Adiponectin and metabolic syndrome in women at menopause

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Abstract
Obesity is associated with premature atherosclerosis, as well as with many metabolic alterations including insulin resistance, dyslipidemia and hypertension. Visceral fat accumulation, particularly, is closely associated with the development of metabolic syndrome. The menopause transition, as well as the early postmenopausal period, is associated with increase in total and central obesity. Among adipocytokines secreted by the adipose tissue adiponectin is the only one that has a protective role in the development of obesity-related disorders, such as type 2 diabetes and cardiovascular disease. This review aims to present a role that adiponectin may play during the progress of menopause in relation to development of menopausal metabolic syndrome.

Keywords: adiponectin, metabolic syndrome, menopause, sex hormones

Introduction
The prevalence of obesity has raised dramatically in recent years. Increased adiposity, particularly, visceral fat accumulation, is closely associated with premature atherosclerosis and many metabolic alterations including insulin resistance, dyslipidemia and hypertension.[1,2,3]. Obesity is one of the most common disorders in climacteric women and occurs in approximately 65% of them [4]. Recent data suggested that menopause status is associated with differences in adipose tissue metabolism in both, the abdominal and gluteal region [5]. Menopause has been shown to contribute to the development of central obesity, insulin resistance and worsening of glucose and lipid metabolism that increase the risk for cardiovascular disease in women.
In obese women higher morbidity and mortality from cardiovascular disease was observed with the progress of climacterium. The primary cause for this situation seems to be a menopausal metabolic syndrome observed in 40% of climacteric women [8].

Adipose tissue produces and releases hormones and other biologically active molecules –adipokines- that regulate several metabolic activites of the human body [1]. Among these adipokines – adiponectin has been shown to directly or indirectly affect insulin sensitivity through modulation of insulin signaling and the molecules involved in glucose and lipid metabolism. Decrease in the circulating levels of adiponectin by genetic and environmental factors is associated with the development of diabetes and the metabolic syndrome [9,10].

The use of adiponectin is suggested as a novel therapeutic tool for diabetes and the visceral obesity metabolic syndrome but evaluation of its effectiveness will require further clinical studies [9].

**Adipose tissue metabolism at menopause.**

Menopause is associated with a raise in follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels and a fall in estrogens. The average age of menopause is 51 years (45 to 55 yrs) [11,12,13,14]. During the transition from the reproductive years through menopause and beyond, women experience many changes, among them changes in adipose tissue metabolism that may contribute to body fat distribution [5,15]. Women have more body fat compared to men, and there is a gender-specific difference in fat distribution. In women, adipose tissue is accumulated especially around the hips, buttocks, and thighs while men have a larger intra-abdominal fat mass [16,17].

Among several hormones, estrogens promote, maintain and control the typical distribution of adipose tissue and its metabolism through still partly unknown mechanisms. Lipolysis in humans is controlled through the $\beta$-adrenergic (lipolytic) and $\alpha_2$-adrenergic (antilipolytic) receptors. In visceral adipocytes adrenaline stimulates lipolysis (high $\beta/\alpha_2$ receptor ratio) but in subcutaneous adipocytes it has an adverse effect ((high $\alpha_2/\beta$ receptor ratio) [18]. Pedersen et al demonstrated that estradiol, only through the estrogen receptor $\alpha$, inhibits adrenaline-stimulated lipolysis in human subcutaneous fat cells by increasing the amount of $\alpha_2$-adrenergic antilipolytic receptors. This may explain how estradiol is related to typical female subcutaneous
adipose tissue distribution because this inhibition is not observed in visceral fat depots. In women, estradiol may shift accumulation of fat from visceral into subcutaneous depots [18].

Premenopausal women have significantly lower risk of developing obesity-related diseases than men. This difference, abolished after menopause, suggests that female sex steroid hormones, mainly estrogens, influence adipogenesis and adipose tissue metabolism [17]. During postmenopausal period women develop increased amounts of visceral fat. The redistribution of body fat, after menopause, may be essential in linking the menopause with metabolic alterations which confer to cardiovascular disease (CVD) risk [16,17].

Changes in the hormone levels at menopause, in particular estrogen deficiency, are associated with an increase in total adiposity, preferentially at visceral region. Recent data suggested that in postmenopausal women low estrogen concentrations, compared with relatively elevated levels of circulating androgens, may explain, at least in part, the body fat redistribution, loss of subcutaneous fat and gain of visceral fat [18,19].

