

CLINICAL PRACTICE UPDATE

Obesity and polycystic ovary syndrome

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Summary

The aetiology of Polycystic Ovary Syndrome (PCOS) is complex and multifactorial. There is much evidence, however, to suggest that adipose tissue plays an important role in the development and maintenance of PCOS pathology. There is a close correlation between adiposity and symptom severity in women with PCOS, and even modest reductions in weight generally translate into significant improvements in menstrual regularity, fertility and hyperandrogenic features. This review article considers the various mechanisms that might underlie this link between excess adiposity and PCOS – including the effects of differential insulin sensitivity, abnormal steroid hormone metabolism and adipocytokine secretion. Greater attention to the therapeutic options available to reduce the impact of excess adiposity on ovarian and metabolic function is essential to the management of PCOS.

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Introduction

Our understanding of adipose tissue physiology and pathophysiology has been transformed over the last few years. This includes our understanding of the complex role of adipose tissue in the regulation of appetite, weight, metabolism and reproductive capacity. Adipose tissue also plays a key role in the pathogenesis of various common and complex disorders such as type 2 diabetes mellitus (T2DM) and polycystic ovary syndrome (PCOS).

Polycystic ovary syndrome is the commonest female endocrinopathy and affects between 6% and 10% of premenopausal women.¹ It is associated with a significantly higher odds ratio for the development of various cardiovascular risk factors.² Despite the high prevalence and significant morbidity resulting from both reproductive and hyperandrogenic features and the associated cardiovascular risk, the aetiology of PCOS remains incompletely understood.

Hyperandrogenaemia (originating from a predominantly ovarian source³) is the most consistent endocrine feature in women with PCOS, and is likely to play a key role in the aetiology of the condition. Indeed, non-PCOS conditions associated with hyperandrogenaemia in women [including congenital adrenal hyperplasia, (CAH⁴)] often mimic PCOS. It is also clear that adiposity plays a crucial role in maintaining and presumably in generating PCOS. Evidence for this includes the often dramatic improvement in menstrual regularity in response to weight reduction in women with PCOS.^{5,6}

Polycystic ovary syndrome is a heterogeneous condition associated with features of the metabolic syndrome. Consequently, studies involving women with PCOS are often confounded by coexisting obesity, insulin resistance and other features of the metabolic syndrome. This can sometimes make it difficult to interpret the role of such adverse metabolic features in the aetiology of PCOS. A description of the mechanisms underlying the development of the metabolic features associated with PCOS is beyond the scope of this review article. Instead, our aim is to focus on how adiposity may contribute to PCOS (based upon mechanisms that have been investigated amongst obese women with PCOS and illustrated in Fig. 1).

The link between adiposity and PCOS

Many women with PCOS (between 38% and 88%) are overweight or obese.^{7,8} Even modest weight loss of 5% body weight has been shown to result in significant improvements in both symptoms of hyperandrogenism and ovulatory function in women with PCOS.^{5,6} There is no doubt, therefore, that adiposity plays a crucial role in the development and maintenance of PCOS and strongly influences the severity of both its clinical and endocrine features in many women with the condition. Obesity per se probably also contributes to features of hyperandrogenism even in women with normal ovaries.⁹

Evidence from family-based and association studies suggest that PCOS has a significant genetic basis, although the genes predisposing to PCOS have yet to be clearly defined. Likely candidate genes for PCOS include those involved in the regulation of ovarian steroidogenesis but also those genes that influence body mass index (BMI) and adiposity. A likely explanation for the mechanisms underlying the development of obesity in women with PCOS is the combined effect of a genetic predisposition to obesity in the context of an obesogenic environment (poor diet and reduced exercise). The

