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PCOS as A Metabolic Disease

Uduak Faith Yellow-Duke[1], Ghassan Salibi[2], Nikolaos Tzenios[3]

[1] Kursk State Medical. University

[123] Charisma University

Abstract

Background: Polycystic Ovary Syndrome (PCOS) is the most common endocrine disorder, affecting 6–20% of women of reproductive age. It has evolved from being perceived solely as a reproductive disorder to being recognized as a complex metabolic disease. Multiple factors contribute to its pathogenesis, including insulin resistance, hyperandrogenism, obesity, chronic low-grade inflammation, and genetic, epigenetic, and environmental influences. The interplay of these factors increases the risk of type 2 diabetes, cardiovascular disease, and other comorbidities, highlighting the metabolic nature of PCOS.

Methods and Materials: This study involved a comprehensive literature review of recent peer-reviewed articles, meta-analyses, and clinical guidelines related to the metabolic aspects of PCOS. Emphasis was placed on pathophysiological mechanisms such as insulin resistance, obesity, dyslipidemia, NAFLD, hypertension, and the role of endocrine disruptors and epigenetic modifications. Additionally, therapeutic approaches, including lifestyle modifications, pharmacological interventions, and surgical options, were evaluated to illustrate current management strategies for PCOS as a metabolic condition.

Results: The findings reinforce that insulin resistance is present in 50–70% of women with PCOS, often leading to compensatory hyperinsulinemia and elevated androgen levels. Obesity exacerbates these metabolic derangements and increases the risk of comorbidities like type 2 diabetes, cardiovascular diseases, and NAFLD. The review also highlights the impact of inflammation, dyslipidemia, and hypertension, which collectively contribute to the metabolic syndrome profile observed in PCOS patients. Evidence suggests that lifestyle interventions, anti-diabetic medications, hormonal therapies, and targeted supplements can significantly improve metabolic and reproductive outcomes.

Conclusion: PCOS should be approached as a metabolic disease due to its strong association with insulin resistance, obesity, and other metabolic complications. Recognizing this helps optimize prevention and management strategies, which should combine lifestyle interventions, pharmacological treatments, and patient education. An individualized, multidisciplinary approach can reduce long-term risks and improve the quality of life for women with PCOS.

Keywords: *PCOS, Insulin Resistance, Metabolic Syndrome, Hyperandrogenism, Obesity*

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Project Summary

1.1 Overview

The most common endocrine disorder, PCOS, affects 6–20% of women who are of reproductive age. Along with metabolic problems, this illness is often linked to several serious physical and psychological morbidities. PCOS has finally changed from being a reproductive condition to something else due to continuous advancements in medical research.

PCOS's possible pathophysiological factors.

Numerous factors, including elevated AMH levels, developmental limitations, endocrine disruptors like BPA, and androgen excess, may improve a PCOS-like phenotype in adults throughout development. The development of weight and affront resistance, as well as exposure to endocrine disruptors and androgen excess, are regarded as pathologic factors that contribute to PCOS during the perinatal period. Additionally, genetic and epigenetic factors may increase the risk of developing PCOS.

1.2 Targets

1. To illustrate PCOS's metabolic features.
2. To evaluate the affront resistance recommendations

PCOS's Metabolic Effects

Among women with PCOS, hyperinsulinemia due to insulin resistance may be a prevalent occurrence. Resistance is also present in 50–70% of women diagnosed with PCOS, which may reduce the body's ability to use glucose and raise the risk of developing type 2 diabetes complications.

Approximately 50 to 80 percent of women with unique PCOS phenotypes from various ethnic backgrounds have been shown to have insulin resistance. Additionally, many PCOS patients may have compensatory hyperinsulinism as a result of abnormalities in insulin receptors and decreased insulin affectability in skeletal muscle and adipose tissue.

The ovarian union of androgens triggered by hyperinsulinemia is the physiological interface between insulin resistance and the elevated androgen levels that characterize it.

