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Review Article

Polycystic Ovary Syndrome: Dietary Approaches to Counteract Insulin Resistance

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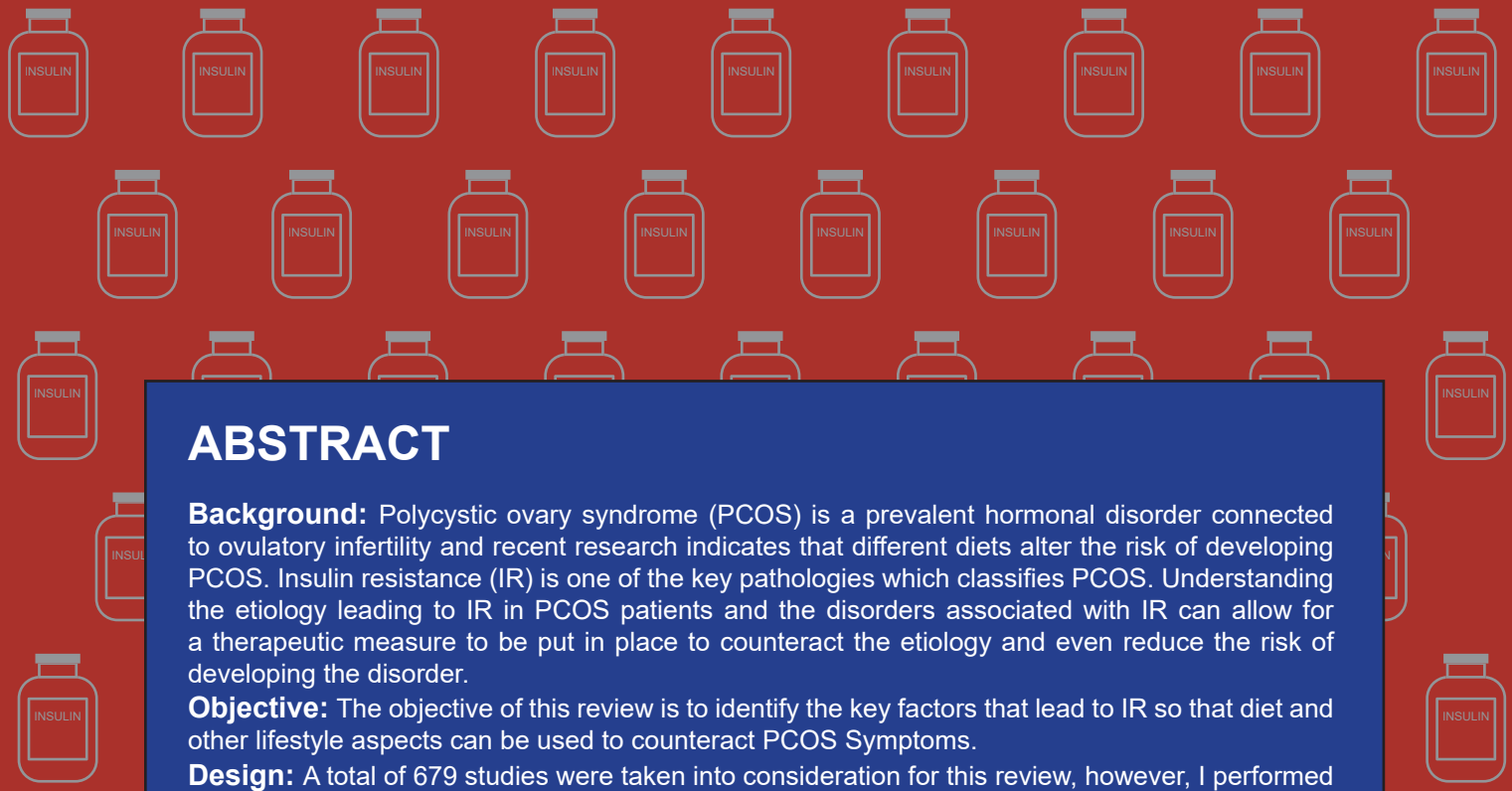

ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is a prevalent hormonal disorder connected to ovulatory infertility and recent research indicates that different diets alter the risk of developing PCOS. Insulin resistance (IR) is one of the key pathologies which classifies PCOS. Understanding the etiology leading to IR in PCOS patients and the disorders associated with IR can allow for a therapeutic measure to be put in place to counteract the etiology and even reduce the risk of developing the disorder.

Objective: The objective of this review is to identify the key factors that lead to IR so that diet and other lifestyle aspects can be used to counteract PCOS Symptoms.