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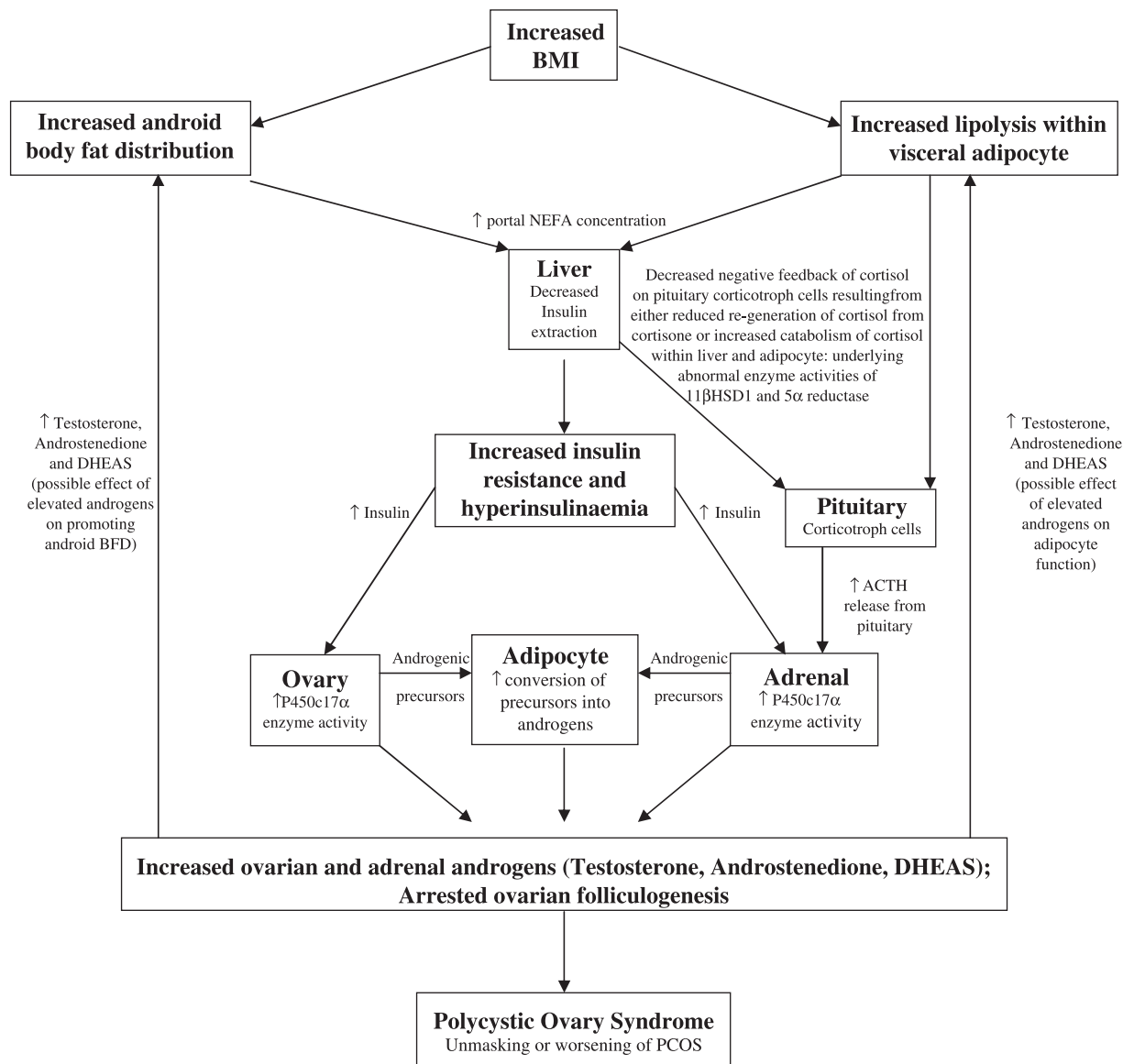


Fig.1 Possible mechanisms linking adiposity with PCOS. 11βHSD1: 11β hydroxysteroid dehydrogenase type 1; NEFA: non-esterified fatty acid; ACTH: adrenocorticotrophic hormone; SHBG: sex hormone-binding globulin; DHEAS: dehydroepiandrosterone sulphate; BMI: body mass index; BFD: body fat distribution.

development of obesity in women with PCOS in turn amplifies and may even unmask the biochemical and clinical abnormalities characteristic of this condition. One implication of this is that many obese women with PCOS may have remained asymptomatic, had they not become obese.

