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Obesity in Polycystic Ovary Syndrome: Two Diseases or One?

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Both obesity and the polycystic ovary syndrome (PCOS) are commonly seen in general population. Obesity is present in about 50% of women with PCOS and contributes to the development of this disorder. This article explores the influences of obesity on the pathogenesis, clinical manifestations, and treatment strategies of PCOS.
Key words: Obesity, polycystic ovary syndrome

Introduction

Both obesity and the polycystic ovary syndrome (PCOS) are commonly seen in the general population. Because weight reduction can effectively ameliorate symptoms of PCOS, it is possible to hypothesize that PCOS may be simply one manifestation of obesity in susceptible women. The purpose of this article is to explore the relationship between obesity and PCOS, to determine what impact obesity has on the manifestations of PCOS, to discuss the role of obesity in the pathogenesis of PCOS, and to review the mechanisms that underlie the frequent association between these two common conditions.

Obesity

Definition: The term “overweight” refers to a weight above the "normal" range, with a body mass index (BMI) of 25-29.9 kg/m^2 (BMI = body weight in kg divided by height in meters^2). The term “obesity” is defined as the presence of a BMI of over 30 kg/m^2 (1). Depending on body fat distribution, obesity can be characterized as “abdominal” obesity (also called central, visceral, android, or male-type obesity) or peripheral (gynoid) obesity. Central obesity can be diagnosed clinically by measuring the waist circumference (WC) or waist-to-hip circumference ratio (WHR) (2). WC larger than 102 cm for men and 88 cm for women or WHR greater than 0.95 in men and 0.85 in women confers high risk for metabolic complications in obese individuals with BMI between 25.0 and 34.9 kg/m^2 (3).

Prevalence: In Western countries, the prevalence of obesity has been increasing drastically over the past few decades. For example, 60% of adults 20 to 74 years of age are now considered overweight or obese in the United States. A trend toward an increase in the prevalence of obesity has also been observed in children and adolescents (1).

Pathogenesis: Over the past decade, several single-gene mutations causing obesity in rodents have been identified. In humans, mutations of the genes for leptin or leptin receptor are extremely rare causes of obesity. The concordance rate for obesity in twin studies is high, but the pattern of inheritance appears to be polygenic, e.g. determined by multiple genes rather than by a single-gene defect, in the great majority of cases. The marked increase in the prevalence of obesity over the last two decades suggests that environmental factors, such as increased energy intake and decreased physical activity, contribute significantly to the pathogenesis of obesity (1).

Clinical features and complications: It is well known that obesity, especially visceral obesity, is associated with an increased risk of morbidity and mortality. Insulin resistance and the metabolic

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syndrome, type 2 diabetes mellitus, dyslipidemia, hypertension, and atherosclerosis have all been shown to be more prevalent in obese individuals. Even in people of nearly normal weight, the presence of excessive visceral fat increases the risk of diabetes, gallstones, hypertension, atherosclerosis, and, in women, breast cancer (2).

Polycıstıc Ovary Syndrome

Definition and prevalence: PCOS is characterized by chronic anovulation with biochemical and/or clinical evidence of androgen excess and without other specific diseases of adrenal, thyroid or pituitary glands that can produce similar manifestations (4). The phenotypic features of PCOS are variable, possibly because of underlying genetic differences in etiology. PCOS is present in 5-10% of reproductive-age women, making PCOS the most common endocrinopathy in this group (4).

Clinical manifestations: The onset of clinical symptoms of PCOS usually occurs perimenarcheally. The hallmark feature of PCOS is *irregular menstrual bleeding*, although anovulatory but regular monthly bleeding can be present in some patients. *Hirsutism* is the most common symptom in young women, followed by *acne.* The prevalence of *infertility* and the *miscarriage* rate are also high in these women (4). *Obesity*, especially visceral obesity, is present in 50% of women with PCOS (1).

Endocrine abnormalities: *Hyperandrogenism* is a defining biochemical feature of PCOS. Serum androgen concentrations are elevated in 50-90% of women with this disorder and e*strogen* production is acyclical and continuous (5).

