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Risk of Type 2 Diabetes Mellitus in Polycystic Ovarian Syndrome[1]

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ABSTRACT

One of the most prevalent endocrine illnesses in women of reproductive age is polycystic ovary syndrome. 6% to 15% of the population are impacted. It is a multifactorial condition .Insulin resistance is a critical component that is important in the pathophysiology of the syndrome and is the main factor connected to the onset of type 2 diabetes mellitus in women with polycystic ovary syndrome, but it is not always a trait present in individuals with the condition. Between 44% and 70% of women with polycystic ovarian syndrome have insulin resistance. The objective of this study is to assess the risk of type 2 diabetes mellitus in individuals with polycystic ovarian syndrome and how the condition is managed.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is an endocrine disorder affecting women of reproductive age. PCOS is a multifactorial disorder characterized by anovulation, hyperandrogenism (a clinical feature), a rise in androgen and luteinizing hormone (LH) concentrations (a biochemical feature), and polycystic ovaries (morphological features)[1, 2]. It affects about 6–15% of the population[3]. PCOS represents a challenge to doctors because of the continuous need for adjustments and modifications to the treatment according to the patient's condition and desires throughout her life[3,4].

In PCOS, there is an increased frequency of gonadotropin-releasing hormone (GnRH) secretion and a high ratio of luteinizing hormone to follicle stimulating hormone (FSH), which are considered the primary causes of PCOS[5], though the exact pathology and etiology have not been well identified. PCOS rises the risk of developing serious complications, including cardiac diseases[5,6], metabolic syndrome, type 2 diabetes mellitus[7], depression, and anxiety[8].

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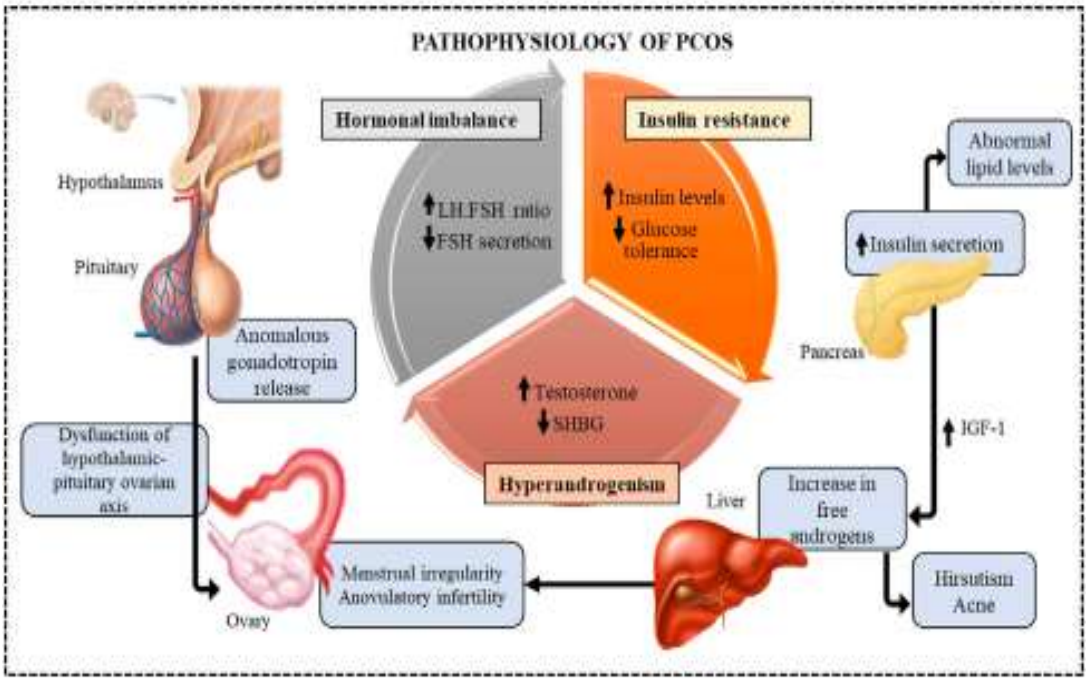

Figure 1. Schematic depiction of PCOS linked mechanism [9].