Design: A total of 679 studies were taken into consideration for this review, however, I performed a literature review of 75 primary papers. Data and findings from these studies were used to gain a better understanding of the dietary etiology of IR in PCOS, and this information can be used to describe a specific diet to counteract its etiology.

Results: Many symptoms and disorders in the biological pathway of PCOS is associated with IR. Clinical studies have established that an increase in carbohydrates, low-density lipoproteins, and triglycerides is associated with IR in PCOS patients. Similar studies have found that a decrease in dietary proteins (especially branched chain amino acid intake), lactate, phosphatidylcholine, high-density lipoproteins, and long-chain fatty acids are also associated with PCOS patients. The drug metformin has also been associated with ameliorating many of the negative impacts imposed by IR in PCOS patients. Addressing these factors and changing diet and lifestyle (such as increased exercise) can help reduce the IR-related effects in PCOS patients.

Keywords: Polycystic Ovary Syndrome, Insulin Resistance, Diet, Therapy

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is a prevalent hormonal disorder connected to ovulatory infertility and metabolic disorders[1]. This disorder primarily affects women of reproductive age[1]. In females, this disorder is associated with endocrinal and metabolic symptoms, and in males, only metabolic symptoms[2]. PCOS is multi-faceted and therefore the pathogenesis is multigenetic[3]. One of the primary pathologies leading to PCOS is insulin resistance (IR). IR can further lead to other metabolic and endocrine complications. The prevalence of PCOS is unclear; however, estimates in subpopulations has revealed a consensus prevalence rate is believed to be about 3-10% for most populations[4]. However, this number may be higher because some affected patients have not been diagnosed due to social and economical factors such as insufficient medical care[1]. In Canada, PCOS is one of the most common endocrine disorders with a prevalence rate of 4-12%[4].

According to the criteria established by the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM), PCOS can only be diagnosed when multiple symptoms are manifested and if other disorders are first excluded[5]. PCOS is characterized by high blood levels of androgens, increased luteinizing hormone secretion, hyperinsulinemia and IR, hormone imbalance, and genetic inheritance[1].

This review will focus on the etiology behind IR and hyperinsulinemia and its association to cascading symptoms of PCOS. Due to the heterogeneity of the disorder, other factors such as obesity and hyperandrogenism will be discussed as well[6,7]. Dietary and lifestyle changes will be analyzed to develop the best interventions to counteract IR and thus reduce the symptoms of PCOS.

METHODS

Search Strategy

PubMed, EMBASE, and the University of Toronto Libraries system were searched using key words “lactate+pcos”, “long-chain fatty acids+pcos”, “triglycerides+pcos”, “low-density lipoproteins+pcos”, “high-density lipoproteins+pcos”, “glucose+pcos”, “phosphatidylcholine+pcos”, and “amino acids+pcos” . The reference list of the studies found were further reviewed to find related publications. Randomized controlled trials and longitudinal studies until April 2020 were considered. The quality of the pooled evidence was assessed using the GRADE (grading of recommendations assessment, development, and evaluation) approach. In total, 679 possible studies were identified.

Study Selection

Inclusion Criteria

Prospective studies investigating the association between PCOS and diet (where the diet can both increase or decrease the risk of PCOS) were included. For a systematic review to be conducted, studies which reported an odds ratio with 95% confidence limits were selected.

Exclusion Criteria

Studies conducted for PCOS are often disadvantaged by small sample sizes, selection biases, and lack of comparability between studies. Studies were excluded if they had sample sizes less than 100 participants, if the results of a study with selection bias could not be replicated by other studies, or if they did not strictly identify participants based on either the Rotterdam Criteria, National Institutes of Health Criteria, or a diagnosis by a healthcare professional.

Data Extraction

Data extracted from the studies included the first author’s last names, publication date, research location, sample size, age range of participants, recruitment procedure, method of PCOS diagnosis, follow-up period, consideration of variables, and type of statistical analysis.

