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An Up-to-Date Review on Link Between Polycystic ovary Syndrome and Insulin Resistence

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ABSTRACT:
Polycystic ovarian syndrome (PCOS) is a highly inherited complex polygenic, multifactorial disorder commonly exhibits hyperandrogenism, ovulatory dysfunction and is associated with obesity, insulin resistance, and subfertility. Overall, insulin resistance and the compensatory hyperinsulinemia affects some 65–70% of women with PCOS.Conventional treatment recommendations for the insulin resistance aspect of PCOS include weight loss, aerobic exercise, and the diabetic drug metformin, which improves insulin sensitivity. The Present article highlights how PCOS increases the risk of Diabetes.

Keywords: Polycystic ovary syndrome, Hyperinsulinemia,Insulin resistance

INTRODUCTION:

Polycystic ovary syndrome, or polycystic ovarian syndrome (PCOS), is a highly prevalent disorder, representing the single most common endocrine–metabolic disorder in women of reproductive age, affecting 6%-15% of the of the global population. [1]Women with PCOS may experience irregular menstrual periods, heavy periods, excess hair, acne, pelvic pain, difficulty getting pregnant, and patches of thick, darker, velvety skin. PCOS affects women of premenopausal age and is characterized by hyperandrogenic features (e.g., hirsutism, acne and alopecia) that result from hyperandrogenemia, and menstrual disturbance including subfertility.

PCOS is a heterogeneous disorder of uncertain cause. There is some evidence that it is a genetic disease. Such evidence includes the familial clustering of cases, greater concordance in monozygotic compared with dizygotic twins and heritability of endocrine and metabolic features of PCOS. There is some evidence that exposure to higher than typical levels of androgens and the anti-Müllerian hormone (AMH) in utero increases the risk of developing PCOS in later life. It may be caused by a combination of environmental pollutants, diet and lifestyle choices, genetic factors, obesity, and gut dysbiosis. [2]

RISK FACTORS:

Risk factors include obesity, a lack of physical exercise, and a family history of someone with the condition. Familial and genetic factors cause predisposition to PCOS. Risk factors for PCOS in adults includes type 1 diabetes, type 2 diabetes, and gestational diabetes. Insulin resistance and adiposity affects 50%–70% of women with PCOS leading to a number of comorbidities including metabolic syndrome, hypertension, dyslipidemia, glucose intolerance, diabetes and cardiovascular diseases. Women with PCOS are at increased risk hepatic steatosis and metabolic syndrome; hypertension, dyslipidemia, vascular thrombosis, cerebrovascular accidents, and possibly cardiovascular events; subfertility and obstetric complications; endometrial atypia or carcinoma, and possibly ovarian malignancy; and mood and psychosexual disorders. [3]

DIAGNOSIS:

The diagnosis of polycystic ovary syndrome (PCOS) is primarily achieved through clinical history and physical findings. The principle features are hirsutism or biochemical evidence of excess androgen production and irregular menstrual bleeding caused by the chronic anovulation. Associated findings

include insulin resistance with compensatory hyperinsulinemia and obesity. Ultrasound imaging of the ovary has facilitated the diagnosis. It is important to exclude conditions that may mimic PCOS, such as hyperthecosis, congenital adrenal hyperplasia, 21-hydroxylase deficiency, Cushing's syndrome, and androgen-producing neoplasms. These disorders are usually revealed by appropriate laboratory assessment. Screening tests include measurement of serum total testosterone, DHEA sulfate, and 17-hydroxyprogesterone. In addition, in the obese individual, determinations of glucose and insulin levels, as well as a lipid profile, are highly recommended.[4]

PATHOPHYSIOLOGY:

The pathophysiology of PCOS is heterogeneous and shaped by the interaction of reproductive dysfunction and metabolic disorders. Hyperandrogenism and insulin resistance exacerbate one another during the development of PCOS, which is also affected by dysfunction of the hypothalamus□pituitary□ovarian axis. PCOS is a highly heritable disorder, and exposure to certain environmental factors causes individuals with predisposing genetic factors to develop PCOS. The environmental factors that drive the development of PCOS pathophysiology make a larger contribution than the genetic factors, and may include the intrauterine environment during the prenatal period, the follicular microenvironment, and lifestyle after birth. Polycystic ovaries develop when the ovaries are stimulated to produce excessive amounts of androgenic hormones, in particular testosterone, by either one or a combination of the following (almost certainly combined with genetic susceptibility) the release of excessive luteinizing hormone (LH) by the anterior pituitary gland and/or through high levels of insulin in the blood (hyperinsulinaemia) in women whose ovaries are sensitive to this stimulus. A majority of women with PCOS have insulin resistance and/or are obese, which is a strong risk factor for insulin resistance, although insulin resistance is a common finding among women with PCOS in normal-weight women as well. Elevated insulin levels contribute to or cause the abnormalities seen in the hypothalamic–pituitary–ovarian axis that led to PCOS. Hyperinsulinemia increases GnRH pulse frequency, which in turn results in an increase in the LH/FSH ratio increased ovarian androgen production; decreased follicular maturation; and decreased SHBG binding. Furthermore, excessive insulin increases the activity of 17α-hydroxylase, which catalyzes the conversion of progesterone to androstenedione, which is in turn converted to testosterone. The combined effects of hyperinsulinemia contribute to an increased risk of PCOS. Adipose tissue possesses aromatase, an enzyme that converts androstenedione to estrone and testosterone to estradiol. The excess of adipose tissue in obese women creates the paradox of having both excess androgens (which are responsible for hirsutism and virilization) and excess estrogens (which inhibit FSH via negative feedback). The syndrome acquired its most widely used name due to the common sign on ultrasound examination of multiple (poly) ovarian cysts. These "cysts" are in fact immature ovarian follicles. The follicles have developed from primordial follicles, but this development has stopped ("arrested") at an early stage, due to the disturbed ovarian function. The follicles may be oriented along the ovarian periphery, appearing as a 'string of pearls' on ultrasound examination. PCOS may be associated with chronic inflammation, with several investigators correlating inflammatory mediators with anovulation and other PCOS symptoms. Similarly, there seems to be a relation between PCOS and an increased level of oxidative stress.[5]

LINK BETWEEN POLYCYSTIC OVARY SYNDROME AND TYPE 2 DIABETES MELLITUS:

Polycystic ovary syndrome (PCOS) is most often defined according to the Rotterdam criteria, which include irregular ovulation, biochemical/clinical hyperandrogenism, and/or polycystic ovaries when other etiologies are excluded. Insulin resistance is part of the pathogenesis of PCOS and insulin resistance is associated with increased risk of type 2 diabetes (T2D) in PCOS. Insulin resistance is closely associated with obesity [6]. Insulin resistance is amplified by obesity. Inherent insulin resistance in PCOS is attributed to inappropriate reaction to insulin in metabolically active marginal tissues including adipose tissue and skeletal muscle. Obese females with PCOS are more susceptible to insulin resistance, which might lead to abnormal glucose and lipid catabolism. Moreover, increasing insulin lowers the circulating

amount of sex hormone-binding globulin (SHBG) and promotes free androgens, which constrains follicle formation resulting in irregular menses and impotency. PCOS females had a significantly larger intake of a diet heavy in sugar. Different adipokines are discharged from the fatty tissues, which have varying effects on insulin resistance. Some, such as visfatin, may stimulate the insulin receptor and have insulin-like activity, although adiponectin has an insulin-sensitizing effect. Adiponectin, released by the adipocyte, is a rich protein that occurs as multimers. It encompasses high, low, and middle molecular weights. Though studies showed the association between adiponectin and PCOS sovereign of BMI, others demonstrated that adiponectin levels were harmfully associated with BMI. These adipokines may be measured as markers of insulin resistance in PCOS patients regardless of BMI. The consumption of total fats, saturated fatty acids, and cholesterol should be reduced for easing the growth of diabetes and heart disorders. They impact the dysfunction of the ovaries. Excessive insulin invention may activate insulin receptors of the pituitary gland to issue luteinizing hormone and worsen the excretion of androgen by the ovary and glands. It may restrict the formation of hepatic SHBG and boosts the levels of free testosterone. Excessive androgen excretion may lead to acne and alopecia signs and may impede the development of ovarian follicles [7]. The association of weight loss and use of insulin-sensitizing drugs with improvements in phenotypic features of PCOS support the hypothesis that insulin resistance plays an important role in the development of PCOS. It would therefore seem clear that PCOS and T2D are linked pathogenically by insulin resistance, which in turn is influenced by obesity. [8]

The hyperinsulinemia appears to be an important factor in maintaining hyperandrogenemia, acting directly to induce excess androgen production by theca cells and also as a co-gonadotropin, augmenting the effect of the increased LH stimulus seen in a majority of women with PCOS. The elevated insulin may exert other actions having been implicated in the central actions of androgen in impairing progesterone inhibition of the GnRH pulse generator. In vitro, insulin increased mRNAs for adrenal steroidogenic enzymes and acutely enhanced adrenal secretory responses to ACTH. [9]

MANAGEMENT OF PCOS:

PCOS has no cure. Treatment may involve Specifically, adoption of a healthy lifestyle with adherence to improved dietary patterns, such the Mediterranean diet, avoidance of consumption of endocrine-disrupting foods and beverages and regular exercise. Recent research suggests that daily exercise including both aerobic and strength activities can improve hormone imbalances. Goals of treatments that need to be considered include Lowering of insulin resistance, Reducing Androgen and Testosterone levels, Restoration of fertility, Treatment of hirsutism or acne and Restoration of regular menstruation, and prevention of endometrial hyperplasia and endometrial cancer. [10]

Where PCOS is associated with overweight or obesity, successful weight loss is the most effective method of restoring normal ovulation/menstruation. Insulin resistance itself can cause increased food cravings and lower energy levels, which can make it difficult to lose weight on a regular weight-loss diet. Still, a low GI diet, in which a significant portion of total carbohydrates is obtained from fruit, vegetables, and whole-grain sources, has resulted in greater menstrual regularity than a macronutrient-matched healthy diet.Reducing intake of food groups that cause inflammation, such as dairy, sugars and simple carbohydrates, can be beneficial. A mediterranean diet is often very effective due to its anti-inflammatory and anti-oxidative properties.Vitamin D deficiency may play some role in the development of the metabolic syndrome, and treatment of any such deficiency is indicated.

Medications for PCOS include oral contraceptives and metformin. The oral contraceptives increase sex hormone binding globulin production, which increases binding of free testosterone. This reduces the symptoms of hirsutism caused by high testosterone and regulates return to normal menstrual periods. The treatment of PCOS patients with insulin sensitizers, such as metformin or thiazolidinediones, increases the ovulation rate and the number of successful pregnancies. The positive action of the insulin-sensitizing treatments could be explained by a decrease in the peripheral insulin resistance but also by a direct action at the ovarian level. [11]

CONCLUSION:

Polycystic ovary syndrome (PCOS) is a heterogeneous condition with a range of clinical, endocrine and metabolic manifestations. Because the aetiology of PCOS is still unclear, it is necessary to develop a management orientated approach to the condition, depending upon the individual patient's needs.The treatment of PCOS patients with insulin sensitizers, such as metformin or thiazolidinediones, increases the ovulation rate and the number of successful pregnancies.

Reference:

1. Conway G, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Franks S, Gambineri A, Kelestimur F, Macut D, Micic D, Pasquali R, Pfeifer M, Pignatelli D, Pugeat M, Yildiz BO ESE PCOS Special Interest Group. The polycystic ovary syndrome: a position statement from the European Society of Endocrinology. Eur J Endocrinol. 2014;171:P1–29.
2. Singh, S., Pal, N., Shubham, S., Sarma, D. K., Verma, V., Marotta, F., & Kumar, M. (2023). Polycystic Ovary Syndrome: Etiology, Current Management, and Future Therapeutics. *Journal of clinical medicine*, *12*(4), 1454.
3. Khan, K. A., Stas, S., & Kurukulasuriya, L. R. (2006). Polycystic ovarian syndrome. Journal of the cardiometabolic syndrome, 1(2), 125–132.
4. Chang, R. J. (2004). A practical approach to the diagnosis of polycystic ovary syndrome. American Journal of Obstetrics and Gynecology, 191(3), 713–717.
5. Harada M. (2022). Pathophysiology of polycystic ovary syndrome revisited: Current understanding and perspectives regarding future research. *Reproductive medicine and biology*, *21*(1), e12487.
6. Ndefo, U. A., Eaton, A., & Green, M. R. (2013). Polycystic ovary syndrome: a review of treatment options with a focus on pharmacological approaches. *P & T : a peer-reviewed journal for formulary management*, *38*(6), 336–355.
7. Purwar, A., & Nagpure, S. (2022). Insulin Resistance in Polycystic Ovarian Syndrome. *Cureus*, *14*(10), e30351.
8. Barber TM, McCarthy MI, Wass JA, Franks S. Obesity and polycystic ovary syndrome. *Clin. Endocrinol. (Oxford)* 65(2), 137–145 (2006).
9. Marshall, J. C., &Dunaif, A. (2012). Should all women with PCOS be treated for insulin resistance?. *Fertility and sterility*, *97*(1), 18–22.
10. Akre, S., Sharma, K., Chakole, S., & Wanjari, M. B. (2022). Recent Advances in the Management of Polycystic Ovary Syndrome: A Review Article. *Cureus*, *14*(8), e27689.
11. Froment, P., & Touraine, P. (2006). Thiazolidinediones and Fertility in Polycystic Ovary Syndrome (PCOS). *PPAR research*, *2006*, 73986.

