Adipokines in reproductive function: a link between obesity and polycystic ovary syndrome

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Abstract

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy associated with infertility and metabolic disorder in women of reproductive age. Dysfunction of adipose tissue has been implicated in the pathophysiology of PCOS. Increasing evidence shows that the dysregulated expression of adipokines, the secreted products of adipose tissue, plays an important role in the pathology of PCOS. Here, we review the role of several identified adipokines that may act as a link between obesity and PCOS. PCOS also reciprocally influences the profile of adipokines. Insight into the underlying mechanisms will help better understand the pathology of PCOS and identify new therapeutic targets of this syndrome.

Key Words
- polycystic ovary syndrome
- adipokines
- obesity
- adipose tissue

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Introduction

Polycystic ovary syndrome (PCOS) is one of the most common causes of female infertility, which affects 5–10% of women of reproductive age. It is a heterogeneous syndrome with the characteristics of hirsutism, acne, anovulation, hyperandrogenemia, polycystic ovaries, and infertility (Goodarzi *et al*. 2011). In most cases, PCOS also involves metabolic alterations such as insulin resistance (IR), hyperinsulinemia, dyslipidemia, and obesity. Additionally, we have recently revealed altered metabolic profiles in PCOS patients, including the enhanced glycolysis, inhibited tricarboxylic acid cycle, and disturbed levels of amino acids (Sun *et al*. 2012, Zhao *et al*. 2012). PCOS can thus lead to an increased risk of developing type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) in patients (Diamanti-Kandarakis & Dunaif 2012).

About 50% of PCOS patients are obese. Although obesity is an increasingly prevalent health problem worldwide, women with PCOS have a greater risk of overweight, obesity, and central obesity (Lim *et al*. 2012). Obesity is defined by abnormal or excessive lipid storage. It is characterized by the increased number and volume of adipocytes. A person with a BMI of 30 kg/m^2 or higher is considered obese according to the World Health Organization criteria. Obesity presents a risk to health. It has been well acknowledged that obesity is associated with various diseases, particularly CVDs, metabolic syndrome, and T2DM. The effects of obesity on female reproduction have also been extensively investigated. Obese women seem to have impaired reproductive potential. The adverse effects of obesity on female fertility include impaired ovulation, irregular menstrual cycle, elevated miscarriage rate, lower implantation, pregnancy rates, etc. (Brewer & Balen 2010). In addition, the distribution of body fat is also important as central/abdominal obesity is associated with IR and has a greater impact on fertility. Women with PCOS are more likely to have central distribution of body fat, which is associated with IR and hyperandrogenemia.

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The presence of obesity can also magnify IR. Obesity is thus one of the crucial parameters and an independent risk factor of PCOS, which plays an important role in the development and manifestations of the clinical, biochemical, and metabolic features of PCOS (Wojciechowski *et al*. 2012).

In obesity, fat mass massively expands in order to store excessive amount of energy. It is currently realized that adipose tissue is not only the main energy reservoir but also a pivotal endocrine organ. Adipose tissue has been revealed to play important roles in the regulation of many physiological processes, such as reproduction, immune response, and glucose and lipid metabolism, by secreting a variety of bioactive cytokines named adipokines. Adipokines comprise both adipose-specific cytokines or cytokines predominantly secreted by adipocytes, such as leptin, resistin, adiponectin (APN), visfatin, and omentin, and nonadipose-specific cytokines such as retinol binding protein-4 (RBP4), lipocalin-2 (LCN2), chemerin, interleukin 6 (IL6), IL1β, and tumor necrosis factor α (TNFα). Abnormal levels of adipokines have been shown to be strongly associated with IR and T2DM. In patients with PCOS, dysfunction of adipose tissue has been observed with the over-production of pro-inflammatory adipokines such as TNFα, and the reduced expression of some 'beneficial adipokines' such as APN. Substantial evidence indicates that obesity plays a pivotal role in the pathogenesis of PCOS. In this review, we discuss the roles of several identified adipose-specific and some of non-adipose-specific adipokines in female reproduction that may act as links between obesity and PCOS. Other adipokines, such as TNFα, IL6, and IL1β, are best known for their association with inflammation and have been reviewed in detail elsewhere (Bohler *et al*. 2010).

Leptin

Named from the Greek *leptos* (meaning thin), leptin is a 167-amino acid protein encoded by the *ob* gene. It is an important hormone involved in the regulation of food intake, energy balance, and body weight (Morris & Rui 2009). Leptin is the first discovered adipokine that has led people to realize the functions of adipose tissue as not only a well-recognized energy reservoir but also a key endocrine organ in the body. Leptin is predominantly secreted by adipose tissue. Its expression is also found in the stomach, placenta, hypothalamus, pituitary, and mammary gland (Zhang *et al*. 1994, Masuzaki *et al*. 1997, Smith-Kirwin *et al*. 1998, Mix *et al*. 1999, Sahu 2004). The leptin receptor (LEPR), also called the obesity receptor (Ob-R), is a single transmembrane domain receptor that is highly expressed in the choroid plexus (Tartaglia *et al*. 1995). There are six isoforms of the LEPR (Ob-Ra, b, c, d, e, and f) due to alternative RNA splicing (Gorska *et al*. 2010). Among them, a soluble isoform Ob-Re is able to regulate serum leptin concentration, whereas only the full-length isoform Ob-Rb can fully transduce activation signal into the cell.

