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The Relationship Between PCOS and Obesity: Which Comes First?

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Introduction

Polycystic ovary syndrome (PCOS) is a common metabolic and endocrine disorder effecting 15- 20% of women of reproductive age. Its clinical features include obesity, **hirsutism**, acne, infertility, and **oligomenorrhea**. **Check Rotterdam Criteria on Page 3**. PCOS is also attributed to several hormonal and metabolic disturbances, including increased **androgen** production and disordered **gonadotropin** secretion leading to menstrual irregularity, hirsutism, and infertility. The origin of PCOS remains unclear, but research has shown that one of the characteristics of this disorder is the excess production of androgens in the ovaries (Alanbay et al. 2012). **Androgen** secretion is the result of abnormal response of the ovary to **gonadotropins**, insulin and insulin-like hormones such as insulin-like growth factor-1 (IGF-1), which enhances LH-stimulated androgen secretion by **theca cells**. Although the condition is not life threatening, the lack of treatment could lead to more serious health issues in the future, such as increased risk of infertility, dysfunctional bleeding, endometrial carcinoma, obesity, type 2 diabetes mellitus, dyslipidemia, hypertension, and increased risk for CVDs (Raisbeck 2009).

Among the risk factors associated with PCOS, overweight (body mass index (BMI) 25–29.9 kg/m2) and obesity (BMI ≥30 kg/m2) have been considered as major contributing factor to overall health concerns among women worldwide. Obesity has also been a determined as a contributing factor to reproductive health problems such as **anovulation**. As body weight increases, incidence of anovulation also increases significantly. Another contributor to reproductive dysfunction is the accumulation of abdominal fat, indicating a higher risk associated with insulin resistance (IR). IR in obese women has been associated with anovulation and increased androgen secretion (Kuchenbecker et al. 2011). Several studies relate obesity as a risk factor of PCOS (Reinehr et al. 2005; Soydinc et al. 2013). Some studies report that overweight and obesity incidence in females with PCOS is as high as 80%.The mechanisms by which obesity influences PCOS ‘ pathophysiology and clinical expression are not fully understood, but obesity is independently associated with IR (Rojas et al. 2014) and sex steroid imbalances that may lead to an increased risk of menstrual irregularities and hyperandrogenemia, similar to PCOS symptoms (Pasquali and Gambineri 2006). On the other hand, others proposed that regardless of physical condition, PCOS could occur. PCOS may develop in women with a BMI in any range including both underweight and overweight women. (McEwen and Hartmann 2018). Considering the close association between PCOS and obesity, the question remains **whether PCOS causes obesity or does obesity cause metabolic changes that lead to PCOS**?

Metabolic Factors

One of the main contributors to PCOS is insulin resistance (IR). Insulin is an important hormone produced by beta cells in the pancreas. It is responsible for the metabolism of glucose reduction of blood glucose levels by stimulating the glucose intake in insulin-sensitive tissue such as those found in the skeletal muscles. IR is common and an early predictor of metabolic diseases. Several studies investigated IR among women diagnosed with PCOS regardless of BMI. A total of 64 women with PCOS and 20 healthy subjects were evaluated using anthropometry, oral glucose tolerance tests, and insulin tolerance tests. Results revealed that β-cell function is elevated in both lean and obese women with PCOS. The authors suggested that insulin hypersecretion may be an important mechanism in the pathogenesis of PCOS.

If the sensitivity of insulin varies, the secretion of insulin also changes. Obese and lean females with PCOS have lower production of insulin sensitivity compared to the amount of insulin secreted in response to blood glucose levels than weight-matched healthy women (Dunaif 1999). IR and hyperinsulinemia are exacerbated in obese individuals. The accumulation of excess intra-abdominal fat increases IR because of its sensitivity to lipolysis and releases more free fatty acids in the circulation and produces several cytokines (i.e. tumor necrosis factor-α [TNF-α], IL-6, leptin, resistin) that occur in IR (Carpentier 2008). In obesity, IR is also related to TNF-α that inhibits insulin receptor signaling (Hotamisligil et al. 1996). Furthermore, 2008). The mechanisms causing insulin resistance in PCOS have many similarities with those seen in relation to visceral adiposity (Kabir et al. 2005). Excess free fatty acids derived from lipolysis/ hydrolysis of acylglycerol in adipocytes accumulate in the hepatic portal veins, and this induces hepatic dysfunction. This condition contributes to elevated glucose secretion, stimulates pancreatic insulin secretion and glucose uptake in adipose tissue (Bergman et al. 2000). This specific insulin resistance, also known as hepatic insulin resistance, is only present in obese women with PCOS and not in healthy women of comparable body weight (Dunaif 1999). The results of these studies demonstrate only a correlational relationship rather than a causal one between obesity and PCOS on glucose production.

