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Literature Reviews

Unveiling the Complex Relationship between Polycystic Ovary Syndrome and Cardiovascular Risk Factors: A Comprehensive Review

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Abstract: Polycystic ovary syndrome remains a relatively unexplored endocrine disorder with significant implications for female health. Despite its prevalence and known associations with various metabolic disorders, the specific link between polycystic ovary syndrome and cardiovascular risk factors, particularly atherosclerosis, remains inadequately understood. This review aims to address the existing research gap by investigating the connection between polycystic ovary syndrome and cardiovascular risk factors. The objectives include examining the predisposition to atherosclerosis in females with polycystic ovary syndrome, assessing the impact of associated conditions like diabetes, dyslipidemia and obesity on cardiovascular health and highlighting the need for further investigation to clarify conflicting evidence in this area. This comprehensive review aims to provide insights into the complex interplay between polycystic ovary syndrome and cardiovascular and cardiometabolic risk factors, emphasizing the necessity for detailed studies to enhance understanding of this widespread condition.

Keywords: Atherosclerosis, Cardiovascular Disease, Ovaries, PCOS

Introduction

Polycystic Ovarian Syndrome (PCOS) remains a complex and insufficiently understood endocrine disorder first identified by Stein and Leventhal in 1935 (Bajuk Studen and Pfeifer, 2022). Despite its long history, the exact etiology of PCOS remains elusive, positioning it as one of the least explored hormone disorders in women. The clinical presentation of PCOS is known to be influenced by a combination of genetic and environmental factors. The diagnostic criteria proposed by the AES in 2009 emphasize the presence of ovarian insufficiency, hyperandrogenism and the exclusion of comorbidities, yet debates persist regarding the variability and complexity of PCOS manifestations, with some patients presenting without overt hyperandrogenism. This diagnostic ambiguity underscores the multifaceted nature of the syndrome, prompting ongoing research efforts to identify distinct phenotypes and relevant biomarkers for the prediction and management of PCOS and its associated consequences (Soares-Jr *et al*., 2019).

This review aims to delve into the intricate interplay between polycystic ovarian syndrome and cardiovascular risk factors, focusing on atherosclerosis and associated metabolic abnormalities. By synthesizing existing knowledge and addressing conflicting evidence, we seek to shed light on the specific connections between PCOS and cardiometabolic health, highlighting the urgency for further investigation to unravel the complexities surrounding this prevalent yet enigmatic condition.

Furthermore, this review will explore the research gap regarding the predisposition of individuals with

PCOS to cardiovascular risk factors, aiming to provide a fresh perspective on the implications of PCOS on cardiovascular health. By emphasizing the importance of clarifying these connections, this review contributes to the evolving understanding of PCOS and its broader health implications.

Methods

For this review article, a comprehensive literature search was conducted using various academic databases, including PubMed, Google Scholar and relevant medical journals. The search terms included "polycystic ovarian syndrome," "PCOS," "cardiovascular risk factors," "atherosclerosis," and "metabolic abnormalities." Articles published between 2000 and 2021 were considered for inclusion.

Inclusion criteria comprised peer-reviewed original research articles, review papers, meta-analyses and clinical studies related to the association between polycystic ovarian syndrome and cardiovascular risk factors. Articles written in English and focusing on human studies were prioritized.

The selected articles were reviewed and relevant information regarding the pathophysiology of PCOS, metabolic abnormalities, cardiovascular risk factors and potential connections between PCOS and atherosclerosis was extracted.

In cases of conflicting data or multiple viewpoints, efforts were made to present a balanced overview of the current evidence. Limitations in the existing literature were also highlighted, underscoring the need for further research to elucidate the complex relationship between PCOS and cardiovascular health.

This review aims to provide a comprehensive and up-to-date analysis of the existing literature on PCOS and cardiovascular risk factors, offering insights into the potential mechanisms underlying these associations and emphasizing the clinical relevance of understanding the impact of PCOS on cardiovascular health.

Metabolic and Related Features Associated with Polycystic Ovary Syndrome

Long-lasting consequences of polycystic ovarian syndrome are associated with a number of metabolic abnormalities following the disorder, such as Insulin Resistance (IR), DM, hyperinsulinemia, dyslipidemia and other CV risk factors. The foundation of the physiology of polycystic ovarian syndrome is believed to be IR, which has negative impacts on numerous target organs (Anagnostis *et al*., 2018). This supports the classification of polycystic ovary syndrome as a multisystem disease. There is an intersection between polycystic ovarian syndrome and Metabolic Syndrome (MS) or IR, as those two clinical conditions have similar features, including high concentrations of TGs in serum, low concentrations of high-density Lp cholesterol in serum, abdominal adiposity, Hypertension (HT) and disrupted metabolism of carbohydrates. MS has been reported to occur in female patients with polycystic ovarian syndrome in 43-46% of cases (Lavor *et al*., 2022). Particularly, IR and hyperinsulinemia greatly contribute to the development of MS and polycystic ovary syndrome, since they are connected to elevated risk for type 2 diabetes, HT, AS and hyperlipidemia. Among female patients with polycystic ovarian syndrome, IR is detected in 50-75% of cases and seemingly is not adiposity-dependent. In half of the female patients with polycystic ovarian syndrome, IR was found to be associated with improper non-insulin-dependent insulin receptor beta-subunit serine phosphorylation. Decreased action of PI3K has also been detected in the muscles of said individuals (Zhao *et al*., 2023).

Regarding the criteria for detecting IR, the hyperinsulinemic-euglycemic clamp technique is still considered the best available procedure. Although, it is not used often because of its more intricate and intrusive nature than that of other techniques that are less accurate, but also less intrusive and more acceptable in clinical study (HOMA-IR, QUICKI). There have been introduced new markers for IR, e.g., adipokines, ghrelin and leptin (Kim, 2009). However, it is still unclear how precise they are. Overall, IR is a distinguishing feature of polycystic ovarian syndrome as shown by hyperinsulinemic-euglycemic clamp, irrespective of the used criteria, while many trials use control groups of female subjects to identify IR. Excessive body weight and adiposity with BMI ranging from 253-999 kg/m^2 were reported to be more frequent in female patients with polycystic ovarian syndrome and to be related to IR and hyperinsulinemia. The incidence of adiposity in individuals with this syndrome depends on demographic factors, being higher in the US and lower in Europe (Herman *et al*., 2023). However, thin and overweight female patients with polycystic ovarian syndrome demonstrate the central distribution of body fat. Moreover, in patients in perimenopause with adiposity and polycystic ovarian syndrome, IGT was detected in 31-35% of cases and T2DM in 7.5-10% of cases. Furthermore, other conditions, e.g., NASH, NAFLD, OSA and hypersomnia have also been found linked to polycystic ovarian syndrome and IR (Jurczewska *et al*., 2023).