Many women with PCOS also manifest an elevated mean serum concentration of *luteinizing hormone* (LH) due to increased amplitude and frequency of LH secretory pulses (6). Circulating *follicle stimulating hormone* (FSH) concentrations are usually normal or low in women with PCOS, resulting in an elevated *LH/FSH ratio* compared with the same ratio in the early follicular phase in age-matched women without PCOS (6). Many women with PCOS regardless of their weight, are also *insulin resistant* and, consequently, *hyperinsulinemic* (7).

Etiology: The site of the primary defect in PCOS is unclear. Hypotheses of the pathogenesis of PCOS can be divided into the following three groups depending on the putative site of primary abnormality.

***Central hypothesis*:** This hypothesis postulates that the primary defect in women with PCOS resides in hypothalamic/pituitary axis. As discussed above, increased LH pulse amplitude and frequency have been reported in women with PCOS. The etiology of these neuroendocrine abnormalities in PCOS remains unclear. Decreased sensitivity of the GnRH pulse generator to inhibition by ovarian steroids, particularly progesterone, has been suggested (8). Abnormalities of leptin and endogenous opioids, leading to excessive stimulation of LH secretion, have also been suggested as well (7).

***Ovarian hypothesis*:** A primary abnormality of steroidogenesis has also been proposed as the cause of PCOS. A possible major site of dysregulation is the enzyme cytochrome P450c17, which posseses 17alpha-hydroxylase and 17,20-lyase activities (7). These two functions of P450c17 determine the ability of adrenal glands and gonads to synthesize 17alpha-hydroxylated glucocorticoids (17 alpha-hydroxylase activity) and/or sex steroids (17,20-lyase activity). Ovarian hypothesis proposes that abnormalities of LH secretion observed in PCOS are secondary to the abnormal sex-steroid feedback on LH secretion: an increased circulating level of estrone, derived through aromatization from androstenedione, may increase the sensitivity of LH-producing gonadotropes to GnRH.

***Insulin hypothesis*:** Insulin resistance is a common feature of PCOS. The etiology of insulin resistance in this disorder is not understood. A lower tissue content of GLUT4 glucose transporters (8), excessive serine phosphorylation of the insulin receptor (which reduces receptor signal transduction), or a defect in the autophosphorylation of tyrosine residues in the insulin receptor (which also reduces signal transduction) (9, 10) have been reported.

The hyperactive insulin/insulin-like growth factor (IGF) system may lead to hyperandrogenism by several mechanisms, including stimulation of P450c17 mRNA expression and activities in the ovaries and adrenal glands. An integrating link between insulin resistance and hyperandrogenemia may be excessive serine phosphorylation, which inhibits the activity of the insulin receptor, thus reducing insulin sensitivity, while also promoting the 17,20-lyase activity of P450c17, thus increasing androgen production (11). Insulin may

also contribute to the excessive LH-secretion observed in women with PCOS by increasing gonadotrope sensitivity to GnRH (12).

Coexistence of PCOS and Obesity

The original report by Stein and Leventhal included obesity as a component of PCOS (13). It is now understood, however, that only about 50% of patients with the syndrome are obese (14). Variable prevalence of obesity in different ethnic groups of PCOS patients has been reported. For example, although the pre-valence of PCOS in Spain is similar to that in the U.S., the prevalence of obesity in PCOS patients in Spain is considerably lower than that in most studies from North America (15). Similarly, the prevalence of obesity in PCOS patients from Asia is lower than in the U.S. (16).

Some information regarding the role of obesity in the pathogenesis of PCOS is available from the studies comparing obese and non-obese patients with PCOS.

Hyperandrogenism, manifested clinically by hirsutism and acne and biochemically by ele-vated serum free testosterone and reduced serum sex hormone binding globulin (SHBG) concentrations, is present more commonly in obese patients with PCOS than in lean PCOS women (17).

The magnitude of obesity, as well as, the preferential distribution of fat in an android fashion, affect the degree of *insulin resistance* in PCOS patients. Consequently, the prevalence of *glucose intolerance* and/or *diabetes mellitus* is higher in obese than in non-obese PCOS women (18).