A study confirms the strong association between metabolic aberrations such as IR and PCOS. IR is clearly manifested among women with weight gain and who are genetically predisposed to develop PCOS. Conversely, weight reduction of women with PCOS reduces the negative impact of PCOS. Mechanisms attributed to the development of IR in PCOS have been established in previous studies. For example, the relationship between visceral adipose tissue and IR has been proven in other studies. This condition alone cannot completely explain the occurrence of IR in PCOS, however, fat distribution in women suggests an explanation as to why IR worsens as women with PCOS gain weight (Barber et al. 2016).

Obesity and PCOS

Although it is true that obesity is a risk factor, the disease has also been diagnosed in lean females, although reproductive issues are generally discovered more frequently in obese females, regardless of PCOS. The risk of anovulatory infertility rises by 24 kg / m2 at BMI and continues to increase as BMI rises. But even a slight proportion of decrease in body fat can restore these women's menstrual cycles. To understand which comes first, obesity or PCOS, studies have investigated this relationship in girls and adolescents. It was noted that girls with a high BMI in childhood had an increased risk of **oligomenorrhea** and a diagnosis of PCOS in young adulthood (age 24), yet the possibility that features of PCOS were already present in these girls cannot be excluded. The researchers investigated if PCOS (or its features) in adolescents is predictive of later class III obesity. PCOS was diagnosed using the Rotterdam criteria in 12 (40%) of 30 oligomenorrheic girls at age 14 years. Of these girls, 33% displayed class III obesity by 24 years of age versus 8.4% of girls without PCOS. Other predictors of class III obesity included **low sex hormone binding globulin (SHBG),** oligomenorrhea, high childhood insulin levels, increased MetS, all of which are recognized as PCOS phenotypes (Glueck et al. 2011). Meanwhile, others conducted a prospective study on 244 randomly selected **postmenarchal** girls from a large population-based birth cohort to investigate the influence of obesity on the development of abnormal ovarian morphology. They found PCOS in 61.1% of the obese girls, but only in 32.1% of the normal- weight girls, suggesting that obesity is a contributing factor (Hickey et al. 2011). These studies illustrate that obesity and PCOS are correlative in their pathogenesis.

Obese females with PCOS were discovered to be at greater danger of developing oligomenorrhea, hyperandrogenemia, insulin resistance, hypercholesterolemia, hypertriglyceridemia, and high serum CRP concentrations than nonobese females. Among obese females with PCOS, metabolic problems were more probable to happen than their healthy counterparts (Baldani et al. 2013). Especially in females with upper-body obesity, the discovery of enhanced androgen production in obese females was revealed. Obesity-related hyperinsulinemia is a significant contributor to ovarian production of androgens in PCOS. By directly stimulating steroidogenesis in ovarian theca and granulosa cells, hyperinsulinemia may lead to hyperandrogenemia. Similar studies have been done on mice and have shown that liver and muscle cells display insulin resistance during constant hyperinsulinemia, while insulin receptors remain sensitive in pituitary and ovarian cells, an adaptation that improves the secretion of pituitary hormones and ovarian androgen production (Nestler, et al 1991).

A systematic and meta-analytical review on existing literature was conducted to determine the prevalence of obesity among women diagnosed with PCOS. Moreover, the researchers intended to determine whether ethnicity, geographic regions, and the diagnostic criteria of PCOS had confounding effects on this relationship. They found that compared to non-obese women, obese women with PCOS were more likely to have poor clinical reproductive presentation. Evidence also suggested that PCOS contributed to obesity. Increased androgen levels in women regardless of PCOS status were found to affect the appetite for high-fat and carbohydrate rich foods. However, other metabolic factors such as hyperinsulinemia, reduced postprandial thermogenesis, and basal metabolic rate and alterations contributed to weight gain in women with PCOS. However, the question remains whether PCOS contributed to obesity or vice versa. Some studies showed that women with PCOS had a greater tendency to accumulate fat in the upper body. This effect had also been found even in normal weight women. Overall, it was concluded that women with PCOS were more likely to be overweight or obese compared to healthy counterparts.