Menopause status may influence adipose tissue metabolism and lipolysis. Lipoprotein lipase (LPL) from adipose tissue is very important in accumulation and distribution of fat stores. It was suggested that regional differences in subcutaneous adipose tissue metabolism are related to menopause status. LPL in the gluteal and abdominal fat tissue seems to be more active in postmenopausal compared with perimenopausal women that, together with concomitant lower lipolysis, may predispose postmenopausal women to increase body fat after menopause [5].

The more atherogenic lipid profile and increased level of the prothrombotic plasminogen activator inhibitor-1 is observed in women after menopause. Additionally, circulating cortisol concentration is increased that is associated with central obesity, elevated blood pressure, insulin resistance and dyslipidemia [17]. It has been reported that increased production of adiponectin, peroxisome proliferator-activated receptor γ (PPARγ) and fatty acid transporter in adipose tissue from gluteal region may be a physiological response to preserve systemic insulin sensitivity in estrogen-deficient women at postmenopause [16]. Among the different possible mechanisms, some investigators have suggested a link between sex hormones and adiponectin metabolism [8,17,20,21,22].
Relationship of adiponectin with sex hormones.

Adiponectin seems to be the most interesting and promising biologically active molecule released from fat cells since it has profound protective actions in the pathogenesis of diabetes mellitus and cardiovascular disease. This protein is also called ADIPOQ, gelatin-binding protein 28, Acrp30 [1,23]. Adiponectin is secreted from adipose tissue and compared with many hormones, is very abundant in the plasma. Human plasma adiponectin concentration is associated with sex and is significantly higher in women than in men. This sexual dimorphism develops during pubertal development in relation to serum androgens. Interestingly, sex differences in circulating adiponectin levels in older adults cannot be explained by sex hormone regulation [1,24,25].

In healthy women, adiponectin concentration increases significantly with age. Plasma concentration of adiponectin inversely relates to visceral fat mass and visceral fat area, however the correlation is weak in peri- and postmenopausal women comparing to that in younger women [26].

The menopausal transition increases serum adiponectin concentration, however, the data related to its levels and association with body fat and regulatory factors are contradictory. FSH in postmenopausal women is undoubtedly significantly and positively associated with higher adiponectin. Two big studies have shown a significant inverse correlation of adiponectin with estradiol that was observed in healthy postmenopausal women, even after adjustment for age and body mass index (BMI) [27,28]. Laughlin et al assessed the determinants of serum adiponectin in postmenopausal women and men aged 50-92 yrs [29] and found positive association of adiponectin with testosterone, and negative with bioavailable estradiol in both sexes. This was not explained by differences in age and adiposity. Recently, it has been reported that dehydroepiandrosterone sulfate (DHEA-S), a precursor of androgens and estrogens, may upregulate adiponectin gene expression in a depot-dependent manner. The effect of DHEA-S was observed only in visceral adipocytes from fat depots of morbidly obese humans [30].

On the other hand, increased levels of free testosterone, low sex hormone-binding globulin (SHBG) in postmenopausal women were shown to be associated with decreased production of adiponectin [31].
The role of adiponectin in physiology and obesity related pathology

Adiponectin is involved in a number of metabolic processes, such as glucose utilization, fatty acid oxidation in muscles, decreased insulin resistance in the liver and the metabolism of adipose tissue, but the physiological role of adiponectin needs further explanation [32,33,34]. Adiponectin accumulates in injured vascular walls, bound to collagens I, III and V present in the subendothelial intima, indicating that it may be involved in the repair process of damaged vasculature [2,35]. Recently it was shown that low adiponectin concentration in postmenopausal women was associated with adverse changes in carotid intima-media thickness and stiffness that was not dependent on other cardiovascular risk factors [36].

Adiponectin level is partially determined by inflammatory marker levels. Most factors with a significant impact on adiponectin regulation have inhibitory effects. These include proinflammatory factors such as cytokines (IL-6, and TNF-α), monocyte chemotactic protein-1 and C-reactive protein (CRP) [27]. Decreased expression and plasma levels of adiponectin may serve as a marker of increased metabolic and inflammatory risk [15]. The association exists between adiponectin gene expression and its plasma levels which results from exclusive secretion of this adipokine by adipocytes. This is not the case for the pro-inflammatory IL-6 or TNF-α gene expression in fat cells because these molecules are also secreted by a number of other cell types. It was found that plasma adiponectin levels and hs-CRP correlate inversely what may suggest that decreased production of adiponectin contributes to the systemic and vascular inflammation commonly found in obesity [15].

