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Obesity, Adipokines and Metabolic Syndrome in Polycystic Ovary Syndrome

Enrico Carmina

Endocrine Unit, Department of Medical and Biological Sciences, University of Palermo, Palermo, Italy

Abstract

The complex mechanisms linking fat excess to metabolic syndrome are not well understood, but several experimental studies have shown that altered production of adipokines plays a main role in development and progression of this disorder. In particular, reduced secretion of adiponectin has a crucial role in inducing insulin resistance but also in determining the clustering of elevated triglycerides and small, dense LDL particles. Increased leptin secretion may be responsible for sympathetic nervous system overactivity and hypertension, while reduced omentin may have an important permissive role in the development of atherogenic processes. Finally, cytokines and other adipokines (resistin, visfatin) determine and modulate the inflammatory process that is an essential component of this condition of cardiovascular risk. Because obesity is prevalent in polycystic ovary syndrome (PCOS), it is not surprising that patients with PCOS present altered adipokine levels and increased prevalence of metabolic syndrome. However, because of the presence of other CV risk factors (androgen excess), in PCOS adipokine dysfunction is particularly severe. Understanding and treating adipokine dysfunction in young women with PCOS is an essential component of any politics of prevention of CV diseases in the general population.

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Metabolic syndrome consists of the clustering in the same subject of some cardiovascular risk factors that depend on insulin resistance and abdominal obesity [1]. Because both insulin resistance and abdominal obesity are classic components of polycystic ovary syndrome (PCOS) [2], it is not surprising that, in this disorder, metabolic syndrome is much more common than in the control population [3]. In fact, also in PCOS, prevalence of metabolic syndrome is strongly correlated with the prevalence of obesity, and populations with lower bodyweight have lower prevalence of metabolic syndrome [4]. However, in women with PCOS, metabolic syndrome appears at an earlier age than in the general population, and is common also in overweight patients [1, 5]. This suggests that, in PCOS, some additional mechanisms may be important in influencing the effects of adipose tissue on the development of metabolic syndrome.

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Table 1. Main adipokines and their possible role in metabolic syndrome

Adipokine	Possible physiologic role	Values in metabolic syndrome	Contribution to metabolic syndrome
Leptin	Regulation of food intake Regulation of SNS activity	Increased	Selective leptin resistance may induce overactivity of the SNS and hypertension
Adiponectin	Insulin-sensitizing hormone Protection of liver cells from negative effects of fat increase	Reduced	Low adiponectin may induce insulin resistance and altered lipid profile
Resistin	Part of the inflammatory pattern linked to adipose tissue excess	No changes	Unclear
Visfatin	Part of the inflammatory pattern linked to adipose tissue excess	Increased	Unclear
Vaspin	Regulation of food intake?	Increased	Unclear
Omentin	Protection of endothelial cells from inflammatory factors	Reduced	Low omentin levels may favor atherogenic complications of visceral fat excess
Chemerin	Regulation of adipogenesis	Increased	Unclear
RBP-4	May impair insulin sensitivity May impair liver function	Variable	Unclear
Cytokines	Part of the inflammatory pattern linked to adipose tissue excess	Increased	Atherogenic and liver complications of visceral fat excess Insulin resistance?

The complex mechanisms linking fat excess to metabolic syndrome are not well understood, but evidence is accumulating that adipokines (hormones, cytokines and other bioactive substances produced by adipose tissue) play a main role in the development of metabolic syndrome [6].

In this review, I will focus mostly on analyzing the current knowledge about adipokines and their effects on the development of metabolic syndrome in the general population. I will then discuss the special mechanisms that may be operating in women with PCOS.

Adipokines and Metabolic Syndrome in General Population

Several adipokines may be important in the development and/or progression of metabolic syndrome. In table 1, a list of main adipokines and their possible role in metabolic syndrome is given.

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Leptin

Leptin is a 146-aminoacid protein which acts mostly as a signaling factor from adipose tissue to the central nervous system to serve as an indicator of energy availability [7]. Increase in fat mass leads to increased secretion of leptin and suppression of food intake. Any increase in fat mass determines an increase in serum leptin, and in general serum leptin correlates very well with total fat mass [7]. In morbid obesity, serum leptin levels are 2–4 times higher than in normal-weight subjects [7].