Parameters of Cardiovascular Disease

Several studies demonstrated that polycystic ovary syndrome can elevate the risk of AS with a Relative Risk (RR) of 7.4 for MI. Endothelial dysfunction has been well-researched and is known to indicate the development of AS and subsequent cardiovascular disease at early stages (Berni *et al*., 2021). As polycystic ovarian syndrome is considered to constitute a female type of MS, that possibly

carries the atherogenic burden, individuals with polycystic ovarian syndrome have a higher CV risk than the control group. In individuals with polycystic ovaries, the likelihood of MI is 7 times higher. Moreover, cardiac cath studies demonstrated that female individuals with this condition exhibit more advanced CAD than those without it. In addition, in patients with polycystic ovarian syndrome, carotid ultrasonography showed severe subclinical AS of the carotid arteries (Bickerton *et al*., 2005).

The elevated risk of CVD in women with polycystic ovarian syndrome may be attributed, in part, to the metabolic disruptions linked to the condition. Women with PCOS are prone to dyslipidemia, adiposity and diabetes (ranging from IGT to DM), all of which are potential CV risk factors. A number of earlier trials have reported irregularities in the metabolism of insulin among thin and overweight patients with polycystic ovarian syndrome (Liao *et al*., 2022).

Polycystic ovarian syndrome can present with dyslipidemia, adiposity and IR, which are factors that promote the development of MS and increase the risk of AS and cardiovascular disease, regardless of whether polycystic ovarian syndrome is present or not (Sangaraju *et al*., 2022). Although high BP is not commonly found in young female patients with polycystic ovarian syndrome, its frequency rises to 40% during the premenopausal period. Nevertheless, the connection between polycystic ovarian syndrome and cardiovascular events has not been conclusively established through epidemiological data (Wu *et al*., 2020).

Elevated CV risk in patients with polycystic ovarian syndrome can also be explained by hyperandrogenaemia.

Hyperandrogenism is a key feature of Polycystic Ovarian Syndrome (PCOS) and plays a significant role in the disorder's manifestations. High levels of androgens, such as testosterone, are often associated with PCOS and can have various metabolic implications for affected individuals (Ye *et al*., 2021).

Research has shown that PCOS patients with hyperandrogenemia tend to exhibit specific metabolic disturbances compared to those without elevated androgen levels. For example, women with PCOS who have high levels of androgens are more likely to present with insulin resistance, higher waist circumference and increased risk of cardiovascular complications. These metabolic parameters are crucial indicators of cardiometabolic risk factors (López-Alarcón *et al*., 2023; Berbrier *et al*., 2023).

Studies have demonstrated that hyperandrogenemia in PCOS patients is linked to an increased prevalence of insulin resistance, which is a common characteristic of the syndrome. Insulin resistance, in turn, can contribute to the development of metabolic syndrome, atherosclerosis and cardiovascular disease. Additionally, individuals with PCOS and hyperandrogenism are more likely to experience difficulties in glucose metabolism and lipid profile abnormalities, further highlighting the relationship between high androgen levels and metabolic dysregulation (Xu and Qiao, 2022; Ding *et al*., 2021).

Furthermore, the presence of hyperandrogenemia in PCOS patients is often associated with more severe clinical presentations and a higher likelihood of developing metabolic complications. These individuals may require tailored treatment approaches to address both their hormonal imbalances and metabolic issues effectively (Dewani *et al*., 2023).

By focusing on the interplay between hyperandrogenism and metabolic parameters in PCOS, healthcare professionals can better understand the complex nature of the syndrome and develop targeted interventions to improve outcomes for affected individuals. Pathological processes that underlie this condition involve a connection between high levels of androgens and disruption in lipid metabolism, as well as a connection between systolic blood pressure and free testosterone (Duică *et al*., 2021). However, the connection between CV risk and hyperandrogenaemia is not generally recognized. Earlier research on female patients with adiposity and polycystic ovarian syndrome has reported that hyperinsulinemia is able to decrease sex hormone-binding globulin. This suggested that in this population sex hormone binding globulin can be a surrogate endpoint of IR. However, other research showed that body mass index and BFP, but not insulin, can independently predict sex hormone-binding globulin in people with and without polycystic ovarian syndrome (Mansour *et al*., 2023).

Cardiometabolic Risk Factors in PCOS

Available evidence demonstrated that Cardiometabolic Risk (CMR) factors are more frequent in female patients with polycystic ovarian syndrome. We schematically provided the relations in the Fig. (1). This condition is often characterized by abdominal adiposity, which greatly affects the gravity of the cardiometabolic and reproductive characteristics of the patients. A meta-analysis that involved 35 research reports demonstrated that the overall incidence of adiposity among female patients with polycystic ovarian syndrome was 49% (Bajuk Studen and Pfeifer, 2022).

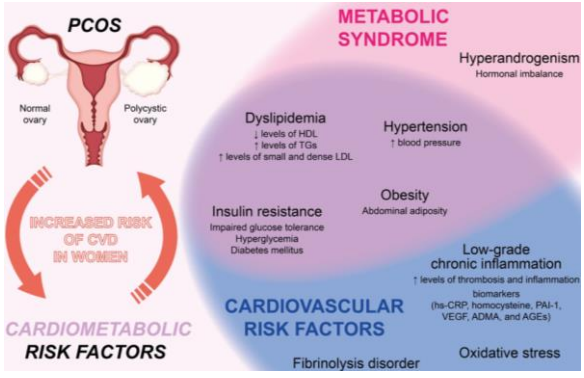

Fig. 1: Association of polycystic ovary syndrome with cardiometabolic risk factors

Atherogenic Dyslipidaemia (AD) is a condition that includes decreased levels of high-density Lp and increased levels of TGs and small and dense low-density Lp particles, which was detected in approximately 70% of individuals with polycystic ovarian syndrome (Madhu *et al*., 2013). A recent meta-analysis reported that female patients with the syndrome tend to have increased concentrations of low-density Lp cholesterol and non-high-density Lp cholesterol, regardless of BMI. Even though there have been conflicting results in research so far, emerging evidence supports the idea that polycystic ovarian syndrome is associated with HT (Wild *et al*., 2011). Research has been conducted recently in 1550 female patients with polycystic ovarian syndrome and a control group of 447 people, the results demonstrated that both systolic and diastolic BP were notably elevated in patients with polycystic ovarian syndrome when corrected for body mass index and age (Profili *et al*., 2024).

IR is a condition in which an organism fails to respond normally to insulin, exogenous or endogenous. IR is the major metabolic disorder in polycystic ovarian syndrome. HEC studies have demonstrated that IR was notably increased even in not overweight female subjects with polycystic ovarian syndrome. From this, it can be implied that this is an inherent characteristic of polycystic ovarian syndrome (Rojas *et al*., 2014). IR is found in about 70% of female patients with the syndrome, although it shows several heterogeneous features, depending on the criteria used and the phenotype of PCOS. Therefore, hyperglycemia and hypoglycemia are more frequently found in perimenopausal patients with polycystic ovarian syndrome. Another meta-analysis demonstrated that female patients with this syndrome have a higher incidence of IGT and DM than those without it. An updated and expanded version of this analysis also supported these results (Witchel *et al*., 2019). The higher incidence of IGT remained considerable in the body mass index-matched group. However, an independent connection between polycystic ovarian syndrome and diabetes was not observed in this meta-analysis, probably because of limitations in a meta-analysis of pooled data, the young age of patients and a small number of diabetes cases. Accordingly, a recent Danish registry demonstrated 4 times elevated incidence of diabetes in female patients with polycystic ovarian syndrome, as well as 4 years earlier diagnosis (Fu *et al*., 2023).