Conclusion

Most of the research in this review has not been able to determine conclusively whether PCOS contributed to obesity or vice versa. However, PCOS could be predicted by obesity as a significant factor. Overweight or obese females were at a higher risk of PCOS than ordinary weight females, but the weight problem does not exclude ordinary weight females from getting PCOS and its problems. Both lean and obese women with PCOS had elevated β-cell function regardless of BMI. Aside from body weight, insulin hypersecretion could be an important mechanism in the pathogenesis of PCOS. Early screening of insulin action in women with PCOS regardless of BMI could prevent serious metabolic complications

Rotterdam Criteria for the Diagnosis

PCOS may be diagnosed if any two of the following are present: (1) clinical or biochemical hyperandrogenism, (2) evidence of oligo-anovulation, (3) polycystic appearing-ovarian morphology on ultrasound, with exclusion of other relevant disorders.

Features of the diagnosis of PCOS.

Feature	Recommended Diagnosis	Considerations
Biochemical Hyperandrogenism	• Elevated total or free testosterone, or calculated indices of free testosterone (FAI, BioT). • DHEAS and ANSD can be consdered	• High-quality assays should be used for the evaluation of analytes
Clinical Hyperandrogenism	• A modified Ferriman–Gallwey score of ≥4 to ≥8	• Threshold level should be considered in the context of patient ethnicity
Oligo-anovulation	• Oligo-amenorrhea (cycles >35 days apart or <8 menses a year)	• If highly suspicious for PCOS, but does not have oligo-amenorrhea, consider serum progesterone or luteinizing hormone assessment
Polycystic ovarian morphology	• ≥20 follicles per ovary in either ovary • ≥10 cm^3 ovarian volume	• Based on transvaginal ultrasonography with a transducer frequency ≥ 8 MHz

- Hirsutism: Excessive hair growth in women in areas typically associated with male hair patterns.
- Oligomenorrhea: Infrequent menstrual periods, typically cycles occurring more than 35 days apart.
- Gonadotropins: Hormones (LH and FSH) that stimulate the gonads (ovaries in women, testes in men) to produce sex hormones.
- Anovulation: The absence of ovulation, where an egg is not released from the ovary during the menstrual cycle.
- Androgen: Male hormones like testosterone influencing traits like hair growth and reproductive functions.
- Lipotoxicity: The harmful effects of excess fat accumulation in tissues not typically involved in fat storage.
- Theca Cells: Cells in the ovaries that produce androgens, which are converted into estrogen by granulosa cells.
- Postmenarchal: Refers to the period after a girl's first menstruation (menarche).

Question 2: Choose the BEST answer (7 marks)

1. Obesity influences PCOS pathophysiology by
A) Causing hyperthyroidism
B) Exacerbating IR and sex steroid imbalances
C) Reducing androgen levels
D) Promoting increased estrogen secretion

2. How does hyperinsulinemia exacerbate hyperandrogenemia in PCOS?
A) Stimulating steroidogenesis in ovarian theca cells
B) Increasing SHBG secretion
C) Suppressing LH production
D) Reducing androgen receptor sensitivity

3. What do studies suggest about the relationship between PCOS and obesity?
A) PCOS only occurs in obese women
B) Obesity always precedes PCOS
C) The relationship between PCOS and obesity is correlative, not causal
D) Lean women with PCOS do not exhibit metabolic issues

4. Which of the following mechanisms is responsible for increased androgen production?
A. Excessive secretion of prolactin
B. Abnormal response of ovaries to gonadotropins and insulin-like hormones
C. Decreased production of estrogen
D. Insufficient LH stimulation of theca cells

5. Insulin in obese women with PCOS from that in healthy women of comparable weight is
A. Increased hepatic IR in obese women with PCOS
B. Lower fasting insulin levels in women with PCOS
C. Reduced β-cell function in women with PCOS
D. Enhanced glucose uptake in adipose tissue of women with PCOS

6. Which of the following factors is strongly correlated with class III obesity in young adulthood among girls with PCOS?
A. Elevated SHBG levels
B. Reduced fasting insulin levels
C. Features of metabolic syndrome
D. High serum CRP concentrations

7. What does the observed insulin sensitivity in ovarian and pituitary cells during chronic hyperinsulinemia suggest?
A. Insulin resistance in these cells leads to decreased androgen production.
B. Hyperinsulinemia enhances ovarian androgen production despite systemic insulin resistance.
C. Ovarian cells become resistant to insulin under hyperinsulinemic conditions.
D. Insulin directly suppresses androgen production in ovarian theca cells.