However, the effects of leptin on the CNS are not limited to hypothalamic regulation of appetite but involve many other cerebral areas and are essential in the regulation of energy expenditure, and glucose metabolism [7, 8]. These effects are determined by increasing sympathetic nerve activity, which in mice increases energy expenditure in interscapular brown adipose tissue.

Because the increase in serum leptin does not influence the alimentary behavior of the obese subjects, it has been suggested that, in most forms of obesity, leptin resistance develops with an unclear mechanism [7]. However, the sympathetic nervous system (SNS) is overactive in obese subjects and in metabolic syndrome [8]. Because the SNS helps regulate blood pressure, heart rate, and hepatic glucose production, selective leptin resistance may be a crucial mechanism linking increased fat mass and metabolic syndrome [8].

Adiponectin

Adiponectin, mostly the high molecular weight isoform, seems to play an important role in protecting the liver, endothelial and muscle cells from the negative effects of fat increase [9]. The activity of adiponectin is mediated by the AMP kinase system and results in enhancing cell nitric oxide (NO) production, increasing fat oxidation and inhibiting inflammatory effects.

Adiponectin is mostly produced in subcutaneous fat [10], and its values are normal or slightly low in metabolically healthy obese subjects, but are low in subjects with visceral obesity [9]. It may be one of the mechanisms that determine more severe metabolic consequences in patients with central obesity [9].

The mechanism of adiponectin decrease in subjects with visceral obesity is not clear. Some authors have suggested that the adiponectin decrease observed in obesity is the consequence of reduced insulin sensitivity and hyperinsulinemia. In fact, adiponectin circulates in inverse proportion to the degree of insulin resistance, and some data suggest that long-term changes in insulin sensitivity may downregulate adiponectin secretion. However, studies in animals have shown that adiponectin improves insulin sensitivity, and there is a growing consensus that adiponectin may be an insulin-sensitizing hormone. Instead, adiponectin decrease in visceral obesity may be the consequence of the increase in cytokines that is an important consequence of visceral obesity [11, 12].

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It has been shown that patients with reduced adiponectin levels have elevated levels of small dense LDL particles [13]. Thus, the clustering of elevated triglycerides (as a result of increased large VLDL production) and small, dense LDL particles in the context of insulin resistance and obesity may be mediated by reductions of adiponectin. These data and other show that low adiponectin plays a main role in determining metabolic syndrome.

Resistin

A further adipose hormone, resistin, in animals has been linked to insulin resistance. However, human resistin is secreted by macrophages rather than adipocytes [14], and recent and growing evidence suggests that human resistin is an inflammatory biomarker that may be part of the inflammatory pattern associated with visceral obesity [14, 15].

Visfatin

This adipokine is produced by many tissues, and may have a role in promoting or maintaining systemic inflammation [15]. In fact, visfatin can induce and maintain the cellular expression of inflammatory cytokines such as TNF-α, IL-1β, and IL-6 [15].

Inside adipose tissue, visfatin is produced by differentiated adipocytes but also by the macrophages, and is part of the complex of adipose factors promoting inflammation [15]. However, the role of visfatin is probably larger, and it has been shown that visfatin may regulate β-cell function and insulin secretion.

Visfatin is increased in obesity and in metabolic syndrome, but this correlation seems to be independent of insulin resistance and mostly linked to the inflammatory pattern.

Vaspin

Vaspin is a member of the serpin (serine protease inhibitor) family that has been found increased in obesity, type 2 diabetes and metabolic syndrome [16]. However, vaspin levels increase with weight loss associated with lifestyle programs, and modifications of other adipokines (adiponectin) do not change its levels [17]. Therefore, the mean and the possible role of vaspin in obesity and metabolic syndrome are unclear.

Interestingly, it has been reported that vaspin may trigger anorectic pathways in the hypothalamus.