In this review we focus on three means by which adiposity may contribute to PCOS:

- adiposity and the consequences of insulin resistance;
- adiposity and the consequences of disturbed steroid metabolism;
- adiposity, appetite and the possible roles of leptin and ghrelin.

Adiposity and insulin resistance

The presence of insulin resistance in women with PCOS (largely reflecting impaired glucose disposal into skeletal muscle) was

established initially in 1980 by Burghen *et al.*¹⁰ It is now known that weight gain in both normal women and those with PCOS is associated with increasing insulin resistance. However, most women with PCOS (between 50% and 90%, depending on the diagnostic criteria used) have insulin resistance to a significantly greater extent than in age and BMI-matched control women, this disparity being more marked for higher BMIs.^{11–13} Furthermore, there is evidence that the use of insulin-sensitizing drugs in women with PCOS (without any associated weight loss) significantly improves the characteristic metabolic and endocrine features, ovulatory function, menstrual cyclicity and fertility rates.^{5,6,14,15} These observations have led to a hypothesis that insulin resistance (and the associated hyperinsulinaemia) plays an important role in the aetiology of PCOS.

Insulin interacts synergistically with LH within the theca cells of polycystic ovaries (in which theca cell hyperplasia is usually present)

to cause activation of the enzyme, P450c17 α , the key enzyme in the biosynthesis of ovarian androgens such as testosterone.^{16–18} A further adverse effect of hyperinsulinaemia on the ovary in women with PCOS includes the arrest of ovarian follicle development at 5–10 mm (thereby contributing towards anovulation).^{19,20} Hyperinsulinaemia may also have adverse effects in women with PCOS through its action at non-ovarian sites. These include the pituitary through enhancement of pituitary LH pulse amplitude,^{12,21} liver through suppression of hepatic synthesis of sex hormone-binding globulin (thereby increasing the free androgen index)^{22,23} and adrenal through stimulation of P450c17 α activity, thereby increasing adrenal androgen production.²⁴

These putative stimulatory effects of insulin in the face of peripheral insulin resistance, may appear paradoxical, but can be explained, in principle, by tissue-specific differences in insulin sensitivity. At the molecular level, it has been established, in studies of T2DM subjects that physiological insulin resistance (which is largely determined by glucose disposal into skeletal muscle) is associated with a specific impairment in the phosphatidylinositol 3-kinase-mediated insulin signal transduction pathway. Signalling through the alternative mitogen-activated protein kinase pathway (which typically mediates insulin's effects on cell growth) is preserved.²⁵ Given the close overlap with T2DM, it is probable that similar effects are obtained in PCOS.^{26,27} If so, the consequence of peripheral insulin resistance (and consequent hyperinsulinaemia) may actually be increased insulin signalling in the ovary, leading to enhanced ovarian steroidogenesis.

In support of the mechanism of insulin-enhancing ovarian steroidogenesis in PCOS is the observation of an increased prevalence of PCOS in women with Type 1 Diabetes Mellitus.²⁸ (The ovaries of these women are often exposed to hyperinsulinaemia as a result of exogenously administered insulin into the systemic circulation.) Support for a post-insulin-receptor signalling defect comes from *in vitro* studies on adipocytes taken from women with PCOS. These show a significant reduction in the abundance of glucose transporter 4 despite there being no abnormalities in insulin receptor number or affinity (compared with adipocytes taken from appropriately weight-matched control women).^{26,29} A similar post-insulin-receptor signalling defect that is pathway-specific may be a possible explanation for the differential resistance to the metabolic and steroidogenic effects of insulin, in the ovaries of women with PCOS.²⁷

There is some controversy regarding the presence of insulin resistance in lean women with PCOS.^{6,11,12,24,30–32} Possible reasons for this controversy include the use of variable definitions of PCOS and differences in ethnicity, family history of T2DM and personal history of gestational DM in women with PCOS and controls between studies.^{32,33} Furthermore, inclusion of variable numbers of anovulatory women with PCOS (who are known to be significantly more insulin resistant than women with PCOS with hyperandrogenism and regular cycles) between studies may have contributed to the controversy regarding insulin resistance in lean women with PCOS.¹⁹ It is likely, however, that insulin resistance (augmented by increasing adiposity), with its associated hyperinsulinaemia, plays an important role in the aetiology of PCOS, particularly in those obese women with the condition. Given its likely importance, an understanding of why many (particularly obese) women with PCOS are significantly

more insulin resistant than their age- and BMI-matched female counterparts is crucial. The possible mechanisms are discussed in succeeding sections.