Whereas IR plays an important role in MS, the latter also occurs more frequently in female patients with polycystic ovarian syndrome than in those without it. Metabolic syndrome involves a number of common cardiovascular risk factors, such as increased waist circumference, decreased high-density-Lp cholesterol levels (less than 40 mg/dL and less than 50 mg/dL in male and female patients respectively), increased TGs (≥150 mg/dL or on therapy), hyperglycemia (FPG ≥100 mg/dL or on therapy) and HT (systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg or anti-HT therapy) (Amisi, 2022). A recent meta-analysis demonstrated that patients with polycystic ovarian syndrome had 3 times higher frequency of metabolic syndrome compared to the control group (Lavor *et al*., 2022).

Polycystic ovarian syndrome has also been found connected to several new cardiovascular risk factors, e.g., LGCI, Oxidative Stress (OS) and fibrinolysis disorder. A number of biomarkers of thrombosis and inflammation, such as hs-CRP, homocysteine, PAI-1, VEGF, ADMA and AGEs, were higher in female patients with this syndrome than in those without, although with a considerable degree of heterogeneity between studies. Furthermore, surrogate endpoints of subclinical artery disease at initial stages, e.g., elevated CIMT and CAC and reduced FMD, are encountered more frequently in individuals with polycystic ovarian syndrome (Hyderali and Mala, 2015).

PCOS and Cardiovascular Disease

In the presence of CMR, cardiovascular risk in female patients with polycystic ovarian syndrome was calculated as five to seven times higher than in the general women population. However, clinical information has not yet confirmed this. A number of clinical trials have reported that cardiovascular risk in female patients with polycystic ovarian syndrome is in fact higher, but not in values derived from risk factors, ranging from 1.5-2 (Alexandraki *et al*., 2011). Cibula and colleagues conducted a study of 28 individuals with polycystic ovarian syndrome, an average age of 52 years. The results demonstrated a 21% incidence of CHD versus 5% in the control group (Cibula, 2000). The Nurses' Health Study included approximately 82.5 thousand women who were observed for fourteen years. The results showed that female patients, who had experienced irregular periods at a young age, exhibited elevated body mass index-independent prevalence of fatal CHD (relative risk 1,25, CI 1.07-1.47) and non-fatal CHD (relative risk 1.67, CI 1.35-2.06) (Wang *et al*., 2020). The WISE population study, which involved the 5-year observation of female patients in post-menopause and not taking hormonal drugs and patients with polycystic ovarian syndrome characteristics (irregular periods, overt hyperandrogenism) showed 1.59 relative risk (CI 1,19-2,12) of non-fatal MI or CV death, independent of body mass index, DM or age, compared to the control group (Kamińska *et al*., 2023). Krentz and colleagues analyzed 713 community-dwelling postmenopausal female patients of the RBS and the results showed that patients without DM with signs of polycystic ovarian syndrome had notably increased incidence of cardiovascular disease than those without the phenotype (relative risk 1.36, CI 1.05-1.76) (Krentz *et al*., 2007). In addition, a study conducted in the UK of 309 women with polycystic ovarian syndrome and 1060 women without it reported that the incidence of stroke was 2,8 times higher in patients with the syndrome than in those without it (CI 1.1-7.1) (Livadas *et al*., 2022).

However, some researchers have found no connection between polycystic ovarian syndrome and cardiovascular disease. One of the first population researches in the United Kingdom performed on 786 individuals with this syndrome, which were observed for thirty years, demonstrated that cardiovascular mortality was not above the population average. These researchers also found a similar rate of coronary heart disease morbidity and mortality in individuals with polycystic ovarian syndrome and in age-matched control groups (Ding *et al.*, 2018). Elting and colleagues conducted a study on 346 women with the syndrome and 8950 control patients with an average age of 39 years, the results showed a similar incidence of CV events in both groups (Lin *et al*., 2021).

Determining the CVD Risk in PCOS Patients: Are Androgens the Answer to the Question

There is evidence indicating that hyperandrogenaemia plays a crucial role in establishing the CMR in different phenotypes of polycystic ovarian syndrome. Recent research examined the endocrine parameters of different phenotypes of polycystic ovarian syndrome using the Rotterdam criteria and found that all phenotypes that involve hyperandrogenaemia exhibited elevated waist circumference and IR (Elsayed *et al*., 2023). Conversely, women with anovulation and Polycystic Ovary Morphology (PCOM), but without hyperandrogenism showed similar results to the control group in terms of these characteristics. Women with ovulation and with hyperandrogenism had less severe clinical and metabolic abnormalities, associated with medium concentrations of androgen (Harada, 2022). Another research of 308 individuals with polycystic ovarian syndrome demonstrated similar results. When corrected for body mass index, patients with hyperandrogenism exhibited three times higher concentrations of androgen, elevated incidence of IGT and IR and elevated levels of TGs compared to patients with ovulation and PCOM. Moreover, the congregation of several CV risk factors, e.g., abdominal adiposity, disrupted lipid metabolism, high IR, high C-reactive protein or homocysteine, is believed to be higher in the classic phenotype of polycystic ovarian syndrome than in the ovulatory one, coinciding with increased concentrations of androgen (Farhadi-Azar *et al*., 2022).

Concentrations of androgen in female individuals decrease with age, particularly after the age of 30 years. The ovaries in post-menopause still generate androgens, thus menopause affects androgen levels in the blood not too obviously. Similarly, concentrations of androgen decrease and clinical signs of polycystic ovarian syndrome alleviate with time, which can lead to the resumption of ovulation. Persistence of hyperandrogenaemia in middle age can define the risk in patients with a history of polycystic ovarian syndrome (Brzozowska and Lewiński, 2020).

In post-menopausal patients, endogenous androgens have been found related to CV risk. Such patients with increased concentrations of androgen exhibit an unfavorable CMR profile, which includes elevated IR, FPG, TGs, CRP, PAI-1, PPET1 and decreased HDL-C, compared to individuals with lower concentrations of these hormones. IR can result in an increase in androgen levels. However, elevated levels of androgen can also lead to the development of IR (Zhao *et al*., 2018).