Leptin is constitutively secreted by adipocytes in proportion to the adipose mass (Budak *et al*. 2006). It suppresses food intake and promotes energy expenditure mainly via its direct effects on hypothalamic neurons (Morris & Rui 2009), and it is thus considered an anti-obese hormone. Mutations of the leptin gene (*ob* gene), which produce only defective and nonfunctional leptin, result in genetically obese mice (*ob/ob* mice) due to hyperphagia and increased lipogenesis (Zhang *et al*. 1994). Similar phenotypes were observed with the characteristics of obesity and diabetes in *db/db* mice that have mutations of the LEPR gene (*db* gene; Chen *et al*. 1996, Lee *et al*. 1996). Leptin levels decrease with fasting and increase in food intake (Ahima *et al*. 1996, Budak *et al*. 2006). At high physiological concentrations, leptin causes a decrease in food intake, an increase in energy expenditure, and a shift to increased fatty acid oxidation. High serum leptin levels are detected in obese patients, who are described as leptin resistant (Myers *et al*. 2010). Several mechanisms have been proposed to be involved in leptin resistance, including impaired leptin trafficking and signaling, endoplasmic reticulum stress, defects in leptin-targeted neural circuits, etc. (Morris & Rui 2009).

In addition to its critical roles in regulating energy homeostasis, leptin is also important in female reproduction. The deficiency of leptin or LEPR due to loss-of-function mutations in the corresponding genes has been linked to infertility and delayed puberty development in humans and rodents. Moreover, leptin and its receptor have been implicated in maintaining other normal female reproductive functions, including lactation, folliculogenesis, ovarian steroidogenesis, the maintenance of mammary gland morphology and function, the development of dominant follicles and oocytes, maturation endometrial development, menstrual cycle regulation (Agarwal *et al*. 1999, Zachow *et al*. 1999), and endometrial receptivity (Marin Bivens & Olster 1997, Bluher & Mantzoros 2007, Israel & Chua 2010, Clempson *et al*. 2011, Dos Santos *et al*. 2012). Leptin signaling also contributes to the hypothalamic–pituitary–gonadal (HPG) axis. In cultured pituitary cells from female rats, leptin could induce the production and secretion of both LH and

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FSH, with or without GNRH (Ogura *et al*. 2001). In addition, mice lacking leptin or the LEPR exhibit low LH levels and incomplete development of reproductive organs. Administration of leptin to *ob/ob* mice induces pubertal development and maturation of reproductive organs, increases LH secretion, and restores fertility, demonstrating the importance of leptin signaling in female reproduction (Donato *et al*. 2011). Abnormal leptin levels have been reported in the peritoneal fluid in women with endometriosis (De Placido *et al*. 2001, Wu *et al*. 2002, Bedaiwy 2005). Additionally, in women with hypothalamic amenorrhea due to energy deficiency, leptin treatment resulted in the recovery of menstruation and corrected the abnormalities in gonadal, GH, and adrenal axes, further indicating the requirement of leptin in normal reproductive and neuroendocrine functions (Welt *et al*. 2004, Chou *et al*. 2011).

The first study on leptin and its signaling in PCOS was reported in 1996 (Brzechffa *et al*. 1996), 2 years after the discovery of leptin (Zhang *et al*. 1994). Data from that study suggested the possible involvement of abnormal leptin signaling in the reproductive system in certain cases of PCOS. Later, a series of studies explored the role of leptin as a potential player in PCOS. It is now widely acknowledged that serum leptin levels are positively correlated with BMI and percent body fat. In addition, leptin level is associated with estrogen or androgen levels and the ratios of E1/sex hormone-binding globulin (SHBG) and E2/SHBG. But no correlation between leptin and androstenedione or testosterone was observed in either control or PCOS groups. It still remains controversial whether serum leptin levels are different in PCOS compared with control subjects, as shown in Table 1. Increased serum leptin concentrations have been observed in women with PCOS in comparison to weight-matched controls in certain studies (Brzechffa *et al*. 1996, Vicennati *et al*. 1998, El Orabi *et al*. 1999, Brannian & Hansen 2002, Pehlivanov & Mitkov 2009, Yildizhan *et al*. 2011). Wang *et al*. (2012*a*) also reported significantly higher mRNA expression of leptin in subcutaneous adipose tissue of PCOS patients compared with controls. Most studies, however, did not find any significant differences in serum leptin levels in women with PCOS when compared with age- and weight-matched controls (Table 1; Chapman *et al*. 1997, Laughlin *et al*. 1997, Mantzoros *et al*. 1997, Micic *et al*. 1997, Rouru *et al*. 1997, Gennarelli *et al*. 1998, Carmina *et al*. 2009). No significant difference was found in circulating leptin levels between the ovulatory and anovulatory PCOS patients either (Carmina *et al*. 2009). Furthermore, a very recent study showed that there was no effect of PCOS on either adipose leptin expression or plasma leptin levels (Svendsen *et al*. 2012). These conflicting results might be explained by the different ethnicity and heterogeneity of the PCOS group, or the different sampling method to get fat biopsies in the studies. In addition, a single nucleotide polymorphism, G19A, detected in leptin gene was not found to be associated with PCOS (Pusalkar *et al*. 2010). Treatment with low-dose oral contraceptives (Sagsoz *et al*. 2009) or administration of conjugated estrogens and anti-androgens (Panidis *et al*. 2000) did not seem to affect serum leptin levels in women with PCOS.

Obesity and IR are crucial parameters of PCOS. As leptin is primarily secreted by adipose tissue, it is interesting to know whether serum leptin levels are correlated with IR in PCOS. No significant differences were observed in serum leptin or LEPR levels between PCOS IR and PCOS non-IR groups (Wang *et al*. 2011). However, Yildizhan *et al*. (2011) observed an association between serum leptin levels with IR in young women with PCOS. Troglitazone is a drug that improved IR and hyperinsulinemia. Treatment with troglitazone did not seem to alter leptin levels (Mantzoros *et al*. 1997). By contrast, administration of metformin, an insulin sensitizer widely used for the treatment of T2DM, considerably reduced serum leptin concentrations in obese (Morin-Papunen *et al*. 1998) and non-obese PCOS patients (Marciniak *et al*. 2009). The correlation between leptin and IR is thus still a matter of debate. Further research is required to clarify the relationship between leptin and IR in PCOS.