A post-binding problem characterized by increased serine phosphorylation and decreased tyrosine phosphorylation may be the primary cause of insulin receptor breakdown, which results in insulin resistance (IR). This leads to decreased insulin enactment of the phosphatidylinositol-3-kinase (PI3k) signalling pathway, which promotes glucose transport. There have been recent developments about insulin resistance in polycystic ovarian disease (PCOS). Numerous analyses have shown the closeness of microRNA alterations in PCOS; however, the fundamental factor remains unclear. By suppressing the expression of insulin-like development calculate 1, Dong et al. have shown that the microRNA miR-122 may contribute to insulin resistance (IR), providing untapped information on the mechanism of IR in polycystic ovarian syndrome (PCOS).

Furthermore, Zhang et al. have recently discovered a link between autophagy and IR. They said intestinal microbiota disruption in PCOS is well known. That tall portability bunch box 1, a damage-associated atomic design particle, can lead to insulin resistance in granulosa cells by inhibiting autophagy. Electroacupuncture therapy eventually identified mitochondrial breakage, endoplasmic reticulum push (ER stretch), and oxidative strain as factors causing insulin resistance.

SHBG levels;

Due to the hepatic concealment of this protein's synthesis, which is triggered by hyperinsulinemia, the levels of SHBG (sex hormone official globulin) may fluctuate in BMI and insulin resistance.

For this reason, a SHBG is a noteworthy indicator of insulin resistance.

2.1.2 Obesity

The majority of women with PCOS are obese. In addition to decreasing insulin resistance and hyperandrogenism, it complicates the metabolic landscape.

When combined, they create a terrible cycle that may increase a person's chance of developing type 2 diabetes and cardiovascular infections. Metabolic disturbing factors also conclude that the sickness may manifest unexpectedly across bodyweight categories. Some theories suggest a variety of clinical pictures may be associated with

the abdominal weight of PCOS. For example, Adipocytes release non-physiological amounts of adipokines, such as retinol official protein-4 (RBP4), leptin, adiponectin, resistin, lipocalin 2, monocyte chemoattractant protein-1 (MCP1), IL6, IL8, TNF-α, and CXC-chemokine ligand 5 (CXCL5), as a result of the breakdown of fat tissue. These may be included in IR. Additionally, follicular development may be impacted by the breakdown of adipose tissue. A subsequent notion suggested that adipocyte-produced IL-10 interferes with folliculogenesis and changes VEGF-induced angiogenesis.

2.1.3 Inflammation

Information on PCOS is also very important. Physicians have documented elevated pro-inflammatory cytokine levels in inflammatory patients. Persistent low-grade Inflammation can alter the metabolic outcomes of this illness by decreasing insulin affectability.

2.1.4 Comorbidities

PCOS-related metabolic breakdown predisposes individuals to several comorbidities, including:

* Cardiovascular diseases, endometrial cancer, type 2 diabetes mellitus, rest apnea, and mental illnesses such as anxiety, sadness, bipolar disorder, and ADHD.

2.1.5 Excessive masculinity

One of the criteria used to diagnose PCOS is hyperandrogenism. There is no discernible difference in the etiology of PCOS between IR, obesity, and hyperandrogenism. IR causes hyperinsulinemia, which lowers the synthesis of sex hormone-binding protein (SHBG) and has a gonadotropin impact on the ovaries, triggering the onset of hyperandrogenism. Androgens can enhance the aggregation of fat tissue, particularly abdominal fat tissue, and induce IR in subcutaneous fat tissue.

A few studies have described other possible effects of hyperandrogenism-induced PCOS. For example, dihydrotestosterone (DHT) may cause mitochondrial separation in PCOS patients' granulosa cells, and an excess of androgens may cause ER stretch, which might degrade the quality of oocytes.

Dyslipidaemia in PCOS;

It has been reported that 70% of PCOS patients have dyslipidemia, with elevated levels of triglycerides (Tgs), free fatty acids, low-density lipoprotein cholesterol (LDL-c), and very-low-density lipoprotein cholesterol (VLDL-c) and decreased levels of high-density lipoprotein cholesterol (HDL-c).