Both extremely high and extremely low concentrations of androgen in post-menopausal patients are related to elevated risk of coronary heart disease. A number of researches in such patients have reported that reduced levels of testosterone are related to more severe AS of carotid arteries than higher, but still normal concentrations (Armeni and Lambrinoudaki, 2022). However, the MESA study, which included 1947 female patients, reported a direct correlation between concentrations of testosterone and CIMT, regardless of body mass index and IR (Cupisti *et al*., 2007). Patel and colleagues studied 344 community-dwelling female patients, ages ranging from 65-98 years. The results showed that patients in the 2nd testosterone quartile exhibited approximately 3 times lower incidence of coronary heart disease than patients in the highest testosterone quartile (Patel *et al*., 2009). A recent analysis of the population of Rancho Bernardo demonstrated that patients in the highest testosterone quintile exhibited an elevated frequency of coronary heart disease over twenty years of observation (relative risk 1.96, CI 1.13-3.41) compared to patients in the middle testosterone quintile, regardless of body mass index, age, tobacco use and abdominal fat (Barrett-Connor, 2013). Nevertheless, one should be aware of the role of coinciding risk factors in CV risk in female individuals with increased concentrations of androgen. In the Women's Health Study, among post-menopausal patients not receiving hormone replacement therapy those who exhibited CV events during observation had considerably higher baseline FAI than those who didn't. However, that difference was eliminated after correction for body mass index, T2DM and increased cholesterol levels (Raj *et al*., 2023). Likewise, the Rotterdam Study reported that patients in the highest testosterone quintile had a 3.7 times higher incidence of serious AS of the aorta than other patients. However, the difference has also been eliminated after correction for body mass index, BP, lipid profile and T2DM (Van Der Burgh *et al*., 2022).

To sum up, PCOS can be considered as a risk factor for subclinical and clinical CVD (Fig. 2).

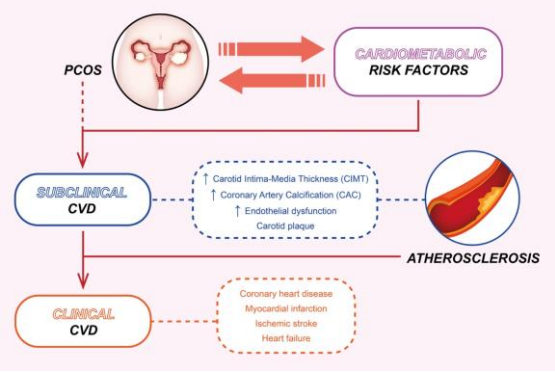

Fig. 2: PCOS is a risk factor for clinical and subclinical cardiovascular disease

Obesity, Insulin Resistance and Chronic Inflammation

Fat tissue also takes part in chronic inflammatory response that is caused by various processes. Lipocytes produce proinflammatory factors, such as resistin, leptin, lipocalin, tumor necrosis factor-alpha, interleukin-6 and interleukin-1 entitled adipokines. Moreover, higher concentrations of free FAs are found in patients with adiposity. Since these molecules are primary ligands for TLRs, they are a crucial promoter of responses of the immune system, innate and adaptive. Moreover, macrophages make up a significant proportion of fat tissue and mostly represent activated M1 macrophage phenotype (De Oliveira Dos Santos *et al*., 2021). Thus, they produce and release proinflammatory cytokines, such as tumor necrosis factor-alpha and interleukin-6, which also can promote inflammation responses in different types of tissue, including ovarian tissue. Proinflammatory signaling molecules derived from macrophages are also critical for inducing IR in peripheral cells sensitive to insulin (Koizume and Miyagi, 2017).

In addition, hypertrophy of fat cells caused by excessive nutrition can cause hypoxia and oxidative stress formation of ROS and necrotic processes in lipocytes. These cases are able to promote inflammatory response and result in continued macrophage and Th cell recruitment and activation. Furthermore, the development and action of B-lymphocytes is disrupted in patients with adiposity and in murine models of adiposity, compared to control groups. This can cause the generation of proinflammatory B-lymphocytes with no antigenic trigger and stimulate IR. These processes enhance the inflammatory response and reflect connections between innate and adaptive immune systems in terms of IR and adiposity (Zatterale *et al*., 2020).

It is noteworthy that in addition to those interconnected signaling pathways, the connection between the response of the immune system and metabolism is reflected on the cell level since preadipocytes proved to be able to turn into macrophages in the appropriate environment (Li *et al*., 2023).

Finally, adiposity and inflammatory response are connected through a number of signaling pathways that also combine pathways to adiposity-associated IR and other common accompanying disorders, such as hepatic steatosis, asthma, T2DM and cardiometabolic disorders (Gutiérrez-Cuevas *et al*., 2021).

Chronic Inflammation in PCOS

Polycystic ovarian syndrome often coexists with IR and adiposity, which affect approximately 65-80% of individuals with this condition. It is also widely known that hyperinsulinemia, adiposity and hyperandrogenism in this disease enhance the effect of each other. Polycystic ovarian syndrome represents a chronic inflammation state which is partly due to excessive abdominal fat and its proinflammatory features (Singh *et al*., 2023). Low-grade chronic inflammation, reflected by increased concentrations of proinflammatory cytokines, is also found in non-overweight patients with polycystic ovarian syndrome. It was generally explained by excessive abdominal fat and intra-abdominal fat deposition which is present in those patients (Rudnicka *et al*., 2021). Recent research reported that body mass index and IR can predict elevated levels of Creative protein and leukocytes. Moreover, individuals with polycystic ovarian syndrome exhibit a specific pro-inflammatory genotype associated with changes in the genes encoding for tumor necrosis factor-alpha, tumor necrosis factor receptor and interleukin-6. In addition, apart from promoting visceral obesity, hyperandrogenism in polycystic ovarian syndrome also has a proinflammatory effect. Excessive concentrations of androgens promote the activation of mononuclear cells, inducing the generation of ROS and activation of nuclear factor kappa B (Aboeldalyl *et al*., 2021). That stimulates the expression of tumor necrosis factor-alpha, interleukin-6 and interleukin-1. Tumor necrosis factor-alpha and interleukin-6 mediate IR. Hyperandrogenism was thus proved to have an adverse effect on the IRS-1/PI3K/Akt insulin signaling pathway (Shabbir *et al*., 2023).

Those connections demonstrate an important connection between metabolic characteristics in polycystic ovarian syndrome and chronic inflammation. Moreover, impaired function of ovaries is connected to induced infiltration of macrophages and elevated expression of tumor necrosis factor-alpha, interleukin-6 and interleukin-8, which leads to activation of the related proinflammatory signaling pathways (Moin *et al*., 2022).

The Association between Pathologies

There is contradictory information on cardiovascular morbidity and mortality in female patients with polycystic ovarian syndrome. Most

research on the subject has a number of limitations since they generally are cross-sectional or retrospective, insufficient sample sizes, vague phenotyping, short-term observation, improper interference control, unclear diagnostic criteria and not optimal evaluation of cardiovascular events. All this makes it hard to compare the results of different studies. The contradictions found in the results can also be explained by a variety of populations, e.g., using samples taken from a community or hospital (Berni *et al*., 2021). Furthermore, multiple researches involved patients in both perimenopause and post-menopause, but most patients with polycystic ovarian syndrome in these trials had not been of age at which cardiovascular disease is common. It remains unclear whether individuals with the polycystic ovarian syndrome experience more acardiovascular events in postmenopause than the average in the population (Mahajan and Sharma, 2021). A multicenter prospective study is currently underway, which includes female patients aged 45-55 with reproductive disturbances, such as polycystic ovarian syndrome and others, to evaluate the diagnostic benefits of cellular biomarkers and CT scans in detecting cardiovascular disease. The study's findings may shed light on cardiovascular disease progression and refine the prediction of cardiovascular risk for such individuals. However, there is presently no data linking the elevated incidence of cardiovascular risk factors in reproductive-aged patients with polycystic ovarian syndrome to higher cardiovascular morbidity and mortality in young and middle age (Mirza *et al*., 2021).