Genetic variants of the HPG axis are associated with a modest but significant effect on the phenotype of PCOS (Valkenburg *et al*. 2009). As described earlier, leptin may affect reproduction by modulating HPG axis function at both central and ovarian levels. Questions are then raised as to whether leptin contributes to the phenotype of PCOS by regulating the HPG axis. Sir-Petermann *et al*. (1999) found that circulating leptin and LH pulses are synchronized in both normal women and patients with PCOS. Thus, the leptin pulse does not seem to be specific to PCOS and the real significance of the apparent copulsatility between LH and leptin needs to be elucidated.

Adiponectin

APN, also referred to as ACRP30 or AdipoQ, is the most abundant secreted protein expressed exclusively in adipose tissue (Campos *et al*. 2007, Bohler *et al*. 2010). There are three major forms of APN: a trimeric low-molecular-weight (LMW) form, a hexameric

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Table 1 Serum levels of adipokines in PCOS patients compared with controls

Adipokines	Serum levels in PCOS compared with controls	References
Leptin	Increased	Brzechffa *et al*. (1996), Vicennati *et al*. (1998), El Orabi *et al*. (1999), Brannian & Hansen (2002), Pehlivanov & Mitkov (2009), and Yildizhan *et al*. (2011)
	Similar	Chapman *et al*. (1997), Laughlin *et al*. (1997), Mantzoros *et al*. (1997), Micic *et al*. (1997), Rouru *et al*. (1997), Gennarelli *et al*. (1998), Carmina *et al*. (2009), and Svendsen *et al*. (2012)
APN	Decreased	Ardawi & Rouzi (2005), Escobar-Morreale *et al*. (2006), Pinhas-Hamiel *et al*. (2009), Manneras-Holm *et al*. (2011), and Shin *et al*. (2011)
	Similar	Orio (2003), Spranger *et al*. (2004), and Lecke *et al*. (2011)
Resistin	Increased	Munir *et al*. (2005)
	Similar	Panidis *et al*. (2004), Seow (2004), Escobar-Morreale *et al*. (2006), Seow *et al*. (2007), Olszanecka-Glinianowicz *et al*. (2011), and Zhang *et al*. (2011)
Visfatin	Increased	Tan *et al*. (2006*a*,*b*), Chan *et al*. (2007), Kowalska *et al*. (2007), Panidis *et al*. (2008), Carmina *et al*. (2009), Ozkaya *et al*. (2010), Plati *et al*. (2010), and Seow *et al*. (2011)
	Similar	Gudducu *et al*. (2012), Lajunen *et al*. (2012), and Olszanecka-Glinianowicz *et al*. (2012)
Omentin-1	Decreased	Tan *et al*. (2008*a*,*b*) and Choi *et al*. (2011)
RBP4	Increased	Carmina *et al*. (2009) and Mahde *et al*. (2009)
Lipocalin-2	Increased	Cakal *et al*. (2011)
	Similar	Panidis *et al*. (2010) and Koiou *et al*. (2012)
Chemerin	Increased	Tan *et al*. (2009)

medium-molecular-weight (MMW) form, and a multimeric high-molecular-weight (HMW) form (Kadowaki & Yamauchi 2005, Michalakis & Segars 2010). Biological effects of APN vary from each different structure, with HMW most actively suppressing hepatic glucose production and LMW most potent for induction of AMP-activated protein kinase (AMPK) activation and fatty acid β-oxidation in skeletal muscle (Michalakis & Segars 2010). Three putative receptors have been identified for APN, namely AdipoR1, AdipoR2, and T-cadherin (T-cad; Hug *et al*. 2004, Kadowaki *et al*. 2006). AdipoR1 and AdipoR2 receptors are ubiquitously expressed and have been demonstrated to be expressed in female reproductive tissues, including ovary, placenta, endometrium, and oviduct (Michalakis & Segars 2010). A body of literature supports the role of AdipoR1 and AdipoR2 in reproduction. By contrast, T-cad (Cdh13) has been shown to be critical for APN-mediated beneficial effects in the heart (Denzel *et al*. 2010). T-cad is a glycolipid-anchored extracellular protein. It has been identified as a receptor for MMW and HMW forms of APN. Although T-cad has been found to be expressed in rat ovaries (Machell *et al*. 2000), the role of T-cad in female reproduction still remains unknown.

Circulating APN levels decrease with obesity and increase with weight loss (Gavrila *et al*. 2003, Escobar-Morreale 2006, Pietilainen *et al*. 2006). The major action of APN is to increase insulin sensitivity by stimulating glucose uptake in the liver and muscle, decreasing hepatic gluconeogenesis, and promoting fatty acid β-oxidation in the skeletal muscle. Consequently, APN reduces triglyceride (TG) accumulation and enhances insulin sensitivity (Bohler *et al*. 2010, Michalakis & Segars 2010). The intracellular signal transduction pathway of APN has been shown to involve the activation of AMPK by APN stimulation (Kadowaki *et al*. 2006, Bohler *et al*. 2010). Several other signaling pathways have also been suggested, including PI3K/Akt and MAPK pathways (Ouchi *et al*. 2004, Luo *et al*. 2005).