The potential role of adiponectin in obesity and related pathologies is directed mainly to protection against atherogenesis and insulin resistance. Some studies suggest that adiponectin could be a marker of risk for developing menopausal metabolic syndrome [8]. Adiponectin has been shown to exert anti-inflammatory and anti-atherogenic properties within the arteries and thus may negatively modulate the process of atherogenesis [1,3,35,37]. Adiponectin increases insulin sensitivity in various models of insulin resistance and in vitro increases the ability of sub-physiologic levels of insulin to suppress glucose production in isolated hepatocytes. This protein intensifies peripheral tissues sensitivity to insulin and its deficiency can contribute to the development of insulin resistance in type 2 diabetes and obesity [3,34,38]. (Figure 1).
Figure 1. Associations adiponectin between insulin resistance, metabolic syndrome and atherosclerosis [39].

The role of adiponectin in pathogenesis of metabolic syndrome of menopause

Estrogen deficiency is increasingly being recognized as a cause of metabolic syndrome, characterized by visceral obesity, insulin resistance, impaired lipid metabolism [40]. Adiponectin plays a role in the pathogenesis of metabolic syndrome. This protein improves glucose tolerance via increasing insulin sensitivity. Adiponectin enhances fatty acid oxidation in liver and muscle, thus reducing triglyceride content in these tissues. Moreover, it stimulates glucose utilization in muscle and inhibits glucose production by the liver, consequently decreasing blood glucose levels. Plasma
adiponectin levels are positively correlated with insulin sensitivity in humans [41,42,43].

Recent studies have indicated that adiponectin levels are significantly lower in obese than in non-obese women at the same stage of postmenopause and lower in those with metabolic syndrome. Lobo et al. reported that weight gain and obesity lead to the increased prevalence of metabolic syndrome in postmenopausal women and use of transdermal hormonal therapy is beneficial overall for reducing many of the parameters of metabolic syndrome [44].

Visceral fat accumulation results in reduced levels of adiponectin. It was reported that centrally located fat was the main determinant of variability in adiponectin concentration in healthy postmenopausal women [45]. From many studies can be concluded that low plasma adiponectin was associated with all the components of the metabolic syndrome. The association of the adiponectin genetic variation with obesity, metabolic syndrome and diabetes mellitus has been found in a Taiwanese elderly population [46]. It seems however, that in humans adiponectin gene does not play a role of the master obesity gene [46]. Decreased adiponectin concentration is rather a predictor of the development of type 2 diabetes than obesity. Low adiponectin level most likely reflects obesity-dependent adipose tissue-specific insulin resistance and mediates the effect of obesity on insulin resistance in the liver and muscles. Most probably, the adipose tissue-specific insulin sensitivity rather than general adiposity itself determines the adiponectin expression in the adipose tissues [46] (Figure 2).

The influence of menopausal status on the relationship between adiponectin and insulin resistance was studied and it was found that significant inverse association between adiponectin and homeostasis model assessment of insulin resistance (HOMA-IR) occurred only after menopause [47]. The authors concluded that adiponectin may play a role in the improvement of insulin sensitivity after, rather than before, menopause [47].

Several counter-regulatory hormones and inflammatory cytokines, such as TNF-α, that mediate insulin resistance, were shown to reduce either adiponectin mRNA expression or protein secretion. High levels of TNF-α and low estradiol play the most important role in development of insulin resistance. It was suggested that adiponectin
Fig. 2 Adiponectin functions as the signal from adipose tissues to the other peripheral tissues to mediate the favorable metabolic effects and end organ protective effects.

decreases the secretion of TNF-α and antagonizes TNF-α by influencing on the expression of many adhesion molecules and the adhesion of monocytes to endothelial cells [41,48]. Recent studies have indicated that TNF-α level depends more on menopause progress than obesity. Moreover, estradiol level was found to be inversely associated with TNF-α [40]. Postmenopausal women had higher TNF-α than perimenopausal, however postmenopausal non-obese showed slightly lower TNF-α levels compared with obese women [8].

The associations between adipocytokines and traditional risk factors for cardiovascular disease were assessed in women at postmenopausal stage. The larger decreases in adiponectin over the menopause transition were associated with greater increase in systolic blood pressure, insulin and insulin resistance and with greater decreases in high density lipoprotein (HDL-cholesterol) [49].
Review of the data confirmed positive association of adiponectin with HDL-cholesterol and negative relation with low-density lipoprotein (LDL-cholesterol) and triglycerides (TG) but not with high total cholesterol [50,51].

Conclusions

Adiponectin should be regarded as a most important among adipocytokines. Decreased adiponectin level, caused by obesity-induced insulin resistance in the adipose tissue, leads to decreased insulin sensitivity in the liver and skeletal muscle and in consequence to insulin resistance-related metabolic phenotypes.

Understanding the mechanisms by which sex hormones affect total and regional body fat distribution and widening our knowledge about pathophysiology of obesity and insulin resistance will have important therapeutic and preventive implications for women at menopause.

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