The CMR associated with polycystic ovarian syndrome is strongly influenced by its phenotype. Research has shown that patients with classic polycystic ovarian syndrome features are at a greater risk of developing cardiometabolic issues compared to patients with different phenotypes. Nevertheless, as patients with polycystic ovarian syndrome age, their phenotype tends to improve, evidenced by a reduction in concentrations of androgen in serum and an improvement in menstrual cycle regularity (Farhadi-Azar *et al*., 2022). This amelioration in the phenotype is also reflected in long-term studies, which indicate that cardiovascular risk factors do not worsen further in post-menopausal patients with polycystic ovarian syndrome. Conversely, CMR profiles of patients with polycystic ovarian syndrome appear to become similar to those of the control group during the post-menopausal period, mostly because of an increase in body weight and abdominal fat storage in control patients, which happens along with menopause. This can explain the similarities in cardiovascular risk profiles of patients with polycystic ovarian syndrome and the control group in the postmenopausal period. In addition, COC use in female patients with the syndrome during reproductive age can possibly protect against cardiovascular disease at an advanced age (Lenart-Lipińska *et al*., 2014).

Hyperandrogenaemia seems to be the major characteristic related to CMR in patients with polycystic ovarian syndrome. Although, currently no obvious connection between androgens and cardiovascular disease has been found. The contradictions in the research results can be explained by a number of limitations of available ways to evaluate levels of androgen. Further research is necessary to determine whether high levels of androgen have a direct impact on the progression of cardiovascular disease, regardless of any related cardiovascular risk factors. To achieve this, advanced techniques like LC-MS and extraction and chromatographic immunoassays must be utilized (Dadachanji *et al*., 2018).

It is important to take into account the ethnic diversity in the way that polycystic ovarian syndrome presents and affects women. Studies show that there are notable distinctions in the incidence and phenotype of CMR factors among patients with polycystic ovarian syndrome of different ethnic backgrounds. However, it is still uncertain if the variations in the incidence of cardiovascular disease related to polycystic ovarian syndrome are based on ethnicity. More investigation is needed to shed light on this topic (Chang *et al*., 2016).

It is necessary to conduct extensive community-based studies that include observation of both healthy individuals and properly phenotyped individuals with polycystic ovarian syndrome from young to late post-menopausal age in order to accurately determine the risk of cardiovascular events in the population. However, such trials require significant funding and many years of research. Another option could be determining a phenotype for polycystic ovarian syndrome in the postmenopausal period, but this is also a difficult task (Ndefo *et al*., 2013). There are not any universally recognized diagnostic criteria for concentrations of androgens in serum in post-menopausal patients. Moreover, the occurrence of polycystic ovarian syndrome seems to be connected to age. It is less common in female patients in the postmenopausal period. Hence, finding a phenotype of polycystic ovarian syndrome corresponding to the post-menopausal phase, using the existing understanding of clinical and pathological characteristics of polycystic ovarian syndrome, has to be an area of focus in future studies (Naz, 2014).

Limitations

Despite the thorough literature search and meticulous review process, this article may have certain limitations that should be acknowledged.

Publication bias: There is a possibility of publication bias, where studies that report significant findings are more likely to be published, potentially skewing the overall interpretation of the literature.

Study heterogeneity: The included studies may vary in terms of design, patient characteristics, diagnostic criteria and methodologies, leading to heterogeneity that could impact the synthesis of results and analysis.

Quality of included studies: The quality of the studies included in this review may vary, which could affect the reliability and generalizability of the conclusions drawn.

Limited scope: Due to the complexity and vastness of the topic, it is possible that certain relevant studies or aspects of PCOS and its association with cardiovascular risk factors may not have been included in this review.

Temporal factors: This review is based on literature available up to 2021 and there may have been significant advancements or new studies published after this time that could impact the conclusions.

Data interpretation: Interpretation of the data and findings presented in the included studies is subject to the authors' judgment and interpretation, which could introduce bias.

Confounding factors: The presence of confounding variables or factors not accounted for in the reviewed studies could affect the observed associations between PCOS and cardiovascular risk factors.

Despite these limitations, this review strives to provide a comprehensive overview of the current understanding of the relationship between polycystic ovarian syndrome and cardiovascular risk factors, while acknowledging the need for further research to address these limitations and enhance our knowledge in this area.

Conclusion

There's a lot of conflicting data regarding whether polycystic ovarian syndrome can lead to the development of metabolic disorders, atherosclerosis and other pathological conditions. Several disorders have been linked to polycystic ovarian syndrome. Various studies have found disruptions in insulin metabolism in both overweight and lean female patients with PCOS. Insulin resistance is a key clinical characteristic of polycystic ovarian syndrome that can contribute to the development of metabolic syndrome, atherosclerosis and cardiovascular disease, though further research is needed to confirm these findings.

Another notable feature of this syndrome is hyperandrogenism, which should not be overlooked. PCOS patients with hyperandrogenemia often exhibit higher waist circumference and insulin resistance compared to those without hyperandrogenemia, who show similar values to the control group. However, understanding the role of androgen levels in the development of cardiometabolic risk factors largely relies on having appropriate diagnostic criteria. Many studies currently face limitations such as small sample sizes, lack of standardized diagnostic criteria and unclear phenotyping.

Accurately phenotyping during the post-menopausal period is also challenging due to age-related factors. This topic warrants extensive future research to validate various hypotheses and establish causal connections effectively.

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Use the same font size for the content of the acknowledgments section.

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Author’s Contributions

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Ethics

Authors are expected to promptly address any ethical concerns that may emerge following the publication of this manuscript.