APN is described as a 'beneficial' adipokine in reproduction (Campos *et al*. 2007). Both ADIPOR1 and ADIPOR2 are expressed in human hypothalamus and pituitary (Rodriguez-Pacheco *et al*. 2006, Kubota *et al*. 2007). It has been shown that APN inhibits LH and GNRH release (Lu *et al*. 2008, Wen *et al*. 2008), indicating its possible role in modulating the central reproductive endocrine axis (Psilopanagioti *et al*. 2009). At physiological levels, APN induces the expression of genes associated with periovulatory remodeling of the ovarian follicle in porcine granulose cells (Ledoux *et al*. 2006). Serum APN levels were observed to increase in women following treatment with human chorionic gonadotropin during the IVF process (Liu *et al*. 2006). Collectively, these results suggest that APN may play an active role in ovulation. Moreover, APN reduced insulin-induced progesterone and androstenedione production as well as insulin-like growth factor 1-induced *LHR*, *CYP11A1*, and *CYP17A1* gene expression in bovine theca cells *in vitro*, indicating the possible involvement of APN in the pathophysiology of

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PCOS via its regulatory effects on steroidogenesis (Lagaly *et al*. 2008). Indeed, circulating APN levels are lower in obese subjects and are negatively correlated with testosterone levels (Orio 2003, Xu *et al*. 2005, Escobar-Morreale 2006). Testosterone has an inhibitory effect on the secretion of HMW APN (Xu *et al*. 2005). In the uterus, the presence of APN, AdipoR1, and AdipoR2 has been demonstrated in the mouse decidual cells of the implantation site and in artificially decidualized cells (Kim *et al*. 2011). Reduced expression of *ADIPOR1* and *ADIPOR2* was also observed in endometria of women with recurrent implantation failure compared with fertile women (Dos Santos *et al*. 2012), suggesting an important role of APN signaling in uterine receptivity and its possible contribution to implantation failures and pregnancy loss in women with maternal metabolic conditions such as obesity and PCOS. Results with respect to serum APN levels in PCOS compared with healthy controls are still controversial (Orio 2003, Spranger *et al*. 2004, Ardawi & Rouzi 2005, Pinhas-Hamiel *et al*. 2009, Lecke *et al*. 2011, Manneras-Holm *et al*. 2011, Shin *et al*. 2011; Table 1). Serum APN concentrations were observed to be reduced in PCOS patients compared with controls in some studies (Ardawi & Rouzi 2005, Escobar-Morreale *et al*. 2006, Pinhas-Hamiel *et al*. 2009, Manneras-Holm *et al*. 2011, Shin *et al*. 2011), whereas in other reports, serum APN concentrations did not seem to differ between PCOS and controls (Orio 2003, Spranger *et al*. 2004, Lecke *et al*. 2011). A meta-analysis revealed that serum APN levels are lower in women with PCOS compared with BMI-matched healthy controls (Toulis *et al*. 2009). In addition, it was found that obese PCOS patients have lower APN levels than non-obese PCOS patients. HMW APN has been demonstrated to be most closely associated with insulin sensitivity (Pajvani *et al*. 2004). It was reported that reduced serum levels of HMW APN are selectively reduced in women with PCOS, independent of BMI and IR (O'Connor *et al*. 2010). Several other reports also support the association of APN levels with IR (Trolle *et al*. 2010, Lecke *et al*. 2011). Metformin has been increasingly used in the treatment of PCOS, which effectively reduces IR in obese PCOS patients. Treatment of metformin for 6 months, however, did not affect APN levels (Trolle *et al*. 2010). Upregulated expression of *ADIPOR1* and *ADIPOR2* at both mRNA and protein levels has been observed in the subcutaneous and omental adipose tissues in insulin-resistant women with PCOS compared with controls (Tan *et al*. 2006*b*). Moreover, a number of studies investigated the association of PCOS with polymorphisms of the APN gene. Gao *et al*. (2012) recently found a significant association of APN T45G polymorphism with PCOS by a meta-analysis. As the most abundant adipokine in the human body, APN seems to play an important role in the pathogenesis of PCOS.

Resistin

Resistin is a small cysteine-rich protein secreted as a 94-amino acid polypeptide. It was first found by Steppan *et al*. (2001) during their study of the effects of PPARγ agonists on glucose homeostasis. Steppan *et al*. named this protein 'resistin' for its property of 'resistance to insulin' in mice and this gene was later designated as *Retn*. In the same year, this adipokine was also discovered by another group (Kim *et al*. 2001) and its inhibitory effect on adipocyte differentiation and its association with IR have made it a potential link between obesity and diabetes.

In mice, resistin is primarily secreted by mature white adipocytes. Resistin has been demonstrated to be involved in IR and T2DM in rodents as circulating resistin levels are increased in diet-induced and genetic forms of obesity and are decreased by the anti-diabetic drug rosiglitazone. Human resistin, however, is mainly secreted by peripheral blood mononuclear cells (Tilg & Moschen 2006). It competes with lipopolysaccharide for the binding to Toll-like receptor 4 and is thus involved in the inflammatory process. The expression of human resistin is predominantly localized in macrophages and stromal cells in adipose tissue rather than adipocytes (Bohler *et al*. 2010, Schwartz & Lazar 2011). A high level of resistin gene expression was observed in human preadipocytes, which decreased during adipocyte differentiation. It should be noted that the relationship between resistin and IR in humans is complicated. It is still a subject of debate as some studies revealed a positive correlation between resistin and IR (Silha *et al*. 2003, Azuma *et al*. 2004, Kunnari *et al*. 2005, Gerrits *et al*. 2012), whereas others failed to detect changes in resistin levels in obesity, IR, or T2DM (Kielstein *et al*. 2003, Lee *et al*. 2003, Pfutzner *et al*. 2003, Heilbronn *et al*. 2004, Chen *et al*. 2005, Akdeniz *et al*. 2011).