METHOD OF DIAGNOSIS

There is no specific test for the diagnosis of PCOS. The diagnosis is based on excluding the other disorders that are related to it in symptoms and reducing the choices. So we should exclude cushing's syndrome, hyperprolactinemia, thyroid diseases, and adrenal gland hyperplasia according to the related investigations[10,11]. The most commonly recommended investigations included measuring the level of related hormones, pelvic examination, and transvaginal ultrasound. Also, previous medical history, changes in weight, and insulin resistance symptoms could be supportive of the diagnosis[12].

According to the Rotterdam criteria (2003), polycystic ovarian syndrome is diagnosed when two out of three of the clinical characteristics (hyperandrogenism, disruption of ovulation, and polycystic ovaries) are present[1].

Numerous attempts to categorize PCOS were made. Lastly, the National Institute of Health (NIH) agreed in 2012 to classify PCOS into four phenotypes. "Phenotype A" includes patients with hyperandrogenism, dysfunction of ovulation, and polycystic ovary, whereas "phenotype B "includes patients with only hyperandrogenism and dysfunction of ovulation. "Phenotype A" and "Phenotype B" were called classic PCOS. "Phenotype C" included patients with hyperandrogenism and polycystic ovaries; it was termed ovulatory PCOS. Last of all, "Phenotype D" was called as non-hyperandrogenic PCOS, and it comprised patients with polycystic ovary and dysfunction of ovulation[13].

From all phenotypes, the classic PCOS have a higher body mass index (BMI), rate of obesity, insulin levels, and insulin resistance (IR). While ovulatory PCOS (phenotype C) has slighter clinical and endocrine changes. Likewise, non-hyperandrogenic (phenotype D) PCOS has a lower ratio of LH / FSH and a higher Sex Hormone Binding Globulin (SHBG) as compared to classic PCOS[14].

INSULIN RESISTANCE IN POLYCYSTIC OVARIAN SYSTEMS

Insulin resistance is an insufficient cell response to insulin[15]. It is a condition in which the pancreatic beta cells must release a higher amount of insulin to maintain a normal glucose level in the blood due to disruption in the binding of insulin to its receptors or ineffective activation of these receptors [16]. Such persistent pancreatic stress causes poor glucose homeostasis, which first shows up as impaired fasting glycemia (IFG) or impaired glucose tolerance (IGT), but once a substantial number of islets become stressed, it causes type 2 diabetes mellitus[17]. IR is the primary element related to the onset of type 2 diabetes mellitus in PCOS. Between 44% - 70% of PCOS patients are reported to have IR[18].

In women with PCOS, IR is tissue selective[19]. Even though the adipose tissue, skeletal muscles, and liver lose their sensitivity toward insulin, the sensitivity of ovaries and adrenal glands persists[20,21].

Conversely, obese PCOS have significantly less sensitivity to insulin as compared to non-obese PCOS. Both obese and non-obese PCOS patients had greater incidences of insulin resistance and hyperinsulinemia than age-matched women. It is definite that insulin resistance precedes type 2 diabetes mellitus development. Studies have shown that between 30 and 40% of PCOS women have impaired glucose tolerance, and 10 percent of PCOS women develop type 2 diabetes by the age of 40[22,23].

According to studies, IR is the primary contributor to obesity because it results in hyperinsulinemia, which stimulates the production of steroid hormones by the ovary and adipose tissue. This lowers the hepatic secretion of (SHBG), which raises free androgen levels. If these levels are elevated chronically, this can result in central obesity through the accumulation of visceral fat, which aggravates PCOS symptoms[24,25]. Acanthosis nigricans, the sole clinical symptom of IR, is associated with both obese and lean patients [26].