Android body fat distribution

The existence of an android body fat distribution (BFD) in women, characterized by adipose tissue distributed mainly in visceral and abdominal subcutaneous depots, is known to be associated with insulin resistance.^{6,11,12,31,34} Furthermore, when women with PCOS are compared with control women matched for abdominal adiposity (a marker of android BFD), the difference in insulin resistance between the two groups is much less marked than if the two groups are matched for BMI.³¹ This implies that in women with PCOS, enhanced insulin resistance may be one consequence of an android BFD.

There is a large body of evidence that android BFD affects the majority (between 50% and 60%) of women with PCOS regardless of BMI. These studies include diverse means of BFD assessment including lipometer, ultrasound and dual-energy X-ray absorptiometry.^{35,36} One possible mechanism of an android BFD is exposure to relatively high concentrations of testosterone during early development. The observation of increased central adiposity in the prenatally androgenized female rhesus monkey is consistent with this hypothesis.³⁷ There is also evidence that elevated serum testosterone concentrations may modify BFD in women during adulthood. Studies in both nonobese female to male transsexuals³⁸ and obese postmenopausal women³⁹ have demonstrated the development of android BFD after 3 years and 9 months of testosterone administration, respectively. Hyperinsulinaemia, through its direct effect on the adipocyte, has also been suggested to be a possible determinant of android BFD in women with PCOS.^{35,40}

In women with PCOS, it is possible that android BFD *per se* contributes to hyperandrogenaemia through its adverse effects on insulin sensitivity and consequent gonadotrophic effects of hyperinsulinaemia on the ovaries. Thus, in women with PCOS, android BFD may be both a cause and an effect of hyperandrogenaemia. There is a vicious circle in which android fat begets android fat, and further exacerbates the predisposition towards weight gain in women with PCOS. The cycle can be interrupted by dietary intervention and/or use of insulin-sensitizing drugs.

Abnormal lipolysis

In addition to abnormal distribution of adipose tissue in women with PCOS, there may also be inherent abnormalities of lipolysis within adipocytes that are site specific. One study has demonstrated that there is a marked (approximately twofold) increase in catecholamine-induced lipolysis within visceral adipocytes isolated from nonobese women with PCOS compared with BMI-matched control women.⁴¹ A selective increase in the function of the postreceptor protein kinase A – hormone sensitive lipase complex may have contributed towards this abnormality. Studies on normal men and women have also demonstrated that testosterone may facilitate non-esterified fatty acid (NEFA) release from visceral adipocytes *in vivo*, although the mechanism is unknown.^{42,43} One may speculate that

the hyperandrogenaemia characteristic of PCOS also facilitates NEFA release from visceral adipocytes in women with the condition.

Enhanced visceral adipocyte lipolysis, by increasing the concentration of portal (and systemic) NEFA, may enhance hepatic gluconeogenesis and reduce insulin extraction and peripheral glucose uptake.^{41,44} The evidence for the abnormal lipolytic mechanisms outlined above, however, is limited and confined to a few *in vitro* studies, specifically in nonobese women with PCOS. Further studies are required to address the following questions that remain unanswered:

- Do these abnormal lipolytic mechanisms also occur *in vivo* in women with PCOS?
- What proportion of nonobese women with PCOS demonstrates such abnormalities of lipolysis?
- Do obese women with PCOS also demonstrate such abnormalities of lipolysis?