References

Aboeldalyl, S., James, C., Seyam, E., Ibrahim, E. M., Shawki, H. E.-D., & Amer, S. (2021). The Role of Chronic Inflammation in Polycystic Ovarian Syndrome—A Systematic Review and Meta-Analysis. *International Journal of Molecular Sciences*, *22*(5), 2734. https://doi.org/10.3390/ijms22052734

Alexandraki, K. I., Kandaraki, E. A., Poulia, K.-A., Piperi, C., Papadimitriou, E., Papaioannou, T. G. (2021). Assessment of Early Markers of Cardiovascular Risk in Polycystic Ovary Syndrome. *TouchREVIEWS in Endocrinology*, *17*(1), 37. https://doi.org/10.17925/ee.2021.17.1.37

Amisi, C. A. (2022). Markers of insulin resistance in Polycystic ovary syndrome women: An update. *World Journal of Diabetes*, *13*(3), 129–149. https://doi.org/10.4239/wjd.v13.i3.129

Anagnostis, P., Tarlatzis, B. C., & Kauffman, R. P. (2018). Polycystic ovarian syndrome (PCOS): Long-term metabolic consequences. *Metabolism*, *86*, 33–43. https://doi.org/10.1016/j.metabol.2017.09.016

Armeni, E., & Lambrinoudaki, I. (2022). Menopause androgens and cardiovascular aging: a narrative review. *Therapeutic Advances in Endocrinology and Metabolism*, *13*, 204201882211299. https://doi.org/10.1177/20420188221129946

Bajuk Studen, K., & Pfeifer, M. (2018). Cardiometabolic risk in polycystic ovary syndrome. *Endocrine Connections*, *7*(7), R238–R251. https://doi.org/10.1530/ec-18-0129

Barrett-Connor, E. (2013). Why Women Have Less Heart Disease than Men and How Diabetes Modifies Women's Usual Cardiac Protection: A 40-Year Rancho Bernardo Cohort Study. *Global Heart*, *8*(2), 95. https://doi.org/10.1016/j.gheart.2012.12.002

Berbrier, D. E., Leone, C. A., Adler, T. E., Bender, J. R., Taylor, H. S., Stachenfeld, N. S., & Usselman, C. W. (2023). Effects of androgen excess and body mass index on endothelial function in women with polycystic ovary syndrome. *Journal of Applied Physiology*, *134*(4), 868–878. https://doi.org/10.1152/japplphysiol.00583.2022

Berni, T. R., Morgan, C. L., & Rees, D. A. (2021). Women With Polycystic Ovary Syndrome Have an Increased Risk of Major Cardiovascular Events: a Population Study. *The Journal of Clinical Endocrinology & Metabolism*, *106*(9), e3369–e3380. https://doi.org/10.1210/clinem/dgab392

Bickerton, A. S. T., Clark, N., Meeking, D., Shaw, K. M., Crook, M., Lumb, P., Turner, C., & Cummings, M. H. (2005). Cardiovascular risk in women with polycystic ovarian syndrome (PCOS). *Journal of Clinical Pathology*, *58*(2), 151–154. https://doi.org/10.1136/jcp.2003.015271

Brzozowska, M., & Lewiński, A. (2020). Changes of androgens levels in menopausal women. *Menopausal Review*, *19*(4), 151–154. https://doi.org/10.5114/pm.2020.101941

Chang, A. Y., Oshiro, J., Ayers, C., & Auchus, R. J. (2016). Influence of race/ethnicity on cardiovascular risk factors in polycystic ovary syndrome, the Dallas Heart Study. *Clinical Endocrinology*, *85*(1), 92–99. https://doi.org/10.1111/cen.12986

Cibula, D. (2000). Increased risk of non-insulin dependent diabetes mellitus, arterial hypertension and coronary artery disease in perimenopausal women with a history of the polycystic ovary syndrome. *Human Reproduction*, *15*(4), 785–789. https://doi.org/10.1093/humrep/15.4.785

Cupisti, S., Dittrich, R., Binder, H., Kajaia, N., Hoffmann, I., Maltaris, T., Beckmann, M., & Mueller, A. (2007). Influence of Body Mass Index on Measured and Calculated Androgen Parameters in Adult Women with Hirsutism and PCOS. *Experimental and Clinical Endocrinology & Diabetes*, *115*(06), 380–386. https://doi.org/10.1055/s-2007-970163

Dadachanji, R., Shaikh, N., & Mukherjee, S. (2018). Genetic Variants Associated with Hyperandrogenemia in PCOS Pathophysiology. *Genetics Research International*, *2018*, 1–12. https://doi.org/10.1155/2018/7624932

De Oliveira Dos Santos, A. R., De Oliveira Zanuso, B., Miola, V. F. B., Barbalho, S. M., Santos Bueno, P. C., Flato, U. A. P., Detregiachi, C. R. P., Buchaim, D. V., Buchaim, R. L., Tofano, R. J., Mendes, C. G., Tofano, V. A. C., & Dos Santos Haber, J. F. (2021). Adipokines, Myokines and Hepatokines: Crosstalk and Metabolic Repercussions. *International Journal of Molecular Sciences*, *22*(5), 2639. https://doi.org/10.3390/ijms22052639

Dewani, D., Karwade, P., & Mahajan, K. S. (2023). The Invisible Struggle: The Psychosocial Aspects of Polycystic Ovary Syndrome. *Cureus*, *15*(12). https://doi.org/10.7759/cureus.51321

Ding, D.-C., Tsai, I.-J., Wang, J.-H., Lin, S.-Z., & Sung, F.-C. (2018). Coronary artery disease risk in young women with polycystic ovary syndrome. *Oncotarget*, *9*(9), 8756–8764. https://doi.org/10.18632/oncotarget.23985

Ding, H., Zhang, J., Zhang, F., Zhang, S., Chen, X., Liang, W., & Xie, Q. (2021). Resistance to the Insulin and Elevated Level of Androgen: A Major Cause of Polycystic Ovary Syndrome. *Frontiers in Endocrinology*, *12*, 741764. https://doi.org/10.3389/fendo.2021.741764

Duică, F., Dănilă, C. A., Boboc, A. E., Antoniadis, P., Condrat, C. E., Onciul, S., Suciu, N., Creţoiu, S. M., Varlas, V. N., & Creţoiu, D. (2021). Impact of Increased Oxidative Stress on Cardiovascular Diseases in Women with Polycystic Ovary Syndrome. *Frontiers in Endocrinology*, *12*, 614679. https://doi.org/10.3389/fendo.2021.614679

Elsayed, A. M., Al-Kaabi, L. S., Al-Abdulla, N. M., Al-Kuwari, M. S., Al-Mulla, A. A., Al-Shamari, R. S., Alhusban, A. K., AlNajjar, A. A., & Doi, S. A. R. (2023). Clinical Phenotypes of PCOS: a Cross-Sectional Study. *Reproductive Sciences*, *30*(11), 3261–3272. https://doi.org/10.1007/s43032-023-01262-4

Farhadi-Azar, M., Behboudi-Gandevani, S., Rahmati, M., Mahboobifard, F., Khalili Pouya, E., Ramezani Tehrani, F., & Azizi, F. (2022). The Prevalence of Polycystic Ovary Syndrome, Its Phenotypes and Cardio-Metabolic Features in a Community Sample of Iranian Population: Tehran Lipid and Glucose Study. *Frontiers in Endocrinology*, *13*, 825528. https://doi.org/10.3389/fendo.2022.825528

Fu, L., Xie, N., Qu, F., Zhou, J., & Wang, F. (2023). The Association between Polycystic Ovary Syndrome and Metabolic Syndrome in Adolescents: A Systematic Review and Meta-analysis. *Reproductive Sciences*, *30*(1), 28–40. https://doi.org/10.1007/s43032-022-00864-8