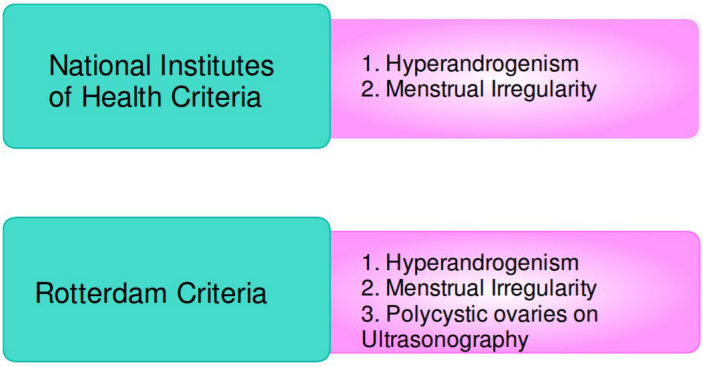

Figure 1 Guidelines for the diagnosis of PCOS and the associated symptoms

DETAILED ANALYSIS OF DIETARY CONSIDERATIONS

Protein Intake

The body’s digestive system breaks down proteins into amino acids (AAs) and the composition of the AAs can alleviate or aggravate symptoms in PCOS patients[8]. Zhang et al. (2014) elucidated the interaction between AA metabolic disturbances (increased and decreased) and an increased risk of IR associated with PCOS[9]. Furthermore, this disruption in AA composition and metabolic profile may be the reason for poor pregnancy outcomes and increased miscarriage risk

in PCOS patients[9]. Specifically, branched-chain AAs (BCAAs) and an increase in a few essential AAs are found to have a strong association with the alleviation of IR in PCOS patients. Extensive evidence of studies not associated with PCOS further illustrates that increased BCAAs and essential AAs are associated with obesity, IR, and type 2 diabetes, all of which are symptoms of PCOS[10,11].

Many studies have drawn an association between increased levels of lysine, leucine, serine, threonine, valine, homocysteine, and glutamic acid in PCOS patients compared to non-PCOS patients[9,12–15]. A decrease of plasma BCAAs compared to other aromatic AAs was directly correlated with the development of PCOS[14]. Among PCOS patients, there were discrepancies between pregnant and non-pregnant patients; pregnant patients have a higher level of aspartic acid and serine, while non-pregnant women have a higher composition of BCAAs[9]. Among all these statistically significant AAs, the findings about valine and glutamic acid are most reliably associated with PCOS since they were independently discovered in many studies. Increased levels of valine and leucine and decreased levels of glycine in the plasma of PCOS patients could also contribute to insulin sensitivity[14].

Evidence collected from these studies indicate that a diet with increased BCAAs and glutamic acid are found in meat, eggs, dairy products, nuts, and legumes[16,17]. This diet decreases the risk of developing PCOS and IR related symptoms[16,17]. The work by Rousseau et al. found that an increase in dietary BCAAs can be correlated with an increase in plasma BCAAs[16].

Carbohydrate Intake

Carbohydrates, both simple and complex, are broken down into monosaccharides including glucose and other monosaccharides. The glycemic index is a ranking method to determine how quickly blood sugar levels are increased after eating[18]. A high glycemic diet is not only associated with IR, but also higher androgen levels[19]. This diet also increases susceptibility to inflammation and oxidative stress which leads to cardiovascular disorders (CD) and estrogen-dependent cancers[19].

A reduced caloric diet can ameliorate symptoms of PCOS by reducing body weight, fat mass, and serum cholesterol[20]. The associated risk of carbohydrates with IR can be attributed to a higher insulin clearance as found by Stassek et al[21]. A reduced carbohydrate intake is associated with overall reduced insulin exposure, which may be the reason for the selective depletion of adipose tissue and preservation of lean body mass[22]. The study by Cutler et al. found that carbohydrates lead to increased IR related symptoms such as obesity, which contradicted the misconception that obesity in PCOS patients is due to overeating or inactivity[23]. Reduction in glycemic index for a prolonged period of time inhibits inflammatory factor synthesis[24]. Additionally, increasing dietary fiber and magnesium and lowering carbohydrate intakes may reduce IR[23,25].

Protein vs. Carbohydrates

Kasim-Karakas et al. elucidated that a diet of proteins can reduce the risk for developing PCOS, whereas a diet of carbohydrates can aggravate symptoms such as IR and hyperinsulinemia due to higher glucose levels[26]. This study further showed that the intake of protein rather than carbohydrates can cause the suppression of the hormone ghrelin (increases body weight and fat mass) due to ghrelin's sensitivity to insulin (higher in a protein diet)[26].

Fat Intake

Fats are a type of lipids made up of fatty acids and triglycerides[27]. Fatty acid composition can be used as biomarkers for several pathologies such as PCOS[28].