Other mechanisms

Variants within the *PPARG* gene encoding peroxisome proliferator-activated receptor-gamma, a nuclear receptor regulating lipid and energy metabolism, could possibly be associated with PCOS and account for some of the insulin resistance that occurs in this condition. Studies on the *pparg2* knock-out mouse suggest that *pparg2* is required for the maintenance of normal insulin sensitivity in mice.⁴⁵ Human studies also provide evidence for a possible role of *PPARG* variants in PCOS aetiology. Studies on women with rare but large-effect mutations in *PPARG* reveal that, in addition to severe insulin resistance, hyperinsulinaemia, partial lipodystrophy and features of the metabolic syndrome, they also present with features of PCOS including oligomenorrhoea and hirsutism. Such case reports include those that describe women who are heterozygous for the proline-467-leucine and valine-290-methionine *PPARG* mutations.⁴⁶ It remains possible that (both known and currently unknown), smaller-effect variants in *PPARG* may play a role in the development and maintenance of insulin resistance in a subgroup of women with PCOS.^{47–49} However, large-scale association studies are required to elucidate such a role.

Finally, one further possible mechanism for insulin resistance in PCOS is through the abnormal release of adipocytokines. This mechanism is speculative, however, as studies relating to adipocytokines and PCOS are lacking.⁵⁰

Adiposity and steroid metabolism

The second group of mechanisms relating adiposity to PCOS relates to the consequences of increased body mass on steroid metabolism. In addition to its effect on insulin sensitivity, the adipocyte is also involved in the metabolism and interconversion of various steroidal hormones (including sex steroids and corticosteroids) in both normal women and men. It has been demonstrated that in normal women with simple obesity, there is, as in women with PCOS, a positive association of BMI with serum androgen concentrations.⁹ In both normal women and those with PCOS,

there is also an inverse association between BMI and serum LH concentrations. It has been suggested that this represents a negative feedback effect of increasing serum androgen concentrations on pituitary LH secretion with increasing BMI (or even a stimulatory effect of insulin on LH).⁵¹ An alternative, and to us a more plausible explanation, is that hyperinsulinaemia in obese women with PCOS is the major factor in causing anovulation, whereas elevated serum LH concentrations are the more likely cause of anovulation in lean women. Thus, lean women tend to have higher LH levels, whereas obese women tend to have lower LH concentrations.

It is likely that one explanation for the association of increasing adiposity with increasing androgenicity in both normal women and those with PCOS may be the result of the effects of increasing adiposity on steroid hormone metabolism within the adipocyte. These mechanisms are discussed in more detail in succeeding sections.

Sex steroid metabolism

In normal women, adrenals and ovaries contribute equally to circulating androgen concentrations. In PCOS, the predominant source of excess androgen is the ovaries. Only about 50% of circulating testosterone is directly secreted by ovaries and adrenals, the remainder being generated by peripheral conversion of the 'weaker' androgens androstenedione and, in the case of the adrenal, dehydroepiandrosterone sulphate. Testosterone may be further metabolized in target tissues into the more potent androgen, 5 α -dihydrotestosterone (DHT) by the action of 5 α -reductase, or to oestradiol (aromatase).⁵² The activities of the various sex steroid-metabolizing enzymes in each target tissue are therefore an important determinant of the tissue-specific concentrations of DHT and oestradiol and may also influence serum concentrations of these hormones. Adipose tissue is one such target tissue. Metabolism of sex steroids within the adipocyte is described in more detail in the next section.

17 β -Hydroxysteroid dehydrogenase

Androstenedione conversion to testosterone (and testosterone to androstenedione) requires the presence of the enzyme, 17 β -hydroxysteroid dehydrogenase (17 β -HSD) in its reductive and oxidative form, respectively. It is likely that 17 β -HSD type 5 represents the main reductive 17 β -HSD isoenzyme responsible for conversion of androstenedione to testosterone (and therefore androgen activation) in human adipose tissue.⁵³ It has been demonstrated that in women with simple obesity, expression of the 17 β -HSD type 5 isoenzyme is site specific (*in vitro* activities being significantly higher in subcutaneous than in omental adipose tissue).⁵³ This may provide one explanation for increasing androgenicity with increasing BMI in both normal women and those with PCOS.