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Omentin

Omentin is an adipokine preferentially produced by visceral adipose that circulates in two isoforms (omentin 1 and 2), with omentin-1 being the most common human circulating isoform. Omentin has an important anti-inflammatory role in the endothelium by preventing the TNF-α-induced COX-2 expression in vascular endothelial cells probably via inhibiting the JNK activation presumably through activation of AMPK/eNOS/NO pathways [18]. There is a close connection between serum omentin and adiponectin levels, and it has been suggested that regulation of omentin may be dependent on adiponectin. It is possible that omentin mediates some of the vascular effects of adiponectin.

Omentin 1 plasma levels and adipose tissue gene expression are reduced in obese and in type 2 diabetics but mostly in patients with metabolic syndrome having cardiovascular diseases [19] and in type 2 diabetes patients with carotid plaque (compared to those without carotid plaque) [20]. These data suggest an important role for omentin in determining vascular effects of metabolic syndrome.

Chemerin

Chemerin is an adipokine that regulates adipocyte development and may have some role in insulin resistance. Gene expression levels of chemerin are elevated in the adipose depots of obese compared with lean animals and markedly increase during differentiation of fibroblasts into mature adipocytes suggesting that the process of adipogenesis is in some way related to the expression or production of this adipokine.

Serum chemerin levels are elevated in patients with obesity and exhibit a positive correlation with various aspects of the metabolic syndrome [21]. It has been suggested that fasting levels of chemerin might be used as biomarker to identify insulin resistance in healthy men without typical characteristics of metabolic disorders and could be an independent predicting marker of the presence and severity of obstructive sleep apnea [22].

Retinol-Binding Protein-4

Retinol-binding protein (RBP-4) is the specific carrier protein for retinol (vitamin A) in blood and is produced by many tissues but mainly by the liver and adipose cells. It was initially hypothesized that RBP-4 may be an adipocyte signal that impairs insulin secretion. More recently, several studies have related increased production of RBP-4 to multiple risk factors for adiposity-related comorbidities. However, contrasting data exist on RBP-4 levels in obesity and metabolic syndrome, and no association with total, visceral or subcutaneous fat has been observed. In children and adolescents,

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serum RBP-4 correlates with liver enzymes and triglycerides and inversely with adiponectin, independent of percent body fat, suggesting a link with liver function [23].

Cytokines

Obesity, but mostly visceral obesity, is associated with chronic low-grade inflammation, and it depends in large part on increased production of different cytokines, including TNF-α, interleukin-6 and MCP-1 inside the adipose tissue [24]. In addition, cytokines, but mostly TNF-α, also seem to be important in inducing insulin resistance by impairing insulin signaling both directly by activation of serine kinases and indirectly by increasing mobilization of free fatty acids (FFA). Increased cytokine production seems to have an important role in downregulating adiponectin production in obese subjects.

Inside the adipose tissue, the cytokines are mostly produced by activated macrophages [25]. It has been suggested that the main stimulus for macrophage colonization of fat is the increased adipose cell death rate that is the consequence of adipocyte hypertrophy [25].

Adipokines and Metabolic Syndrome in General Population: Trying to Get a Full View

Mechanisms determining development and progression of metabolic syndrome are still incompletely understood. However, it is clear that in the general population the excess of adipose tissue and in particular of visceral fat is the main determinant of this risk condition. In fact, in obese subjects, insulin resistance, while essential for determining the appearance of most elements of metabolic syndrome, is only the consequence of visceral fat excess.

Most authors believe that in obese subjects insulin resistance is determined by liver accumulation of FFA released by visceral fat. However, recent evidence suggests that as adipose tissue mass expands, FFA release is downregulated, not increased [26]. The changes in adipose tissue lipolysis observed in obese subjects may simply reflect an adaptation to consistently high ambient insulin concentrations. Other mechanisms, and in particular dysfunctional regulation of adipokines, are probably more important to explain insulin resistance in the obese state.