Long-Chain Fatty Acids (LCFA)

LCFA are fatty acids have aliphatic tails containing 13 to 21 carbons[28]. One of the more common LCFA found to be beneficial in alleviating risk of developing PCOS is Omega-3 polyunsaturated fatty acids (n-3 PUFAs)[29]. In this case, n-3 PUFAs were found to be one of the few LCFAs to have a substantial impact on decreasing the risk of developing PCOS. N-3 PUFAs were found to be beneficial for PCOS patients because it is associated with anti-obesity effects, glycemic and hormonal homeostasis, anti-inflammatory effects, and an enhancement of endothelial function[30]. Increased LCFA intake can lead to significant metabolic and endocrine effects such as an increase in glucose and decrease in plasma free fatty acids[31]. PUFAs modulate hormonal and lipid profiles and improve androgenic profiles[32]. Furthermore, Rafraf et al. found that n-3 PUFAs improved oxidative stress in women with PCOS[33,34]. A discrepancy in the findings is that Li et al. found that obese PCOS patients are associated with lower levels of PUFAs and higher levels of saturated LCFAs as compared to the lean controls[35]. Future studies needed to understand the inverse correlation between BMI and PUFAs.

The ingestion of LCFA promotes IR and a proinflammatory state are dietary consumption of trans fatty acids. Further research needs to be conducted to understand the biochemical pathway associated with this finding[36].

N-3 PUFA may be a treatment for PCOS, more specifically, the symptoms of IR, high LDL, and triglycerides[37]. Ingestion of PUFA may directly influence insulin secretion and resistance and indirectly affect plasma AA levels[38]. Increased fatty acids leads to a lower IR[39]. N-3 PUFA supplements have been found in the study by Salek et al. to alleviate symptoms of PCOS, however a clear association has not been made between the symptoms and dietary impacts[30].

Triglycerides

Triglyceride levels have been found to be higher in the blood of PCOS patients[40]. If there is a high amount of triglycerides compared to a low amount of high density lipoproteins (HDL), the prevalence of IR is higher[41–43]. Contradicting evidence shows that when associated with obese and diabetic PCOS patients, PCOS is mainly characterized by hypertriglyceridemia[44]. Hypertriglyceridemia can lead to a higher risk of visceral obesity and non-alcoholic fatty liver disease[44]. A high fat intake right before fasting time (sleeping through the night) may cause reduced fat energy consumption due to the diminished ability for lipid oxidation, which may lead to hypertriglyceridemia in PCOS patients[45].

An increased plasma triglyceride levels in obese adolescent patients provides evidence of early subclinical cardiovascular disorder (CD) risk due to impaired insulin metabolism and hyperandrogenemia[46]. This trend can be seen in patients older than 30 years of age irrespective of body mass index as there is prevalent hypertension and increased carotid intima media thickness of common carotid arteries[47]. Rashidi et al. found that in obese women, the triglyceride level is higher whereas cholesterol is higher in lean women[48].High triglycerides levels are associated with hyperandrogenism in PCOS patients[49]. Huddleston et al. found that increasing age among reproductive-aged women with PCOS leads to a steeper increase in CD associated with IR including triglycerides even though they additionally observed a decline in biochemical hyperandrogenaemia over time[50].

Transport Systems of Fats

Improper transportation of fats can lead to dyslipidemia, which is an accumulation of fats in the blood[6]. Patients with PCOS have dyslipidemia which is caused by an interplay between genetics, adiposity, and environmental factors[6,51–53]

High-Density Lipoproteins (HDL)

PCOS patients have an atherogenic lipid plasma profile with decreased levels of HDL as a result of their insulin resistant state[54]. The association of PCOS patients with CD can be attributed to the lower levels of HDL and higher levels of LDL. Rajkhowa et al. found that this association with lower HDL levels and PCOS is more evident in obese patients compared to lean patients[55]. Obese female patients with PCOS have a distinct metabolic signature during fasting and hyperinsulinemia[13]. Specifically, the level of triglycerides has a reciprocal relationship with HDL-C and the ratio of triglycerides and HDL-C is associated with IR for PCOS patients[43,56]. A reduction in HDL reduces antioxidant and anti-inflammatory pathways which leads to high levels of ROS and inflammatory factors[55].

Low-Density Lipoproteins (LDL)

PCOS patients have high LDL levels including an increase in atherogenic small dense LDL[28]. This increase in plasma LDL can be attributed to IR. Increased very low-density lipoprotein production and reduced clearance of lipoprotein lipase due to IR leads to hypertriacylglycerolemia through the reverse cholesterol transport pathway. This results in low HDL and high LDL levels[32]. Dyslipidemia caused by IR and unfavourable proatherogenic lipoprotein ratios is found in PCOS female patients and not in controls[57,58]. This may result in an increased risk of premature atherosclerosis[57]. An increase of small dense LDL is associated with an increased risk of developing CD by 3- to 7- fold[32]. This quantitative risk factor does not include the risk associated with increased LDL cholesterol concentration. Elevated serum lipoproteins may also contribute to the development of atherosclerosis and increased CD[59]. Increased levels of LDL are also related with abnormal ovarian function due to its influence on the irregular development of follicles[56]. Abnormalities in the early stages of folliculogenesis are one of the main causes of anovulation in PCOS[60].