Endometrial carcinoma is associated with anovulation and unopposed estrogen action. Obesity increases the risk of this malignancy in PCOS (19). *Oligomenorrhea* (20) and *infertility* (21) are also more common in obese women with PCOS when compared with non-obese PCOS patients, probably reflecting unopposed estrogen action and anovulation.

Accelerated *LH pulse frequency* is seen in many patients with PCOS, but reduced LH pulse amplitude and lower mean circulating LH concentrations are present in obese compared to lean PCOS women (22).

The *ovarian IGF* system may be affected by the presence of obesity. Obesity can produce either reduced or increased IGF activity. The reduced activity may occur because growth hormone (GH) pulse amplitude is inhibited by the presence of obesity, leading to a reduction in circulating GH levels and, consequently, to the reduced hepatic IGF production (20). Excess IGF activity in the presence of obesity may occur because of the insulin-mediated IGF-binding protein-1 (IGFBP-1) suppression (7). Contrary to the obese PCOS patients, whose IGF activity may be either increased or decreased, non-obese PCOS patients manifest increased IGF activity, mostly because of comparatively higher mean circulating GH concentrations compared to those seen in obese PCOS women (20).

Several features of PCOS have not been consistently shown to be influenced by obesity. *Dyslipidemia* (high serum concentration of low density lipoprotein, low serum concentration of high density lipoprotein, and hypertriglyceri-demia) is present in both obese and lean PCOS women. Of these abnormalities, hypertriglyceridemia is more pronounced in obese PCOS patients than in their lean counterparts (23). The prevalence of *hypertension* has been reported to be high in patients with PCOS but, after adjustment for BMI, no difference is seen in prevalence of hypertension between the women with PCOS and control populations (24, 25). The studies, that have examined the effects of obesity in PCOS on long-term cardiovascular risk have been inconclusive (26), similar to the studies that have assessed the role of obesity in the risk of gestational diabetes (27, 28) and preeclampsia (27, 29) in PCOS women.

Insulin Resistance as a Pathophysiologic Link Between PCOS and Obesity

Insulin resistance is almost universally present in obese individuals and is commonly observed in both obese and non-obese women with PCOS.

Insulin resistance and obesity: Insulin resistance is common in obesity (1). It has been hypothesized that free fatty acids (FFA), released from adipocytes through triglyceride lipolysis (30), lead to hyperinsulinemia by interfering with hepatic insulin extraction (31). FFA also inhibit peripheral glucose uptake by both fat and muscle (32,33). Alterations in insulin receptor number and in postbinding receptor activity have been reported in

obesity (33). Tumor necrosis factor (TNFα), another possible etiologic factor in the development of insulin resitance in obesity, circulates in increased amounts in obese individuals. TNFα interferes with the insulin receptor signaling by inhibiting the tyrosine kinase activity of the insulin receptor beta-subunit (34).

Insulin resistance and PCOS: An association between insulin resistance (with consequent hyperinsulinemia) and hyperandrogenism has been reported repeatedly. The hypothesis which postulates that hyperandrogenemia causes insulin resistance in PCOS has not been supported by evidence, since normalization of circulating androgen concentrations by oophorectomy or anti-androgenic agents has no impact on insulin resistance (35). The hypothesis, which postulates that hyperinsulinemia contributes to the development of hyperandrogenism in PCOS, has received experimental support.

Contributions of insulin resistance to the development of PCOS: Both obese and nonobese women with PCOS are insulin resistant and hyperinsulinemic compared with weight- and age-matched control women (7). However, insulin resistance in obese PCOS women is significantly more pronounced than in non-obese PCOS women (20).

SHBG: Production of SHBG by the liver is inhibited by insulin, independent of the sex steroid effect on SHBG-production. Serum SHBG concentration is low in women with PCOS (7), resulting in higher circulating concentrations of free androgens.