5 α -Reductase

The enzyme, 5 α -reductase is expressed mainly in skin and liver but also within the adipocyte. 5 α -Reductase converts testosterone to DHT but is also involved in the catabolism of cortisol. This latter

mechanism is discussed in more detail in succeeding sections. There is some evidence that women with PCOS have enhanced peripheral 5α -reductase activity compared with age- and BMI-matched control women, thereby generating higher tissue concentrations of the more potent androgen DHT. Through a comparison of urinary steroid excretion in eleven patients with PCOS vs. control women, Stewart *et al.*⁵⁴ were the first to report an increased ratio of 5α - to 5β -reduced glucocorticoid and androgen metabolites in PCOS. Subsequently, a further comparison of eight women with PCOS against eight control women who were given an oral challenge with DHEA demonstrated that women with PCOS had significantly higher increases in serum DHT ($P < 0.01$) and its main metabolite androstenediol glucuronide ($P < 0.05$).⁵⁵ Increased 5α -reductase activity in the adipocyte could therefore be one mechanism by which obese women with PCOS display increased androgenicity.

Aromatase

Although the ovaries are the principal source of oestradiol in normal premenopausal women, oestrogens are also produced within peripheral tissues.⁵² Cytochrome P-450 aromatase is a key enzyme for oestrogen biosynthesis both within the ovary and peripherally. Encoded by the gene *CYP19*, aromatase expression is tissue specific. In the ovary aromatase is, of course, regulated by FSH but within the adipose tissue is under the control of glucocorticoids, class 1 cytokines and tissue necrosis factor- α .⁵² Aromatase catalyses the conversions of testosterone to oestradiol, of androstenedione to oestrone and of 16α -hydroxylated dehydroepiandrosterone to oestriol.⁵⁶

It has been proposed that PCOS may result from reduced aromatase activity. Evidence for this comes from the observation of some of the features of PCOS manifesting in patients with aromatase deficiency, resulting from rare loss-of-function mutations.⁵⁷ Furthermore, a recent study suggested that common variation at the aromatase gene is associated with both androgen excess (including increased circulating testosterone concentrations) and with variation in PCOS symptom score in young women.⁵⁸ The numbers of subjects in this study, however, were relatively small and other studies have failed to find such an association.⁵⁹ Overall, however, there are too few studies relating to aromatase activity in women with PCOS to draw any firm conclusions regarding its role in the aetiology of PCOS.

Cortisol/cortisone metabolism

In normal men and women, the activities of various enzymes involved in the metabolism and interconversion of cortisol and cortisone influence the feedback effect of cortisol on the pituitary. This in turn influences pituitary ACTH release and consequently the production of adrenal androgens. Two key enzymes involved in the metabolism of cortisol include 11β -hydroxysteroid dehydrogenase type 1, 11β -HSD1 (involved in the conversion of cortisone to cortisol) and 5α -reductase (involved in the catabolism of cortisol, and also the conversion of testosterone to DHT as discussed previously). It has been demonstrated that in normal men and women, obesity is associated with impairment of 11β -HSD1

and enhanced 5α -reductase activities.^{60,61} It has also been shown that 11β -HSD1 activity is strongly related to BFD, with android obesity (but not gynoid obesity) being associated with reduced 11β -HSD1 activity in both sexes.⁶¹ In a further study, the activity of 11β -HSD1 in normal men was shown to be significantly inversely correlated with visceral fat mass. Interestingly in the same study, men with T2DM showed no such impairment of 11β -HSD1 activity with increasing visceral fat mass.⁶²

In a large study comparing urinary cortisol metabolites in 65 women with PCOS with 45 BMI-matched normal control women, women with PCOS had significantly higher ratios of 11-oxo to 11-hydroxy metabolites of cortisol than the control women (1.4 times higher, $P < 0.001$).⁶³ This reflects impaired 11β -HSD1 enzyme activity in women with PCOS compared with controls. In this study, 55% of the nonobese women with PCOS and 24% of the obese women with PCOS had evidence of reduced 11β -HSD1 activity. In a further study comparing lean women with PCOS against control women closely matched for BMI, it was demonstrated that women with PCOS had significantly greater 5α -reductase and lower 11β -HSD1 enzyme activities than controls. In the same study, 42 women with PCOS with a broad range of BMI were studied and it was demonstrated that in these women, there was increased 11β -HSD1 enzyme activity with increasing central fat distribution, the opposite to what has been shown to occur in normal men and women with simple obesity.⁶⁴ In this study, hyperandrogenism was excluded as a major factor regulating the activities of both 5α -reductase and 11β -HSD1 enzymes. Finally, Stewart *et al.*⁵⁴ and Chin *et al.*⁶⁵ both demonstrated significantly higher 5α -reductase enzyme activities and a marked elevation of total cortisol metabolites [consistent with hypothalamo-pituitary adrenal (HPA-axis) activation] in women with PCOS compared with normal control women.