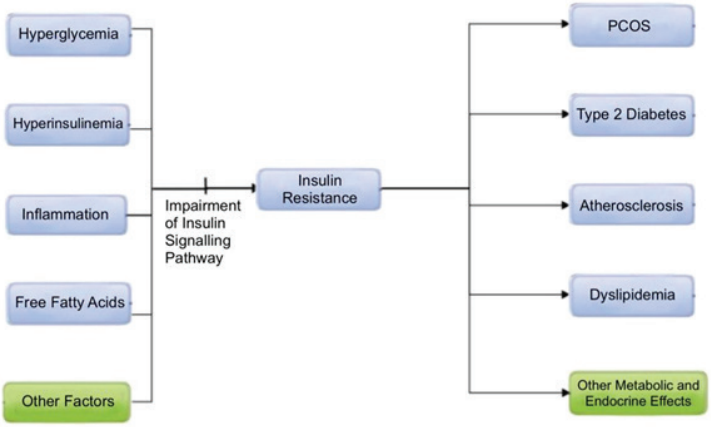

Figure 2 Summary of factors leading to and disorders caused by IR. The arrows indicate causal claims.

Ameliorating the Atherogenic Lipid Profile

Metabolic complications due to proatherogenic lipid profile changes should be taken into consideration when considering therapeutic strategies for PCOS patients[61]. Potential therapies associated with decreasing the risk of developing CD in association with PCOS patients and hyperinsulinemia is the use of the drug metformin[62]. Metformin can be considered as a prophylactic therapy[62]. Metformin decreases oxidized lipids in the blood which improves oxidative stress[63].

Along with changes in diet, it has been found that moderate-intensity exercise can improve components of the lipoprotein profile of PCOS patients so that there is less risk of developing the aforementioned disorders[64,65]. Dokras et al. has found that the use of oral contraceptive pills combined with lifestyle changes as stated above can lead to improved HDL-C function[66].

Phosphatidylcholine

Phosphatidylcholine is a major class of human plasma phospholipids and is composed of highly diverse fatty acids[67]. It is important for follicular growth and may influence the metabolism of glucose and lipids[67]. PCOS patients are reported to have abnormally higher levels of plasma phosphatidylcholine[35,68]. This lipid may be useful as a biomarker for the plasma carbohydrate to fat ratio, especially during the menstrual cycle luteal phase[34,41,69–71]. Hypertriglyceridemia as previously discussed can lead to an increase in inflammatory mediators such as the of the prostaglandin E2 pathway and oxo-leukotrienes in PCOS patients[45]. Phosphatidylcholine may be important for insulin production which then impacts other parts of the follicular growth pathways[72]. The main sources of phosphatidylcholine from dietary intake are eggs, meat, and supplementation[73].

Lactate

When the body does not have enough oxygen to break down the carbohydrates into glucose, the substance lactate is produced in order to supply ATP[74]. Lactate production is associated with the growth and maturation of ovarian follicles[60,75,76]. Irregular lactate production associated with PCOS may induce dyslipidemia, low-grade inflammation, and AA metabolism in follicular fluids[77]. Insulin is hypothesized to stimulate lactate formation by granulosa-lutein cells which are impaired in insulin resistant PCOS patients[78]. Gunalan et al. hypothesizes that dietary supplementation with lactate may help alleviate symptoms of PCOS[79]. The drug metformin was found to also stimulate lactate production by enhancing the function of suboptimal insulin concentrations. IR, hyperinsulinemia, and obesity lead to insufficient lactate production which leads to abnormal menstrual cycles, folliculogenesis, and fertility[76,80]. Positive changes in lifestyle and diet may lead to spontaneous ovulation and improve fertility rate in the majority of patients[80].

CONCLUSION

PCOS is a multifaceted disorder and identifying the specific risks of developing disorders associated with PCOS can aid in selecting appropriate interventions to improve the health of patients. Clinical studies have found strong associations between supplementation of various compounds and improving symptoms of PCOS; however, further studies need to take place to find more reliable evidence of dietary intake of compounds and their impact on PCOS. Overall, an increase in protein (specifically BCAA) intake instead of carbohydrates, increase in n-3 PUFA, phosphatidylcholine, lactate, and the use of the drug metformin combined with exercise is deemed to be appropriate lifestyle changes that will counteract IR in PCOS and thereby reduce the impact of this disorder.

COMPETITING INTERESTS

No competing interests declared.

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