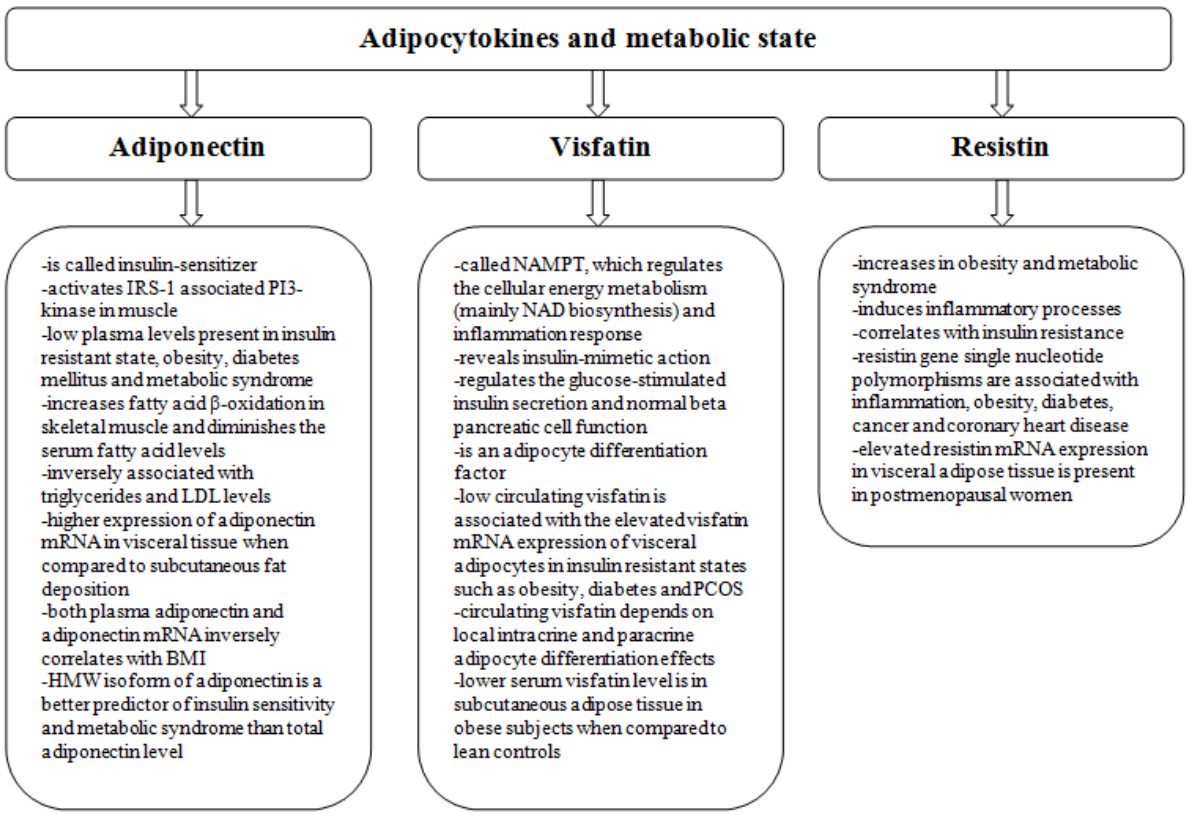
The author has any conflict of financial or other interest.

FIGURE 1: Adipocytokines in connection with metabolic state.



IRS-1- insulin-receptor substrate-1, PI3-kinase - phosphatidylinositol 3 kinase, HMW - high-molecular weight

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