As a secreted circulating protein, resistin can exert its functions in both endocrine and paracrine manners (Schwartz & Lazar 2011). In rodent liver and muscle, resistin has been shown to inhibit AMPK and thus decrease hepatic gluconeogenesis and stimulate muscle glucose uptake (Banerjee *et al*. 2004, Muse *et al*. 2004). In mouse adipose tissue, resistin activates suppressor of cytokine signaling-3 (SOCS-3), an anti-inflammatory mediator (Steppan *et al*. 2005), which is known to suppress insulin

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signaling in several tissues (Senn *et al*. 2003). In primary human aortic endothelial cells, resistin activates p38 MAPK and thus upregulates phosphatase and tensin homolog deleted on chromosome 10 (PTEN) expression (Shen *et al*. 2006), suggesting an inhibitory effect of resistin on insulin signaling. In a very recent study, Sanchez-Solana *et al*. (2012) identified mouse resistin as a ligand for the tyrosine kinase-like orphan receptor (ROR1) to regulate SOCS-3, glucose transporter 4 (GLUT4), and GLUT1 expression and to modulate glucose uptake and promote adipogenesis of 3T3-L1 cells, which thus opens a new line of research to explain the underlying mechanisms of resistin action in adipogenesis and the development of IR. In addition to its expression in adipose tissue and macrophages, resistin mRNA was also found in hypothalamo–pituitary axis, rat testis, and rat and bovine ovaries (Maillard *et al*. 2011), and resistin has been suggested to affect bovine and rat granulose cell steroidogenesis and proliferation (Maillard *et al*. 2011, Spicer *et al*. 2011).

Data regarding the levels of resistin in PCOS patients are still controversial (Table 1). Seow (2004) did not find any significant difference in either serum or follicular fluid resistin levels between PCOS and control groups, which is supported by several other studies (Panidis *et al*. 2004, Escobar-Morreale *et al*. 2006, Seow *et al*. 2007, Olszanecka-Glinianowicz *et al*. 2011, Zhang *et al*. 2011), even though serum APN levels were significantly lower in obese than in normal-weight women (Escobar-Morreale *et al*. 2006). Escobar-Morreale *et al*. (2006) showed that serum resistin levels were increased in overweight and obese women compared with lean subjects, irrespective of their PCOS or controls status. Although resistin mRNA levels were twofold higher in adipocytes from PCOS than in those from normal controls (Seow 2004), adipocyte-produced resistin does not seem to play a key role in the body as adipocytes are not the major source of circulating resistin in humans. Adipocyte resistin mRNA expression was reported to be significantly decreased after laparoscopic ovarian electrocautery in both obese and lean women with PCOS (Seow *et al*. 2007). Moreover, no significant difference in plasma resistin levels was observed between PCOS-IR and PCOS-non-IR groups (Zhang *et al*. 2011). On the other hand, Munir *et al*. (2005) found a 40% increase in mean serum resistin concentration in PCOS patients and a positive correlation with BMI and testosterone. In addition, resistin was observed to synergize with insulin to augment ovarian androgen production by enhancing 17α-hydroxylase mRNA expression and activity in ovarian theca cells.

In a study on resistin promoter, no strong evidence was found for association of variation in resistin gene promoter with the phenotypes of PCOS (Urbanek *et al*. 2003). Instead, the resistin gene polymorphism is associated with BMI in women with PCOS, suggesting that resistin might be related to adiposity in PCOS (Xita *et al*. 2004). In addition, in a randomized placebo-controlled study, treatment with the insulin sensitizer rosiglitazone significantly reduced serum resistin levels in overweight women with PCOS, implying the contribution of resistin to insulin sensitivity improvement during treatment (Majuri *et al*. 2007). In summary, resistin seems to be an important adipokine that is involved in obesity, IR, and PCOS.

Visfatin

Visfatin, previously known as pre-B cell colony enhancing factor (PBEF; Samal *et al*. 1994), is a highly conserved, 52 kDa protein expressed in a variety of tissues and cell types, including adipocytes, lymphocytes, bone marrow, liver, muscle, trophoblast, and fetal membranes (Fukuhara *et al*. 2005). Visfatin was initially discovered by Fukuhara *et al*. (2005) who found that the mRNA level of a secreted protein was much more abundant in visceral fat than in subcutaneous fat and was thus named visfatin. Data from *in vitro* experiments showed that visfatin stimulates glucose uptake in adipocytes and muscle cells and suppresses glucose release from hepatocytes (Fukuhara *et al*. 2005, Hug & Lodish 2005). It was reported that visfatin binds to insulin receptor at a different site from that of insulin and exhibits insulin-mimetic actions. Administration of recombinant visfatin lowered plasma glucose levels in mice. In addition, heterozygous knockout mice (visfatin$^{+/-}$) in which one copy of the visfatin gene has been deleted have higher plasma glucose levels under both fasting and feeding conditions compared with wild-type mice. The relationship between visfatin and insulin action, however, is currently unclear due to the retraction of part of the work originally published in Science (Fukuhara *et al*. 2007).

Although there are conflicting data on the relationship between visfatin and obesity (Haider *et al*. 2006, Pagano 2006, Choi *et al*. 2007, Filippatos *et al*. 2007, Panidis *et al*. 2008, Chang *et al*. 2010), a recent meta-analysis revealed that plasma visfatin is significantly increased in subjects diagnosed with overweight/obesity, T2DM, metabolic syndrome, and CVD (Chang *et al*. 2011). Circulating visfatin levels were also found to be positively associated with IR (Chang *et al*. 2011). The changes

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observed in visfatin levels after exercise or gastric banding surgery are also controversial. On the one hand, it was shown in some reports that visfatin mRNA level in adipose tissue was increased in response to exercise and the circulating visfatin concentration was upregulated after weight loss induced by gastroplastic surgery (Krzyzanowska *et al*. 2006, Frydelund-Larsen *et al*. 2007). Serum visfatin concentration was also reported to increase after bariatric surgery related to the amount of weight lost in morbidly obese women (Botella-Carretero *et al*. 2008). On the other hand, in some other studies, plasma visfatin levels in obese subjects were reported to reduce with weight loss, either by exercise or gastric banding surgery (Haider *et al*. 2006, Choi *et al*. 2007). This discrepancy is difficult to explain. It may result from the different BMI value after weight loss, the type of surgical procedure, or other complex factors such as genetic variation and individual glucose tolerance state.