Ovarian androgen production: Many investigators have shown a direct stimulatory effect of insulin on androgen, estrogen and progesterone production by human or animal granulosa and thecal cells in vitro. Furthermore, it has been demonstrated that ovarian cells from women with PCOS are sensitive to insulin despite systemic insulin resistance, suggesting that insulin may act through the type 1 IGF-receptor or may activate alternative insulin receptor signaling pathways. Studies utilizing anti-IGF-1-receptor antibodies have demonstrated, however, that insulin effects in the ovary are usually mediated by the insulin receptor, rather than by the type 1 IGF-receptor. Evidence for alternate insulin receptor signaling pathways in the ovary has been reported recently (36) (Table 1).

Table 1. Insulin effects related to ovarian function.

(Adapted from Poretsky L. et al. "The insulin–related ovarian regulatory system in health and disease." Endocr Rev 20 (4): 535-582.) 1999, with permission from the Endocrine Society.)

Insulin effect	Organ
Directly stimulates steroidogenesis	ovary
Synergistically acts with LH and FSH to stimulate steroidogenesis	ovary
Stimulates 17 alpha-hydroxylase	ovary
Stimulates or inhibits aromatase	ovary, adipose tissue
Up-regulates LH receptors	ovary
Promotes ovarian growth and cyst formation synergistically with LH and hCG	ovary
Down-regulates insulin receptors	ovary
Up-regulates type 1 IGF receptors or hybrid insulin/type1 IGF receptors	ovary
Inhibits IGFBP-1 production	ovary, liver
Potentiates the effect of GnRH on LH and FSH	hypothalamus, pituitary
Inhibits SHBG production	liver

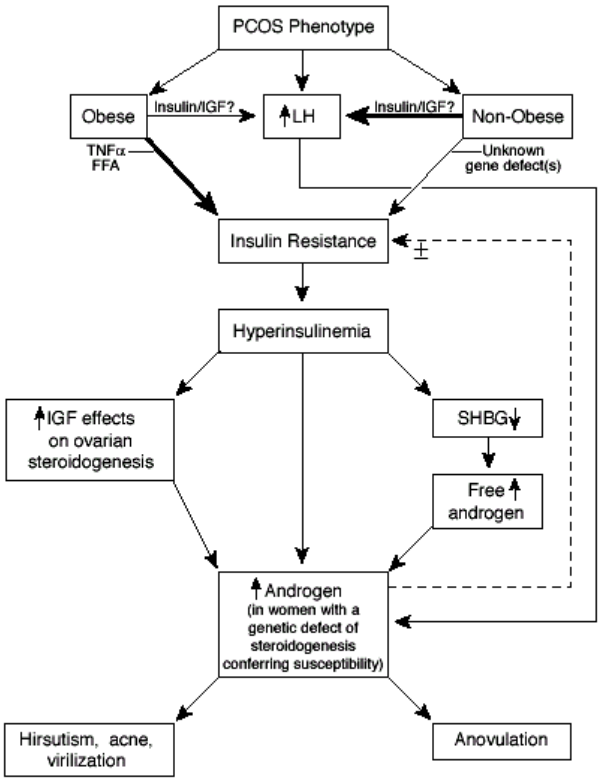

Figure 1. Pathogenesis of hyperandrogenism in obese and nonobese women with PCOS.

Insulin resistance (IR), caused by obesity or genetic susceptibility in nonobese women, results in hyperandrogenism (HA) through the effects of hyperinsulinemia on SHBG, IGF-system, gonadotropins and ovarian/adrenal steroidogenesis. Please see the text for details.

IGFs and IGF-binding protein (IGFBPs): The significance of the IGF-system in ovarian steroidogenesis has been examined in multiple studies. Both IGF-I and IGF-II are structurally homologous to proinsulin and can stimulate ovarian steroidogenesis. IGFBPs regulate the function of IGFs by binding IGFs and thus reducing bioavailable concentrations of IGFs and their ability to activate receptors. IGFBP-1, one member of the IGFBP-family, is produced in the liver and in the ovary; IGFBP-1 production is inhibited by insulin in both these organs. Low circulating and intraovarian concentrations of IGFBP-1 in hyperinsulinemic states may result in elevated concentration of bioavailable IGFs and may consequently contribute to the increased steroidogenic activity in the ovaries of women with PCOS (7) (Figure 1).