In this respect, the reduction of adiponectin levels seems to play the main role. Because adiponectin is mainly produced in the subcutaneous fat, it has been hypothesized that increased production of cytokines inside the visceral fat is the mechanism that inhibits subcutaneous production of adiponectin. The process may be initiated by increased death of adipose cells consequent to excessive enlargement of adipose cells. It is followed by colonization and activation of macrophages and by increased

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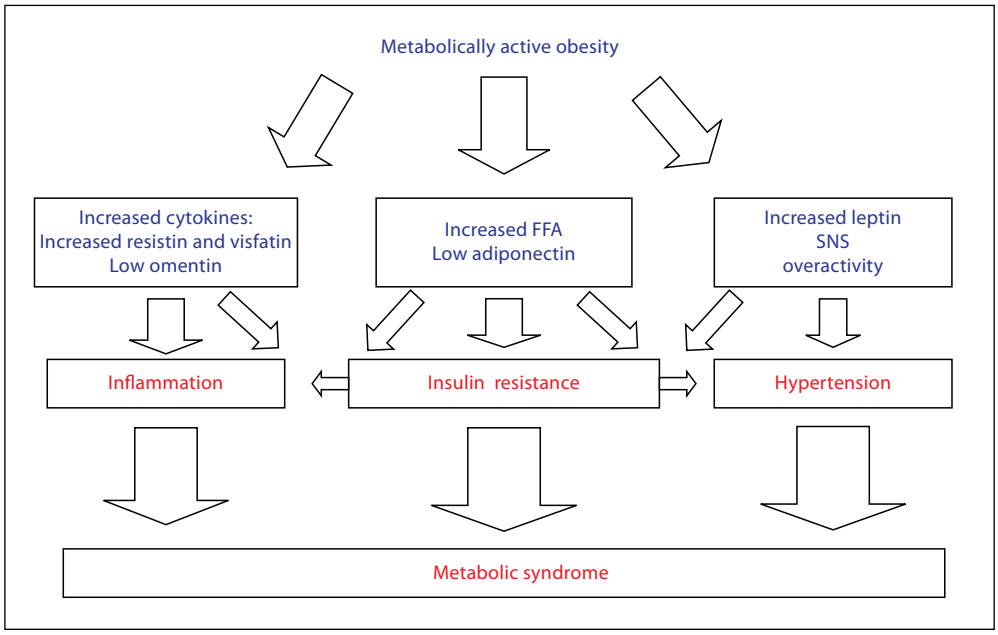


Fig. 1. Effect of adipose products on development and characteristics of metabolic syndrome.

production of several inflammatory factors, mainly cytokines but also some adipokines (resistin, visfatin).

According to some authors, impaired new adipogenesis inside visceral fat plays a pivotal role in this process. In fact, in response to the need of new adipose storage, stromal cells from the subcutaneous adipose tissue regions may proliferate and differentiate in mature adipocytes, while this process is less efficient in visceral fat depots. It probably determines differences in adipocyte size between different fat depots and increases cell death rate in visceral fat.

Several other adipokines probably participate in the development and the evolution of the metabolic syndrome. In fact, increased leptin has an important role in SNS overactivity and hypertension, while reduced omentin may have an important permissive role in the development of atherogenic process inside the cardiovascular system.

A hypothetic schematic view of the effects of adipocyte dysfunction in visceral obesity is shown in figures 1 and 2.

Adipokine Production in PCOS

Many studies have shown that adipokine secretion is altered in PCOS. However, because obesity is prevalent in this disorder, this is not surprising. As a group, patients with PCOS present higher leptin, cytokines and other inflammatory cytokines

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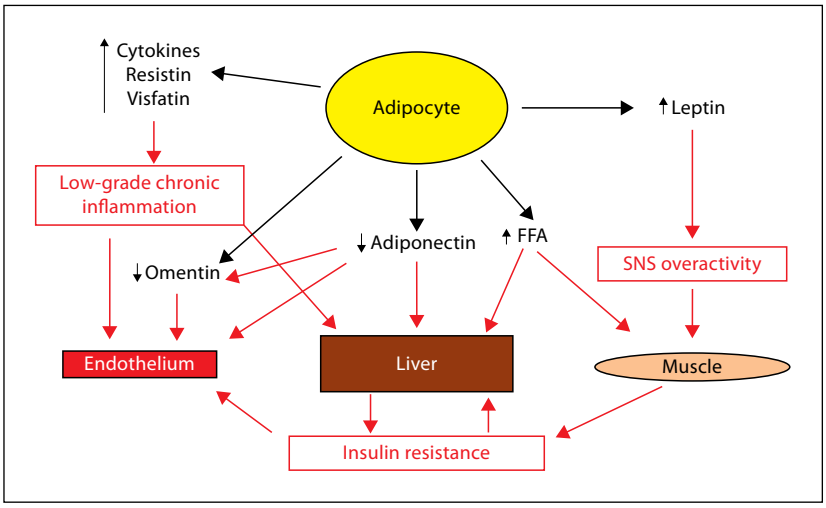


Fig. 2. Adipocyte function in metabolically active obesity.