RISK OF TYPE 2 DIABETES MELLITUS IN POLYCYSTIC OVARIAN SYSTEMS

Prediabetes, the precursor to type 2 diabetes, and type 2 diabetes are four to seven times more likely to occur in women with PCOS than in healthy women[23]. In women of reproductive age, the prevalence of type 2 diabetes mellitus ranges from 1% to 3%[24], but it ranges from 1.5 to 12.4% in PCOS women[27].

It has been proposed that a number of variables have a causative role in the occurrence of prediabetes and type 2 diabetes in PCOS-affected women. Traditional risk factors including genetic, obesity, and family history of PCOS and diabetes[28].

Given that PCOS women frequently have IR and ß cell dysfunction, two prerequisites for type 2 diabetes development, the onset of type 2 diabetes in PCOS may be partially predicted. The majority of women with PCOS have been reported to have significant levels of IR compared to their normal BMI counterparts. Obesity should also be taken into account as it might have an additional impact on the degree of IR seen in these women [29]. These individuals show a significantly greater frequency of pancreatic ß-cell dysfunction than their regularly ovulating, non-hyperandrogenic counterparts[30].

The development of prediabetes and type 2 diabetes is not only dependent on obesity, as it has been shown that even slender women with PCOS are at a significant risk of glucose abnormalities. But there is no doubt that being overweight is a serious extra risk factor[28].

In addition, luteinizing hormone pulsatility is enhanced in PCOS patients, which leads to a rise in ovarian and adrenal androgen production which together with IR lead to increase in the testosterone concentrations[31]. Higher levels of bioavailable testosterone also predicted the onset of type 2 diabetes, and there was a clear link between IR and testosterone[32]. The risk for type 2 diabetes was shown to be increased by around 42% in individuals with high free androgen titers[33].

It is still unclear, however, whether PCOS increases the risk of type 2 diabetes or if PCOS-affected women are more likely to be fat[34-36]. Having PCOS does not automatically result in type 2 diabetes; rather, it develops as a result of either an increase in adipose tissue or hyperandrogenemia, according to a recent meta-analysis of genetic data[37].

In the meanwhile, it is important to recognize the contribution of aging to the emergence of type 2 diabetes. In a logistic regression study, the interaction between age and BMI was the most important factor in predicting type 2 diabetes. Additionally, data compiled from multiple research have shown a positive correlation between age and BMI and type 2 diabetes or intermediate hyperglycemia in females with PCOS [38,39].

A cross sectional study revealed that increase the age could improve the IR in PCOS women. In particular, lean women with PCOS show gradual improvement in the IR with aging while obese women established the similar degree of IR over the years[40],this improvement could be as a result of the reduction in androgen production after the age of 40 in PCOS women so that no worsening in IR through the years. Actually, non-PCOS women's insulin sensitivity decreases with time, almost invariably leading to type 2 diabetes[41].

In contrast, a variety of IR values have been seen throughout time in women with PCOS, appearing there is improvement in thin women and deterioration in obese women only [42,43]. Therefore, non-linear development to type 2 diabetes is extremely common in PCOS, and this significantly relates to the level of obesity. Celik et al.

discovered that obese women with PCOS had a four-times greater likelihood of developing IGT than non-obese women[44]. The second discovery was made by Rubin et al., who discovered that PCOS patients who were slender had the same risk of type 2 diabetes as healthy women[45].

Dysfunction in the muscle mitochondrial[45] and the microbiome of gut are additional causes underlying the pathophysiology of prediabetes and type 2 diabetes in individuals with PCOS[46]; the existence of precise species of bacteria in the gut that are linked to reduced androgen levels supports the latter idea[47].