Other Pathogenetic Links Between PCOS and Obesity

Aromatase: The aromatase cytochrome P450 (P450arom) catalyzes the rate-limiting step in the conversion of C19 steroids (testosterone and androstenedione) to C18 estrogens (estradiol and estrone). Aromatase is present in both the ovary and the adipose tissue. Peripheral aromatization of androstenedione to estrone increases as a function of body weight (37, 38), contributing to higher circulating estrogen concentrations in obese women with PCOS. In the ovary, testosterone and androstenedione are produced by thecal cells and then converted to estradiol and estrone, respectively, by P450arom activity in the granulosa cells. Granulosa cell aromatase activity is a function of follicular size (39); low aromatase activity in atretic follicles of PCOS ovaries results in lower local estrogen and higher androgen concentrations, thus initiating a vicious cycle of enhanced follicular atresia.

TNFα: Serum concentrations of TNFα are high in hyperandrogenic women (40), including women with PCOS. This finding disappears in obese women when circulating TNFα concentration is adjusted for body weight; in normal-weight women with PCOS the increased circulating TNFα concentration persists. The effect of TNFα on ovarian steroidogenesis is not clear. TNFα has been shown to enhance the proliferative effect of insulin and IGF-I on ovarian cells (41), but, on the other hand, TNFα inhibits gonadotropin-stimulated steroidogenesis (42).

Leptin: Leptin is a 167-amino acid protein synthesized by adipose tissue. It circulates in plasma in free and bound forms. Leptin serves as a feedback signal from the adipocyte to the brain the purpose of which is to control adipose mass (43): leptin injections decrease food intake and cause weight loss in leptin deficient (ob/ob) mice (44). Leptin concentrations are regulated by the state of nutrition and by a variety of hormonal factors (43). With the exception of very rare cases of leptin gene mutations which are characterized by low circulating leptin concentration, in the great majority of obese individuals circulating leptin concentration positively correlates with body adiposity and adipocyte size, suggesting that obesity is a leptin resistant state (43).

Several studies in both animals and humans have demonstrated that body weight and fat content need to reach a certain "critical" level to assure fertility (45). Leptin is thought to be the link between reproduction and body weight. Ob/ob mice with leptin gene deficiency are infertile and obese. In these animals leptin administration reverses the hypogonadism independently of any change in the body weight (46). It has been shown that leptin concentrations rise before puberty in boys (47) and that leptin can accelerate onset of puberty in a normal mouse (48). Starvation-induced hypogonadism can be reversed by leptin administration (49). Whether the leptin effects on reproduction occur at the level of the brain or the ovary remains unclear.

In patients with PCOS circulating leptin concentrations do not consistently correlate with androgen concentrations (50, 51) and insulin sensitizers do not have any effect on leptin concentrations independently of weight change (51, 52). When adjusted for body weight, leptin concentrations in women with PCOS are not increased (51, 53)

Obesity and the Treatment of PCOS

Therapeutic options for obese PCOS patients include weight loss, insulin sensitizers (metformin, troglitazone, D-chiro-inositol), anti-androgens, and oral contraceptive agents. Studies of various therapeutic approaches to PCOS have centered on their effects on hyperandrogenism, menstrual irregularity, fertility and insulin sensitivity.

Weight loss: Numerous studies have examined the effects of weight loss in obese women with PCOS. A very-low-calorie diet, leading to a reduction in weight, produces improvement in insulin sensitivity and a reduction in circulating fasting insulin concentrations (54, 55). Improved insulin sensitivity leads to a reduction in the degree of hyperandrogenism. Most consistently, a decline in circulating free testosterone concentrations and an increase in circulating SHBG levels are noted after weight loss in obese PCOS women (54). Weight reduction also results in normalization of the menstrual cycle, increase in the number of ovulatory cycles assessed by circulating progesterone concentrations, and increased rate of conception in obese women with PCOS (54, 56).