It has previously been reported that the gene expression and circulating levels of visfatin were increased in women with PCOS compared with age- and BMI-matched controls (Tan *et al*. 2006*a*, Chan *et al*. 2007, Kowalska *et al*. 2007, Panidis *et al*. 2008, Carmina *et al*. 2009, Ozkaya *et al*. 2010, Plati *et al*. 2010, Seow *et al*. 2011), as shown in Table 1. However, several recently published studies did not find a difference in plasma or serum visfatin levels between patients with PCOS and control groups (Guducu *et al*. 2012, Lajunen *et al*. 2012, Olszanecka-Glinianowicz *et al*. 2012). Moreover, Chan *et al*. (2007) did not observe any correlation between visfatin concentrations and testosterone, insulin, and LH levels in either PCOS or control groups. A positive correlation, however, was found between plasma visfatin concentration, fasting insulin, and homeostasis model assessment (HOMA)-IR, as reported by Tan *et al*. (2006*a*). It is interesting to find that visfatin levels in PCOS women were significantly reduced after a 3-month treatment with metformin and visfatin could differentiate between women with or without increased diabetogenic risk at a cutoff value of 19.24 ng/ml (Ozkaya *et al*. 2010). In addition, such a treatment resulted in a significant decrease in BMI, HOMA-IR, fasting insulin, and free testosterone, suggesting the possible involvement of visfatin in the pathophysiology of PCOS and its related complications. Many studies also demonstrated that visfatin displayed pro-inflammatory properties and modulated immune functions (Moschen *et al*. 2007, Adya *et al*. 2008, Romacho *et al*. 2009, Fan *et al*. 2011, Jacques *et al*. 2012). Visfatin was reported to induce NF-κB signaling in human endothelial cells and activated MMP-2/9, indicating its possible role in the pathogenesis of PCOS with its pro-inflammatory characteristics (Adya *et al*. 2008).

Omentin-1

Omentin-1, also named omentin, is a novel visceral fat depot-specific secretory protein identified by Yang *et al*. (2006) from a human omental fat cDNA library. It is predominantly produced by visceral adipose tissue in humans and rhesus monkeys (Yang *et al*. 2006). The expression of omentin-1 has also been detected in other tissues at low levels and omentin-1 is thus named intelectin (Tsuji *et al*. 2001), intestinal lactoferrin receptor (Suzuki *et al*. 2001), or endothelial lectin (Lee *et al*. 2001). A homolog of omentin, referred to as omentin-2, shares 83% amino acid identity with omentin/intelectin (omentin-1; Lee *et al*. 2001). Omentin-1 and omentin-2 genes are localized adjacently in the 1q22–q23 chromosomal region that has been linked to T2DM in various populations (Hanson *et al*. 1998, Elbein *et al*. 1999, Vionnet *et al*. 2000, Wiltshire *et al*. 2001).

It has been reported that omentin-1 is the major circulating form of omentins in human plasma. Plasma omentin-1 concentrations were negatively correlated with BMI, waist circumference, and IR as measured by HOMA and positively correlated with APN and HDL levels (de Souza Batista *et al*. 2007). Circulating omentin-1 levels were found to increase after weight loss-induced improvement of insulin sensitivity (Moreno-Navarrete *et al*. 2010). In addition, omentin-1 levels decrease in pre-diabetic stage, T1DM, and newly diagnosed, untreated T2DM patients (Tan *et al*. 2008*b*, Pan *et al*. 2010). It has been shown that omentin-1 enhances insulin sensitivity by activating Akt and increases insulin-stimulated glucose uptake both by subcutaneous and omental adipocytes *in vitro* (Yang *et al*. 2006). But unlike visfatin, omentin-1 does not stimulate basal glucose transport on its own, suggesting the lack of intrinsic insulin-mimetic activity of omentin-1.

In the setting of PCOS, plasma omentin-1 concentrations were found to decrease in non-obese women with normal glucose tolerance and PCOS and overweight insulin-resistant women with PCOS when compared with control subjects (Table 1; Tan *et al*. 2008*a*, Choi *et al*. 2011). In addition, the expression of omentin-1 at both mRNA and protein levels in omental adipose tissue is decreased in non-obese women with PCOS compared with controls (Tan *et al*. 2008*a*). Mahde *et al*. (2009) demonstrated that 93.33 and 98.30% of PCOS patients have

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abnormal ratios of omentin-1 to insulin and omentin-1 to resistin respectively. Treatment with metformin for 3 or 6 months significantly increased serum omentin-1 levels as well as the ratio of omentin-1 to insulin in PCOS patients (Shaker *et al*. 2010, Tan *et al*. 2010*a*). It should be noted that omentin-1 has been shown to display anti-inflammatory properties as well (Tan *et al*. 2010*b*, Yamawaki *et al*. 2011, Kazama *et al*. 2012). For instance, omentin-1 can attenuate TNFα-induced inflammation both in endothelial cells and in vascular smooth muscle cells (Yamawaki *et al*. 2011, Kazama *et al*. 2012). These data suggest that dysregulated omentin-1 levels may contribute to the pathophysiology of PCOS.