To reduce disease-related morbidity and death, the International Diabetes Federation encourages early detection, diagnosis, and treatment of type 2 diabetes mellitus[48]. One recommendation is to do an oral glucose tolerance test every two years for those with normal glucose tolerance and once a year for people with IGT. This is due to the fact that patients with abnormal glucose levels are more likely to develop type 2 diabetes [41]. Fasting insulin more than 20 mIU/mL may be a signal for IR. PCOS patients' glycemic status can be assessed using an oral glucose tolerance test (OGT)(cut-off value 11.1 mmol/l), fasting plasma glucose (FPG), or hemoglobin A1c (HbA1c)(higher than 6.5%) to diagnose diabetes[21].

MANAGEMENT OF TYPE 2 DIABETES MELLITUS IN PCOS

The mainstay of treatment for lowering the risk of type 2 diabetes in PCOS, particularly those who are overweight or obese, is lifestyle intervention, which includes food changes and exercising regularly [49]. Structured exercise programs are effective in the prevention and treatment of metabolic syndrome, obesity, type 2 diabetes, and cardiovascular disease (CVD)[50]. Lifestyle interventions have a significant positive effect on both reproductive consequences and glucose homeostasis in PCOS patients. These advantages are just as important as those attained by metformin[51].

In a meta-analysis research, that studied how different dietary components affected PCOS women's metabolic and reproductive outcomes, it was shown that monounsaturated fat diets caused more substantial weight reduction, and low glycemic index diets improved menstruation problems and decreased insulin resistance[52]. Physical activity usually complements dietary therapies in the treatment of PCOS[53].

One of the most widely used insulin-sensitizing medications is metformin ,it is used to manage type 2 diabetes[54]. It works by improving peripheral tissues' sensitivity to insulin, reducing hepatic glucose production, and enhancing glucose absorption[55]. Particularly in PCOS patients who are obese, higher metformin dosages have been demonstrated to be beneficial in reducing weight and improving lipid profiles[56].

Another medication is pioglitazone, which lowers blood sugar levels mainly by improving peripheral glucose uptake and controlling adipogenesis and insulin action. It improve ovulation, hyperandrogenism, and insulin resistance in PCOS women[57]. Despite pioglitazone's positive impact on PCOS's metabolic parameters, there is a lot of worry about the medication's propensity to cause congestive heart failure, cardiac damage, and pulmonary edema as a result of fluid retention[58].

Glucagon like peptide1(GLP-1) is an" incretin hormone "it acts by stimulating the production of glucose dependent insulin which known as the "incretin effect," mainly after meals[59]. Incretin action is impaired in insulin resistance disorders and type 2 diabetes, and a another study showed reduction in incretin hormone level in PCOS patients[60].So, targeting this system has therefore emerged as a useful therapeutic strategy for management of type 2 diabetes[61], resulting in weight loss and improved glycemic control in type 2 diabetic patients. GLP-1 agonists on the market include liraglutide, semaglutide, dulaglutide, and exenatide[62].

Gliptins are antihyperglycemic medications that are used after metformin as a second or third-line therapy for treating type 2 diabetes[63]. They act by inhibiting the dipeptidyl peptidase-4 enzyme (DPP-4) that degrades GLP-1 produced internally (64).

Sodium glucose cotransporter-2 inhibitors (SGLT-2) are also used to treat type 2 diabetes. Their mode of action includes inhibiting SGLT-2 in the proximal convoluted tubule of the kidney, which lowers glucose reabsorption and raises urine glucose excretion (65). They can also boost ß-cell activity, lessen oxidative damage and inflammation, improve calorie deposition, and aid in weight reduction through a variety of distinct biochemical mechanisms, all of which can promote insulin sensitivity.(66)

Myoinositol, a carbocyclic sugar called inositol is widely distributed in both plant and animal cells (67). In humans, it is mainly produced in both the kidney and liver, and it normally exists in meat, beans, grains, and corn (68). Both

type 1 and type 2 diabetes have been associated with abnormal inositol production and metabolism (69). Numerous diseases, including type 2 diabetes, gestational diabetes, and PCOS, have been treated using inositol as a dietary supplement (70).

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