(visfatin, vaspin, chemerin) and lower adiponectin and omentin circulating levels than the young female population.

However, when PCOS women are compared with controls matched for body-weight, some of these differences disappear, suggesting that some changes are exclusively linked to excessive adipose tissue. Many other differences remain, indicating that in PCOS adipocyte dysfunction is not only determined by the simple fat excess.

Although some discrepancy between the studies exists, probably depending on the heterogeneity of the syndrome and on differences in prevalence of obesity and fat distribution in different ethnic population, most studies have shown that, compared to weight-matched controls, women with PCOS present [26–32] (1) reduced secretion of adiponectin and omentin, (2) increased secretion of cytokines (mainly TNF-α and IL-18), visfatin, vaspin and chemerin, (3) normal secretion of leptin and resistin, (4) variable values (increased, normal, low) of RBP-4.

These findings are in large part explained by the increased prevalence of visceral (abdominal) fat in PCOS. In fact, women with PCOS present increased quantity of visceral fat not only in obese but also in overweight and in many (30–50%) normal-weight patients. Because most premenopausal obese women present increased visceral fat [2], it is not surprising that the difference in some adipocyte products is more evident in normal-weight or overweight PCOS women (compared to weight matched controls) than in obese PCOS women (compared to obese controls).

It has been shown that the same mechanisms that, in the general population, affect adipokine production are also present in women with PCOS. In fact, it has

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been demonstrated that also in PCOS adiponectin production in subcutaneous fat is reduced by increased secretion of cytokines by macrophages colonizing the adipose tissue.

Androgens and Adipokine Production in PCOS

Several data suggest that the adipocyte dysfunction in PCOS is not exclusively determined by increase in visceral fat. In particular, some studies have shown that the increased androgen levels that are characteristic of the syndrome may affect adipokine production and, in this way, increase prevalence and cardiovascular effects of metabolic syndrome.

The evidence that androgens influence adiponectin and adipose inflammatory factor production may be summarized as follows [33, 34]:

- While most studies evaluating total circulating adiponectin did not show any correlation between its levels and circulating androgens, it has been shown that androgen administration specifically reduces adipocyte production of HW-adiponectin, and in PCOS, HW adiponectin is negatively correlated with free testosterone levels.
- Androgens are positively correlated with TNF-α and interleukin-18 circulating levels, and androgen administration activates macrophage production of cytokines. The relationships between androgens and inflammation are complex and may be partially independent of the effects of androgens on adipose tissue. However, these data suggest that, in PCOS, increased fat production of cytokines and inflammatory adipokines is the consequence of a double mechanism involving not only increased visceral fat but also androgen activation of intra-adipose macrophages.
- While few data and some discrepancy in the results exist, it has been reported that in PCOS increased androgens are correlated with omentin reduction with a linear decrease in omentin for any quartile of free testosterone levels.

Conclusions

In PCOS, an adipocyte dysfunction exists and has a main role in determining insulin resistance and prevalence and morbidity of metabolic syndrome. This adipocyte dysfunction is the consequence of increased visceral fat in obese and non-obese subjects but also of the androgen excess that is characteristic of the disorder.

A better knowledge of the mechanisms of adipocyte dysfunction may improve our ability to treat PCOS women reducing their risk of future adverse cardiovascular events.

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Enrico Carmina, MD
Endocrine Unit, Department of Medical and Biological Sciences, University of Palermo
Via delle Croci 47
IT–90139 Palermo (Italy)
Tel. +39 091 332377, E-Mail enrico.carmina@ae-society.org

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