Gutiérrez-Cuevas, J., Santos, A., & Armendariz-Borunda, J. (2021). Pathophysiological Molecular Mechanisms of Obesity: A Link between MAFLD and NASH with Cardiovascular Diseases. *International Journal of Molecular Sciences*, *22*(21), 11629. https://doi.org/10.3390/ijms222111629

Harada, M. (2022). Pathophysiology of polycystic ovary syndrome revisited: Current understanding and perspectives regarding future research. *Reproductive Medicine and Biology*, *21*(1), e12487. https://doi.org/10.1002/rmb2.12487

Herman, R., Sikonja, J., Jensterle, M., Janez, A., & Dolzan, V. (2023). Insulin Metabolism in Polycystic Ovary Syndrome: Secretion, Signaling and Clearance. *International Journal of Molecular Sciences*, *24*(4), 3140. https://doi.org/10.3390/ijms24043140

Hyderali, B. N., & Mala, K. (2015). Oxidative stress and cardiovascular complications in polycystic ovarian syndrome. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, *191*, 15–22. https://doi.org/10.1016/j.ejogrb.2015.05.005

Jurczewska, J., Ostrowska, J., Chełchowska, M., Panczyk, M., Rudnicka, E., Kucharski, M., Smolarczyk, R., & Szostak-Węgierek, D. (2023). Abdominal Obesity in Women with Polycystic Ovary Syndrome and Its Relationship with Diet, Physical Activity and Insulin Resistance: A Pilot Study. *Nutrients*, *15*(16), 3652. https://doi.org/10.3390/nu15163652

Kamińska, M. S., Schneider-Matyka, D., Rachubińska, K., Panczyk, M., Grochans, E., & Cybulska, A. M. (2023). Menopause Predisposes Women to Increased Risk of Cardiovascular Disease. *Journal of Clinical Medicine*, *12*(22), 7058. https://doi.org/10.3390/jcm12227058

Kim, J. K. (2009). Hyperinsulinemic–Euglycemic Clamp to Assess Insulin Sensitivity *In Vivo*. In *Type 2 Diabetes* (Vol. 560, pp. 221–238). Humana Press. https://doi.org/10.1007/978-1-59745-448-3_15

Koizume, S., & Miyagi, Y. (2017). Potential Coagulation Factor-Driven Pro-Inflammatory Responses in Ovarian Cancer Tissues Associated with Insufficient O_2 and Plasma Supply. *International Journal of Molecular Sciences*, *18*(4), 809. https://doi.org/10.3390/ijms18040809

Krentz, A. J., von Mühlen, D., & Barrett-Connor, E. (2007). Searching for polycystic ovary syndrome in postmenopausal women. *Menopause*, *14*(2), 284–292. https://doi.org/10.1097/gme.0b013e31802cc7ab

Lavor, C. B. H., Viana Júnior, A. B., & Medeiros, F. das C. (2022). Polycystic Ovary Syndrome and Metabolic Syndrome: Clinical and Laboratory Findings and Non-Alcoholic Fatty Liver Disease Assessed by Elastography. *Revista Brasileira de Ginecologia e Obstetrícia / RBGO Gynecology and Obstetrics*, *44*(03), 287–294. https://doi.org/10.1055/s-0041-1741032

Lenart-Lipińska, M., Matyjaszek-Matuszek, B., Woźniakowska, E., Solski, J., Tarach, J. S., & Paszkowski, T. (2014). Polycystic ovary syndrome: clinical implication in perimenopause. *Menopausal Review*, *6*, 348–351. https://doi.org/10.5114/pm.2014.47988

Li, X., Ren, Y., Chang, K., Wu, W., Griffiths, H. R., Lu, S., & Gao, D. (2023). Adipose tissue macrophages as potential targets for obesity and metabolic diseases. *Frontiers in Immunology*, *14*, 1153915. https://doi.org/10.3389/fimmu.2023.1153915

Liao, W.-T., Huang, J.-Y., Lee, M.-T., Yang, Y.-C., & Wu, C.-C. (2022). Higher risk of type 2 diabetes in young women with polycystic ovary syndrome: A 10-year retrospective cohort study. *World Journal of Diabetes*, *13*(3), 240–250. https://doi.org/10.4239/wjd.v13.i3.240

Lin, Y.-W., Wang, J.-Y., & Lin, M.-H. (2021). Stroke risk associated with NSAIDs uses in women with dysmenorrhea: A population-based cohort study. *PLOS ONE*, *16*(11), e0259047. https://doi.org/10.1371/journal.pone.0259047

Livadas, S., Anagnostis, P., Bosdou, J. K., Bantouna, D., & Paparodis, R. (2022). Polycystic ovary syndrome and type 2 diabetes mellitus: A state-of-the-art review. *World Journal of Diabetes*, *13*(1), 5–26. https://doi.org/10.4239/wjd.v13.i1.5

López-Alarcón, M., Vital-Reyes, V. S., Almeida-Gutiérrez, E., Maldonado-Hernández, J., Flores-Chávez, S., Domínguez-Salgado, J. M., Vite-Bautista, J., Cruz-Martínez, D., Barradas-Vázquez, A. S., & Z'Cruz-López, R. (2023). Obesity and Hyperandrogenemia in Polycystic Ovary Syndrome: Clinical Implications. *Journal of Personalized Medicine*, *13*(9), 1319. https://doi.org/10.3390/jpm13091319

Madhu, K., Manjunath, C., Rawal, J., & Irani, P. (2013). Atherogenic dyslipidemia. *Indian Journal of Endocrinology and Metabolism*, *17*(6), 969–976. https://doi.org/10.4103/2230-8210.122600

Mahajan, N., & Sharma, S. (2021). Polycystic ovarian syndrome and menopause in forty plus women. *Journal of Mid-Life Health*, *12*(1), 3–7. https://doi.org/10.4103/jmh.jmh_8_21

Mansour, A., Mirahmad, M., Mohajeri-Tehrani, M. R., Jamalizadeh, M., Hosseinimousa, S., Rashidi, F., Asili, P., & Sajjadi-Jazi, S. M. (2023). Risk factors for insulin resistance related to polycystic ovarian syndrome in Iranian population. *Scientific Reports*, *13*(1), 10269. https://doi.org/10.1038/s41598-023-37513-2

Mirza, F. G., Tahlak, M. A., Hazari, K., Khamis, A. H., & Atiomo, W. (2023). Prevalence of Polycystic Ovary Syndrome amongst Females Aged between 15 and 45 Years at a Major Women's Hospital in Dubai, United Arab Emirates. *International Journal of Environmental Research and Public Health*, *20*(9), 5717. https://doi.org/10.3390/ijerph20095717

Moin, A. S. M., Sathyapalan, T., Atkin, S. L., & Butler, A. E. (2022). Inflammatory Markers in Non-Obese Women with Polycystic Ovary Syndrome Are Not Elevated and Show No Correlation with Vitamin D Metabolites. *Nutrients*, *14*(17), 3540. https://doi.org/10.3390/nu14173540