Additionally, dyslipidemia was thought to have an impact on PCOS patients' long-term outcomes.

According to studies, women with PCOS had a more harmful lipid profile and were more likely to have non-fatal cerebrovascular illnesses in the future.

2.1.7 Nonalcoholic fatty liver disease (NAFLD)

Patients with minimal or very little alcohol usage may develop nonalcoholic fatty liver disease (NAFLD), a progressive, chronic condition marked by hepatic fat buildup that is histologically identical to alcoholic liver disease.

Several studies have confirmed that women with PCOS have a higher prevalence of NAFLD. Furthermore, it is widely accepted that improved hepatic steatosis in women with PCOS is a result of elevated testosterone levels. Hepatic steatosis in PCOS rats can be caused by elevated endogenous testosterone triggered by letrozole, as demonstrated by Li et al. in 2020. They also discovered that hyperandrogenism suppressed the AMP-activated protein kinase alpha (AMPKa) signalling, which controls the lipid digestion system, in livers treated with letrozole and HepG2 cells treated with dihydrotestosterone (DHT).

Environmental factors;

The pathophysiology of PCOS has also been connected to environmental variables. As was previously discussed, obesity is the most prevalent cause of insulin resistance, and both insulin resistance and the associated hyperinsulinemia are thought to be important factors in the development of PCOS. The pathogenesis of this endocrine disorder may thus entail all-natural factors that might cause weight gain or obesity and alter insulin action. The two main factors that will induce or exacerbate the metabolic and regenerative deviations from the norm of PCOS are diet and lifestyle. Poor eating habits and a sedentary lifestyle may be linked to insulin resistance, weight gain, and

Helps to exacerbate PCOS's metabolic and regenerative features. Supporting the role of these natural factors in the pathophysiology of PCOS, it has been observed that improving insulin affectability through lifestyle and calorie-count changes is sufficient to improve a few lists of regenerative symptoms in women with PCOS, including irregular menstrual cycles and anovulation.

Hypertension;

According to the American College of Cardiology (ACC)/American Heart Association (AHA), hypertension (HTN) is defined as systolic blood pressure (SBP) more than or equal to 130 mmHg and diastolic blood pressure greater than or equal to 80 mmHg. Using these criteria, PCOS patients were 24% more likely to have HTN than women in good health.

In PCOS individuals, hypertension is brought on by the renin-angiotensin system being stimulated. Previous research has shown that aldosterone levels are higher in PCOS individuals than in those with the same age and BMI.

Additionally, the emergence of HTN in female PCOS patients has been linked to an imbalance in the autonomic nervous system, increased renal salt reabsorption, and decreased nitric oxide.

Endocrine disruptors;

The pathophysiology of PCOS may potentially involve endocrine disruptors. Endocrine disruptors are synthetic substances in the environment that can potentially interfere with the endocrine system.

These substances, present in metal cans, plastic bottles, cleansers, toys, cosmetics, pesticides, fragrances, home goods, and other items, may harm one's health. The most prevalent endocrine disruptor whose effects on health have been extensively studied is bisphenol A (BPA). This substance could be a synthetic substance that acts like estrogen. According to preclinical research on female rats, lambs, and monkeys, prenatal exposure to BPA may alter the hypothalamic-pituitary-ovarian axis, resulting in a PCOS-like phenotype that includes infertility, anovulation, and polycystic ovaries.

Epigenetic influences;

One potential underlying mechanism linking early excessive androgen exposure to the development of PCOS in maturity is inappropriate epigenetic reprogramming. In particular, these epigenetic modifications can alter gene expression patterns and may increase the risk of PCOS development in later stages. It has been demonstrated that early postnatal exposure to androgens results in epigenetic changes that enhance the expression of genes linked to ovarian function, such as histone deacetylase 3 (HDAC3), nuclear corepressor 1 (NCOR1), luteinizing hormone receptor (LHR), and peroxisome proliferator-activated receptor-γ (PPAR-γ).