Insulin sensitizers: Similar to weight loss, insulin sensitizers (such as metformin, troglitazone, and D-chiro-inositol) have beneficial effects in obese PCOS women. *Metformin*, a biguanide, is the most extensively studied of these agents. In one study, for example, 8 weeks of treatment with metformin resulted in a 35% reduction in the area under the insulin curve during a glucose tolerance test, a 52% reduction in circulating free testosterone concentrations and a 33% increase in circulating SHBG concentrations in 26 obese women with PCOS. These effects were accompanied by an improvement in the regularity of menstrual cycles (57). In another study, Insulin sensitivity, assessed by an oral glucose tolerance test, improved in PCOS patients treated with metformin as evidenced by a reduction in the mean area under the insulin curve (58). Combination treatment with weight loss and metformin also leads to an enhancement of insulin sensitivity and improvement in hyperandrogenism and menstrual irregularities (52). In contrast to these and other studies demonstrating benefits of metformin in obese PCOS women, two studies have shown no statistically significant enhancement of insulin sensitivity in women with PCOS after treatment with metformin versus placebo (59, 60).

At least two studies have examined the effects of a *thiazolidinedione*, troglitazone, in PCOS women. The studies demonstrated an improvement in insulin sensitivity and in circulating androgen levels in women treated with troglitazone in comparison with the placebo group (61, 62).

Inositol phosphoglycan mediators are involved in insulin action. After insulin binds to its receptor, these mediators are generated at the cell membrane and affect intracellular metabolic processes (63). Some PCOS patients may have a deficiency of one inositol phosphoglycan, D-chiro-inositol, leading to insulin resistance. Treatment of obese PCOS women with D-chiro-inositol led to improvement of insulin sensitivity, decline in circulating free testosterone levels, and an increase in circulating SHBG levels in one study. These effects were accompanied by a significant increase in the rates of ovulation (63).

Studies of *anti-androgenic agents* have shown improvement in the reduction of hyperandrogenism usually, although not always, without significant impact on insulin resistance. In one study, patients treated with flutamide exhibited a significant improvement in hirsutism and a reduction of circulating androgen levels but no change in insulin sensitivity (64). In another study treatment with anti-androgens (flutamide, spironolactone, or buserelin) reduced circulating androgen levels and led to greater improvement in insulin sensitivity in lean than in obese PCOS patients (65).

Oral contraceptive agents are used for treatment of patients with PCOS. They produce mild improvement in both insulin sensitivity (66) and hyperandrogenism in obese PCOS patients (67).

In summary, obese women with PCOS exhibit insulin resistance, hyperandrogenism, and menstrual irregularities. Improvement in insulin sensitivity, achieved by a variety of approaches, is the common pathway that results in the reduction of circulating androgen levels and normalization of the menstrual and ovulatory function. Studies on the new thiazolidinediones need to be carried out to confirm beneficial effects of troglitazone, which has been removed from the market because of liver toxicity. Anti-androgens and oral contraceptive agents improve the hyperandrogenism but have no consistent effects on insulin sensitivity.

Conclusions

Because both obesity and PCOS are common polygenic syndromes, the two alternative answers, proposed in the title of this article to the question posed by the title, are probably both incorrect, or at

least oversimplified, Obesity and polycystic ovary syndrome probably represent not one, not two, but *many* disease states, each characterized by its own combination of genes involved in the development of the disease and its own set of clinical manifestations. Until the details of the pathogenesis of these distinct states are better understood, it is safe to conclude that presence of obesity has a significant impact on some, but not all, manifestations of PCOS. Obesity increases androgen production, aromatase activity and insulin resistance, leading to more significant degrees of hirsutism, acne and hyperestrogenemia, also increasing the prevalence of infertility and irregular menstrual bleeding, glucose intolerance and diabetes mellitus. However, the prevalence of hypertension, dyslipidemia, gestational diabetes, and preeclampsia in patients with PCOS does not appear to be significantly impacted by the presence of obesity. The pathogenetic mechanism that mediates contributions of obesity to the clinical picture of PCOS appears to involve insulin resistance and hyperinsulinemia, the magnitude of which is greater in obese than in non-obese PCOS women. Therapeutic approaches that focus on the reduction of insulin resistance are beneficial in patients with PCOS.

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