The two enzymes, 11β -HSD1 and 5α -reductase, are expressed predominantly within the liver. Analyses of results from urinary steroid profiles therefore mainly reflect hepatic 11β -HSD1 and 5α -reductase activities. These enzymes are also expressed within adipose tissue. The correlations of the activity of 11β -HSD1 with visceral fat mass (both in normal men and women with simple obesity and in women with PCOS) demonstrated in some of the studies described previously suggest that adiposity (particularly visceral adiposity) may influence HPA-axis activity and therefore adrenal androgen production both in simple obesity and women with PCOS. Regardless of their sites of action however, there is evidence that some women with PCOS may have abnormalities in the activities of both the 11β -HSD1 and 5α -reductase enzymes compared with BMI-matched control women. The nature of these dysregulated enzyme activities in women with PCOS, how they differ from those that occur in normal men and women with simple obesity and their prevalence among women with PCOS are all issues that need to be confirmed with further studies. However, there seems to be an agreement in the literature regarding increased 5α -reductase activity in women with PCOS.^{54,55,64,65} Although not all of these studies assessed DHT concentrations, it would seem a plausible hypothesis that increased 5α -reductase activities in women with PCOS may result in both increased DHT and increased adrenal androgen production. These occur because of increased conversion of testosterone to DHT and increased catabolism of cortisol (and

thus reduced negative feedback of cortisol on the pituitary corticotroph cells), respectively.

Adiposity and weight and appetite regulation

As PCOS is a condition associated with (and worsened by) obesity, it is possible that abnormalities in appetite- and weight-regulating hormones may play a role in its aetiology. Two such hormones, leptin and ghrelin, have been studied in PCOS and evidence relating to each of these is discussed in succeeding sections.

Leptin

In addition to its role in the regulation of appetite, body weight and metabolism, leptin is also likely to directly influence reproductive capacity in women. There is, for example, a correlation between serum leptin and LH pulsatility in normal humans.⁶⁶ This link between adiposity and reproductive capacity is perhaps not surprising from an evolutionary point of view in that it ensures optimal nutritional status for conception and pregnancy. It has been proposed that abnormally high serum concentrations of serum leptin may provide a link between PCOS and ovarian dysfunction (leading to anovulation and infertility) in some women with this condition.⁶⁷ Consistent with this hypothesis are the observations that leptin receptors have been demonstrated in human ovaries and in preovulatory human ovarian follicles.⁶⁸ Furthermore, hyperleptinaemia has been shown to contribute towards the lowered sensitivity of dominant ovarian follicles to IGF-1, resulting in anovulation and impaired regulation of human ovarian follicle development.⁶⁹

In normal humans, serum leptin levels are highly correlated with percentage body fat.⁷⁰ The results of most studies on serum leptin concentrations in PCOS also reveal a close correlation of serum leptin with percentage body fat.^{70,71} Serum leptin concentrations do not, however, seem to be correlated with PCOS *per se* but rather with adiposity (a normal physiological association).^{71–73} Furthermore, there are no significant differences in serum leptin concentrations between ovulatory and anovulatory women with PCOS, implying that serum leptin probably does not play an important role in regulating ovulation in these women.⁷¹ It remains possible, however, that leptin plays some part in the pathogenesis of PCOS in obese women with the syndrome. Further studies are required to elucidate the presence of any significant and independent correlations between serum leptin levels and other biochemical and phenotypic features of PCOS in these women.

Ghrelin

In addition to the peptide hormone, ghrelin, being a natural ligand of the GH secretagogue receptor, it has also been demonstrated to enhance appetite, reduce fat utilization and cause adiposity following central or peripheral administration to both rodents and humans.⁷⁴ Gastric expression (and consequent plasma concentrations) of ghrelin typically increase on fasting and decrease following food intake.