Retinol binding protein-4

RBP4 is a protein synthesized mainly by hepatocytes, followed by adipocytes. It has been regarded as a novel adipokine since a study on adipose-specific *Glut4* knockout mice in 2005 (Yang *et al*. 2005). Although it is a transport protein for vitamin A (retinol), RBP4 has been recognized as an adipokine that affects systemic insulin sensitivity and glucose homeostasis (Graham *et al*. 2006). Serum RBP4 levels are upregulated in insulin-resistant states in humans and in mice. On the other hand, serum RBP4 can also provoke IR. In mice, peritoneal injection of recombinant human RBP4 induces systemic IR. Conversely, genetic deletion of RBP4 enhances insulin sensitivity. A negative correlation was found between plasma RBP4 levels and peripheral insulin sensitivity. In addition, RBP4 has been related to obesity. Circulating RBP4 levels and *RBP4* mRNA expression in visceral and subcutaneous abdominal adipose tissue are increased in obese patients compared with lean subjects. Reduction in body weight after dietary interventions, especially with a carbohydrate-restricted diet, results in decreased serum RBP4 levels (Volek *et al*. 2009). In human subcutaneous and omental adipose tissue explants, 17β-estradiol significantly increased *RBP4* mRNA expression, protein levels, and secretion into the culture media. By contrast, testosterone, insulin, androstenedione, or DHEA-S did not have a marked effect on *RBP4* expression (Tan *et al*. 2007).

Up until now, there have been only a few studies investigating the involvement of RBP4 in the pathophysiology of PCOS. A significant increase in serum RBP4 levels has been observed in PCOS patients compared with controls (Table 1; Carmina *et al*. 2009, Mahde *et al*. 2009). Obese or overweight women with PCOS have increased serum RBP4 levels compared with age- and BMI-matched healthy controls (Tan *et al*. 2007, Yildizhan *et al*. 2011). Additionally, there was a significant increase in *RBP4* mRNA in subcutaneous and omental adipose tissue as well as isolated adipocytes of overweight PCOS women compared with controls (Tan *et al*. 2007). No significant correlation was found between RBP4 and IR in subjects with PCOS. However, there was a positive correlation between RBP4 levels and LH and TG. In addition, no difference in serum RBP4 levels was observed between ovulatory and anovulatory PCOS patients (Carmina *et al*. 2009). In PCOS patients who underwent controlled ovarian hyperstimulation for an IVF–embryo transfer, serum RBP4 was found to be significantly decreased during the process (Orvieto *et al*. 2010). But there is no correlation between serum RBP4 levels and IVF treatment variables or outcome. It is also noteworthy that retinoids, which include retinol and its derivatives, have been found to regulate androgen biosynthesis and steroidogenic enzyme expression in normal and PCOS theca cells (Wood *et al*. 2004). Wickenheisser *et al*. further demonstrated that retinol stimulated *CYP17* mRNA accumulation and promoter function in PCOS but not normal theca cells in humans, which could contribute to the excessive theca-derived androgen production in PCOS patients (Wickenheisser *et al*. 2005). It would thus be intriguing to measure the hepatic level of RBP4 that transports retinol from the liver to target tissues. Indeed, women with PCOS had a statistical trend for higher RBP4 compared with controls (Sopher *et al*. 2012). But the relationship between retinol, RBP4, and the increased ovarian androgen synthesis in women with PCOS needs to be evaluated in future studies.

Lipocalin-2

LCN2, also named neutrophil gelatinase-associated lipocalin (NGAL), is a 25 kDa glucoprotein belonging to the lipocalin superfamily (Triebel *et al*. 1992, Kjeldsen *et al*. 1993). It is able to transport small lipophilic ligands, such as lipopolysaccharides (Bratt *et al*. 1999), through the hydrophilic body fluid and acts as a bacteriostatic protein. LCN2 was first isolated from human neutrophils and has now been found to be expressed in several types of cells, including adipocytes (Zhang *et al*. 2008), macrophages (Zhang *et al*. 2008), brain endothelial cells (Hamzic *et al*. 2012), hepatocytes (Jayaraman *et al*. 2005), endometrial carcinoma cells (Mannelqvist *et al*. 2012), and erythroid progenitor cells (Miharada *et al*. 2005).

LCN2 has been implicated in diverse physiological and pathophysiological processes, including apoptosis, ion transport, inflammation, cell survival, tumorigenesis,

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and atherosclerosis. Emerging evidence suggests that LCN2 is a novel adipokine that contributes to obesity and IR. In reproduction, it was found that serum LCN2 concentrations in pregnant women with preeclampsia were significantly different from those in healthy pregnant women, suggesting a possible role for LCN2 in the pathogenesis of preeclampsia (Stepan *et al*. 2010, Cemgil Arikan *et al*. 2011).

In women with PCOS, Cakal *et al*. (2011) found a significant increase in serum LCN2 levels compared with BMI-matched controls (Table 1). Two other groups, however, revealed that PCOS *per se* does not affect LCN2 levels (Panidis *et al*. 2010, Koiou *et al*. 2012). Instead, obesity is associated with elevated serum LCN2. Weight loss consequently induces a significant decrease in LCN2 levels in overweight/obese patients with PCOS.

Chemerin

Chemerin, also known as tazarotene-induced gene 2 (*TIG2*) or retinoic acid receptor responder 2 (RARRES2), is a novel chemoattractant protein identified as a natural ligand of orphan receptor ChemR23 in 2003 by the group of Parmentier and Communi (Wittamer *et al*. 2003). It is synthesized as an inactive precursor, prochemerin, and is then rapidly converted to its active form by proteolytic cleavage during inflammation.