Treatment;

Treatments for PCOS, its specific symptoms, and associated conditions may vary, but they may include medication, lifestyle changes, and techniques to control acne and excessive hair growth.

Because PCOS can present with a wide range of symptoms, medical practitioners may use several therapies to address this disorder and its symptoms.

The doctor's and patient's treatment objectives would mostly be determined by the patient's urgent requirements, such as getting pregnant or regulating their menstrual cycle.

3.1 Lifestyle modifications;

This might involve calorie tracking, eating in a calorie deficit, exercising, and losing weight, which can provide a solid starting point for improving metabolism. A Mediterranean diet with vegetables, complete foods, whole grains, and solid fats can help with hormonal adjustment and advancement. Even a modest weight loss—for example, 5% of body weight—could greatly impact this illness.

Low-carb diet: Diets heavy in carbohydrates may raise insulin levels. Diets low in carbohydrates may be helpful for PCOS patients. Choose complex carbs, which help stabilize blood glucose levels and raise them more gradually.

Eat anti-inflammatory foods:

PCOS patients frequently have Inflammation, which can interfere with hormones. To control Inflammation, a patient's diet should include anti-inflammatory foods such as: Natural items high in antioxidants, such as blueberries, cherries, strawberries, and blackberries; wild-caught salmon, sardines, tuna, and mackerel; and green vegetables, such as kale, spinach, chard, cabbage, Brussels sprouts, and arugula.

Consuming fermented foods, such as kefir, Greek yogurt, cottage cheese, kombucha, probiotics, onions, sauerkraut, kimchi, apple cider vinegar, and sourdough bread, can improve gut barrier function, lower Inflammation, improve digestion, regulate immunity, and increase intestinal microflora.

3.2 Pharmacological Interventions:

Analogs of glucagon-like peptide-1 (GLP-1) have recently emerged as innovative anti-diabetic medications with amazing therapeutic profiles, improving glycemic control and reducing weight loss. A few studies have examined this intestinal hormone's metabolic and regenerative effects in this population. In obese women with PCOS, these further explain how GLP1 medication lowers body weight, controls the menstrual cycle, and may lessen hyperandrogenism. According to a subsequent meta-analysis, GLP-1 therapy may improve insulin sensitivity and other metabolic parameters more effectively than metformin, suggesting that GLP-1 is a useful pharmaceutical option for treating obese PCOS patients.

Oral contraceptive birth control pills:

Direct estrogen and androgen production are reduced by pills that contain both progestin and estrogen. In addition to reducing the risk of endometrial cancer, regulating these hormone levels can also treat hirsutism, acne, and sporadic death.

* Progestin treatment: Progestin can control periods and prevent endometrial cancer if used for 10–14 days over 1–2 months. This progestin therapy, which doesn't raise testosterone levels, won't impact pregnancy. If the patient does not want to become

pregnant, the progestin-only minipill or the progestin-containing intrauterine device can be a much better option.

* Clomiphene citrate:

During the follicular phase of the menstrual cycle, this oral anti-estrogen medication is administered. For women who do not ovulate but want to become pregnant, it aids in the inducement of ovulation or the creation of eggs.

Clomiphene belongs to a group of drugs known as ovulatory stimulants. It functions similarly to estrogen, which triggers the development and release of eggs from the ovaries.

* Femara (letrozole):

Because women who have PCOS typically have elevated estrogen levels, this breast cancer medication can assist with PCOS by lowering the body's estrogen levels.

The patient will take letrozole every day beginning on Cycle Day 3 (the first day of menstruation is Cycle Day 1) and continuing until Cycle Day 7. An initial dosage of 2.5 mg is advised when beginning. The dosage can be increased as necessary; the majority of providers utilize a maximum of 7.5 mg.

* Metformin. This type 2 diabetes medication lowers insulin levels and helps with insulin resistance. Should the patient's clomiphene citrate treatment fail to result in pregnancy, the physician may suggest using metformin to aid in ovulation. In patients with prediabetes, metformin can help them lose weight and prevent type 2 diabetes from developing.