Most of the studies on ghrelin in women with PCOS have demonstrated a significant negative correlation between insulin resistance and plasma concentrations of ghrelin.^{75–77} The concentra-

tion of fasting plasma ghrelin in women with PCOS therefore appears to be dependent upon insulin resistance (with fasting plasma ghrelin concentrations being lower than expected and even comparable to levels from gastrectomized subjects⁷⁶ in those insulin-resistant women with PCOS). In women with PCOS with normal insulin sensitivity, ghrelin concentrations seem comparable to those in matched controls.^{75,76} There is some doubt, however, as to the causal relationship between concentrations of plasma insulin and ghrelin, with one study of women with PCOS, suggesting that the primary association is between ghrelin and androgens (rather than ghrelin and insulin).⁷⁸

In addition to the studies on fasting ghrelin levels, there is also evidence that postprandial reductions in plasma ghrelin concentrations may be less marked in women with PCOS compared with controls. It has been hypothesized that this may account for reduced satiety and increased hunger following a test meal in women with PCOS compared with controls.⁷⁹

The limited evidence (based on a few studies) suggests that abnormal ghrelin concentrations may play a role in appetite dysregulation, and therefore weight gain, in women with PCOS.

Conclusions

It is clear that the aetiology of PCOS is complex, multifactorial and remains incompletely understood. The precise role that adipose tissue plays is also unclear. To explore this role further, it has been useful and timely to apply our understanding of adipocyte physiology/pathophysiology, which has been transformed in recent years. This review has outlined the main aspects of this application. There remains an important unanswered question, however: is adipose tissue an innocent bystander or is it a major factor in the aetiology of PCOS?

As with T2DM, the development of PCOS is strongly associated with weight gain. It is possible, however, for women to develop PCOS without being overweight or obese. Therefore, although adiposity is associated with PCOS, it is not always necessary for its development. Furthermore, the association of (particularly android) adiposity with PCOS development does not necessarily imply that such adiposity causes PCOS. Indeed, it is known that exposure to high serum concentrations of testosterone in normal women can lead to the development of android adiposity.^{38,39} It seems likely that in women with PCOS, the development of android adiposity results at least in part from the effect of hyperandrogenaemia on the adipocyte. Evidence for this comes from experimental observations in the prenatally androgenized female sheep and rhesus monkey. These reveal that genetically determined hyper-secretion of ovarian androgens during foetal and later development results in deposition of fat in an android distribution. These observations are supported by data from human studies.³⁷

Simple (including android) obesity in women does not always result in the development of PCOS. It is incorrect therefore to state that obesity causes PCOS. There is evidence, however, that obesity worsens the phenotype (both metabolic and reproductive) in many women with the condition and weight loss remains the best therapy we have.^{5,6} In a woman genetically predisposed to developing PCOS, weight gain may be enough to unmask the condition (which may

otherwise have remained asymptomatic). Thus, weight gain is an important (both genetic and environmental) contributor to phenotype in many women with PCOS. Furthermore, it may be the distribution of adiposity (namely android adiposity resulting in insulin resistance and consequent worsening of hyperandrogenaemia) that is important for PCOS development. Apart from BFD, the evidence reviewed suggests that in a proportion of women with PCOS, adipose tissue behaves differently from that in BMI-matched control women. This behaviour includes abnormalities of lipolysis, steroid hormone metabolism (both sex steroids and cortisol) and of appetite regulation by circulating adipocyte-derived factors. It is not clear whether these abnormalities are primary activators or whether they simply result from other features of PCOS (such as hyperandrogenaemia).

The prevalence of PCOS is likely to increase in parallel with the obesity epidemic. The complex aetiology of PCOS is influenced by genetic and environmental (particularly dietary) factors. Both of these factors determine adiposity, which in turn influences the severity and expression of PCOS. Given the complexity of adipocyte physiology and pathophysiology, it is likely that we have only just begun to understand the mechanisms linking adiposity and obesity with PCOS.

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