Chemerin exerts its potent leukocyte chemoattractant properties on leukocyte populations through its receptor ChemR23, a G protein-coupled seven-transmembrane receptor, which is also known as chemokine-like receptor 1 (CMKLR1). ChemR23 is predominantly expressed by immature myeloid and plasmacytoid dendritic cells, monocytes/macrophages, and natural killer (NK) cells (Parolini *et al*. 2007). Two other G protein-coupled receptors (GPRs) have been reported to bind chemerin with high affinity, namely GPR1 (Barnea *et al*. 2008) and C-C chemokine receptor-like 2 (CCLR2; Zabel *et al*. 2008). GPR1 is most closely related to ChemR23, but the expression pattern of GPR1 is different from ChemR23, with the main expression of GPR1 in the liver, intestine, kidney, and adipose tissue. CCLR2 is expressed at high levels by lung endothelial cells and at lower levels by liver endothelium *in vivo* (Monnier *et al*. 2012). It has been suggested to increase local concentrations of bioactive chemerin to facilitate the interaction between chemerin and CMKLR1 on adjacent cells (Zabel *et al*. 2008, Monnier *et al*. 2012).

In addition to its function in immunity, chemerin also plays a role in adipogenesis, adipocyte metabolism, and glucose metabolism. Chemerin has been identified as a novel adipokine due to its high expression in white adipocytes (Goralski *et al*. 2007) and has been demonstrated to be associated with obesity, metabolic syndrome, and T2DM (Bozaoglu *et al*. 2007, Goralski *et al*. 2007, Chu *et al*. 2012, Yamawaki *et al*. 2012). Bozaoglu *et al*. (2007) reported that plasma chemerin concentrations are strongly associated with BMI, plasma TGs, and blood pressure. Chemerin can regulate insulin sensitivity and insulin secretion. Conversely, insulin induces chemerin release from adipocytes (Bauer *et al*. 2012).

In reproduction, it has been shown that chemerin is present in human cord blood (Mazaki-Tovi *et al*. 2012). Upregulated chemerin levels in the decidua likely contribute to NK cell accumulation and vascular remodeling during early pregnancy (Carlino *et al*. 2012). Garces *et al*. (2012) showed that chemerin is expressed in rat placenta and serum chemerin levels were significantly decreased as gestation progressed, suggesting that chemerin may be an important regulator of maternal–fetal metabolism and metabolic homeostasis during pregnancy.

In patients with PCOS, Tan *et al*. (2009) detected a significant increase in serum chemerin, subcutaneous, and omental adipose tissue chemerin mRNA level and protein expression. Additionally, treatment with metformin for 6 months markedly decreased serum chemerin levels in PCOS patients. In a 5α-dihydrotestosterone-induced rat model, expression of chemerin and its ChemR23 receptor was significantly higher in the ovaries at both mRNA and protein levels (Wang *et al*. 2012*b*). Interestingly, chemerin can negatively regulate FSH-induced

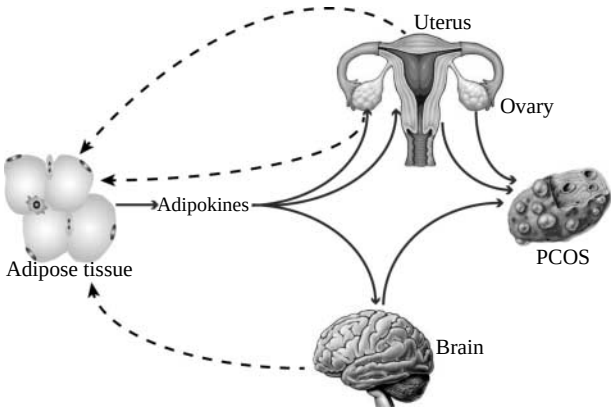

Figure 1
Schematic representation of a link between obesity and PCOS via adipokines. Adipokines, the secreted products of adipose tissue, can affect the brain, ovary, and endometrium and thus contribute to the pathology of PCOS. On the other hand, PCOS can also reciprocally influence the secretion of adipokines. Adipokines may thus act as a link between obesity and PCOS.

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follicular steroidogenesis and thus contribute to the pathogenesis of PCOS.

Conclusions

Obesity is highly present in PCOS patients and represents an independent and crucial risk factor for PCOS. Adipose tissue may communicate with the brain, ovaries, and uterus via adipokines, the adipose tissue-secreted products, to have an impact on both reproductive functions and metabolic features of women with PCOS (Fig. 1). Although the profile of most adipokines is still unknown in PCOS due to the conflicting data, the dysregulated adipokine levels in PCOS patients suggest that adipokines contribute to the pathology of PCOS. On the other hand, PCOS is also associated with higher central abdominal fat depots independent of obesity. Given the abnormal adipokine profile in women with PCOS irrespective of the presence or absence of obesity, PCOS may reciprocally influence the secretion of adipokines. Adipokines may thus serve as an endocrine link between obesity and PCOS, as shown in Fig. 1. It is also noteworthy that it was the circulating adipokine levels that were measured in most studies. However, it is still unknown whether all adipokines have endocrine actions. Circulating adipokine levels may not reflect the events occurring at the tissue levels by autocrine or paracrine mechanisms. Therefore, the use of circulating measurements is a limitation of most studies published to date. In addition, no adipokines have been identified so far as candidate molecules in genomic and proteomic studies of human omental adipose tissue in PCOS (Corton *et al*. 2008, Escobar-Morreale *et al*. 2008).

Our current understanding of the role for adipokines in PCOS is far from complete. The heterogeneity of clinical manifestations of PCOS patients makes this syndrome even challenging in the field of endocrinology, metabolism, and reproduction. Further work will thus be necessary to better understand the role of adipokines in reproductive functions that may act as a link between obesity and PCOS.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review reported.

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