Aldactone, or Spironolactone, counteracts the effects of androgen on the skin, preventing the onset of cystic acne and hirsutism. By inhibiting androgen receptors, including those on hair follicles, it functions as an anti-androgen, preventing testosterone from binding and producing its hirsutism-causing effects. Additionally, spironolactone lowers the amount of androgen produced by the adrenal glands and ovaries.

* Vaniqa, or eflornithine. The growth of facial hair can be controlled with this cream. Pregnant women should not use this cream since it may damage the unborn child. It includes eflornithine, a medication that inhibits the hair follicle-resident enzyme ornithine decarboxylase activity. Slow hair development is the outcome of blocking this enzyme.

* Mechanical methods for short-term hair removal can be somewhat effective, including shaving, fading, culling, waxing, and using depilatories (creams that break down hair). Some of these practices, like shaving and sugaring, are linked to skin problems and may increase the number of ingrown hairs. Additionally, certain depilatories might result in rashes and irritation.

*Supplements;

•Inositol

One kind of sugar that may influence insulin resistance is inositol. Research indicates that using inositol supplements may help lower insulin sensitivity, lower testosterone levels, and aid in menstrual cycle control.

•Chromium

Chromium enhances insulin's effects, which might help explain the connection between insulin resistance and chromium insufficiency. Research indicates a chromium supplement may help lower insulin sensitivity and blood glucose levels.

•Vitex

Vitex, sometimes called a virtuous tree or chaste berry, is a home treatment for PMS. According to studies, it regulates the body's levels of estrogen and progesterone. It has been shown to control menstruation regularity in women with PMS, menopausal symptoms, infertility, and even PCOS.

•Cinnamon

According to recent research, cinnamon greatly reduces insulin sensitivity and blood sugar levels. There is evidence that it may also help women with PCOS control their menstrual cycles.

•Dark cohosh

Dark cohosh is a home remedy frequently used to treat infertility in women. According to some research, it may make women with PCOS more likely to become pregnant.

•Electrical hair removal

Two options for hair removal include electrolysis and laser hair removal. A needle is inserted into each hair follicle during electrolysis. The needle current sends out an electric pulse. The follicle is injured by the current and eventually dies as a result.

Using light to eliminate unwanted hair, the laser hair removal method may be a medical procedure.

* Drugs that decrease cholesterol (statins) if the patient has elevated blood cholesterol levels * Derivation of cyproterone acetic acid * Flutamide * Finasteride

* Common treatments for cystic acne, which is frequently observed in women with PCOS, include retinoid, antibiotic, and antimicrobial medications.
The severity of the skin breakout determines this specific therapy. The drugs are available in many forms, such as tablets, creams, or gels, and in a range of quality; a medication may be necessary for more severe conditions. Retinoids should not be used by anyone who is or wants to become pregnant since they might result in inherent discrepancies.
•IVF treatment
In vitro preparation (IVF) therapy is recommended for patients with PCOS whose drugs do not help them become pregnant. This involves fertilizing the uterus with eggs that are taken from the ovaries. The fertilized egg or eggs are then placed back into the uterus to guarantee a proper pregnancy.
•Surgery;
For PCOS-related problems that don't respond to medication, laparoscopic ovarian drilling (LOD), a small surgical procedure, may be an alternative.
A laparoscope is a long, thin microscope the doctor inserts into a small cut on the lower belly while the patient is under general anesthesia. After that, the ovaries will undergo surgical manipulation to produce androgens (male hormones) by destroying the tissue with heat or a laser. This facilitates the patient's immediate ovulation.

It should be acknowledged that Polycystic Ovary Syndrome is a metabolic disease that plays a significant role in the development of insulin resistance, metabolic syndrome, and obesity. Patients with this condition can improve their quality of life and reduce their long-term risk by changing their lifestyle and using medications prescribed by medical professionals.

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