Naz, R. K. (2014). Polycystic ovary syndrome current status and future perspective. *Frontiers in Bioscience*, *E6*(1), 104–119. https://doi.org/10.2741/e695

Ndefo, U. A., Eaton, A., & Green, M. R. (2013). Polycystic ovary syndrome: a review of treatment options with a focus on pharmacological approaches. *Pharmacy and Therapeutics*, *38*(6), 336. https://doi.org/10.1186/s12905-020-00919-5

Patel, S. M., Ratcliffe, S. J., Reilly, M. P., Weinstein, R., Bhasin, S., Blackman, M. R., Cauley, J. A., Sutton-Tyrrell, K., Robbins, J., Fried, L. P., & Cappola, A. R. (2009). Higher Serum Testosterone Concentration in Older Women is Associated with Insulin Resistance, Metabolic Syndrome and Cardiovascular Disease. *The Journal of Clinical Endocrinology & Metabolism*, *94*(12), 4776–4784. https://doi.org/10.1210/jc.2009-0740

Profili, N. I., Castelli, R., Gidaro, A., Manetti, R., Maioli, M., Petrillo, M., Capobianco, G., & Delitala, A. P. (2024). Possible Effect of Polycystic Ovary Syndrome (PCOS) on Cardiovascular Disease (CVD): An Update. *Journal of Clinical Medicine*, *13*(3), 698. https://doi.org/10.3390/jcm13030698

Raj, A., Chakole, S., Agrawal, S., Gupta, A., Khekade, H., Prasad, R., Lohakare, T., & Wanjari, M. (2023). The Impact of Menopause on Cardiovascular Aging: A Comprehensive Review of Androgen Influences. *Cureus*, *15*(8), e43569. https://doi.org/10.7759/cureus.43569

Rojas, J., Chávez, M., Olivar, L., Rojas, M., Morillo, J., Mejías, J., Calvo, M., & Bermúdez, V. (2014). Polycystic Ovary Syndrome, Insulin Resistance and Obesity: Navigating the Pathophysiologic Labyrinth. *International Journal of Reproductive Medicine*, *2014*, 1–17. https://doi.org/10.1155/2014/719050

Rudnicka, E., Suchta, K., Grymowicz, M., Calik-Ksepka, A., Smolarczyk, K., Duszewska, A. M., Smolarczyk, R., & Meczekalski, B. (2021). Chronic Low Grade Inflammation in Pathogenesis of PCOS. *International Journal of Molecular Sciences*, *22*(7), 3789. https://doi.org/10.3390/ijms22073789

Sangaraju, S. L., Yepez, D., Grandes, X. A., Talanki Manjunatha, R., & Habib, S. (2022). Cardio-Metabolic Disease and Polycystic Ovarian Syndrome (PCOS): A Narrative Review. *Cureus*, *14*(5). https://doi.org/10.7759/cureus.25076

Shabbir, S., Khurram, E., Moorthi, V. S., Eissa, Y. T. H., Kamal, M. A., & Butler, A. E. (2023). The interplay between androgens and the immune response in polycystic ovary syndrome. *Journal of Translational Medicine*, *21*(1), 259. https://doi.org/10.1186/s12967-023-04116-4

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. https://doi.org/10.3390/jcm12041454

Soares-Jr, J. M., Sá, M. F. S. de, & Baracat, E. C. (2019). New Criteria for the Clinical Diagnosis of Hyperandrogenism in Polycystic Ovarian Syndrome and the Risk of Overdiagnosis. *Revista Brasileira de Ginecologia e Obstetrícia / RBGO Gynecology and Obstetrics*, *41*(06), 361–362. https://doi.org/10.1055/s-0039-1693530

Van Der Burgh, A. C., Khan, S. R., Neggers, S. J. C. M. M., Hoorn, E. J., & Chaker, L. (2022). The role of serum testosterone and dehydroepiandrosterone sulfate in kidney function and clinical outcomes in chronic kidney disease: a systematic review and meta-analysis. *Endocrine Connections*, *11*(6). https://doi.org/10.1530/ec-22-0061

Wang, Y.-X., Arvizu, M., Rich-Edwards, J. W., Stuart, J. J., Manson, J. E., Missmer, S. A., Pan, A., & Chavarro, J. E. (2020). Menstrual cycle regularity and length across the reproductive lifespan and risk of premature mortality: prospective cohort study. *BMJ*, *371*, m3464. https://doi.org/10.1136/bmj.m3464

Wild, R. A., Rizzo, M., Clifton, S., & Carmina, E. (2011). Lipid levels in polycystic ovary syndrome: systematic review and meta-analysis. *Fertility and Sterility*, *95*(3), 1073-1079.e11. https://doi.org/10.1016/j.fertnstert.2010.12.027

Witchel, S. F., Oberfield, S. E., & Peña, A. S. (2019). Polycystic Ovary Syndrome: Pathophysiology, Presentation and Treatment with Emphasis on Adolescent Girls. *Journal of the Endocrine Society*, *3*(8), 1545–1573. https://doi.org/10.1210/js.2019-00078

Wu, C.-H., Chiu, L.-T., Chang, Y.-J., Lee, C.-I., Lee, M.-S., Lee, T.-H., & Wei, J. C.-C. (2020). Hypertension Risk in Young Women with Polycystic Ovary Syndrome: A Nationwide Population-Based Cohort Study. *Frontiers in Medicine*, *7*, 574651. https://doi.org/10.3389/fmed.2020.574651

Xu, Y., & Qiao, J. (2022). Association of Insulin Resistance and Elevated Androgen Levels with Polycystic Ovarian Syndrome (PCOS): A Review of Literature. *Journal of Healthcare Engineering*, *2022*(1), 1–13. https://doi.org/10.1155/2022/9240569

Ye, W., Xie, T., Song, Y., & Zhou, L. (2021). The role of androgen and its related signals in PCOS. *Journal of Cellular and Molecular Medicine*, *25*(4), 1825–1837. https://doi.org/10.1111/jcmm.16205

Zatterale, F., Longo, M., Naderi, J., Raciti, G. A., Desiderio, A., Miele, C., & Beguinot, F. (2020). Chronic Adipose Tissue Inflammation Linking Obesity to Insulin Resistance and Type 2 Diabetes. *Frontiers in Physiology*, *10*, 1607. https://doi.org/10.3389/fphys.2019.01607

Zhao, D., Guallar, E., Ouyang, P., Subramanya, V., Vaidya, D., Ndumele, C. E., Lima, J. A., Allison, M. A., Shah, S. J., Bertoni, A. G., Budoff, M. J., Post, W. S., & Michos, E. D. (2018). Endogenous Sex Hormones and Incident Cardiovascular Disease in Post-Menopausal Women. *Journal of the American College of Cardiology*, *71*(22), 2555–2566. https://doi.org/10.1016/j.jacc.2018.01.083

Zhao, H., Zhang, J., Cheng, X., Nie, X., & He, B. (2023). Insulin resistance in polycystic ovary syndrome across various tissues: an updated review of pathogenesis, evaluation and treatment. *Journal of Ovarian Research*, *16*(1), 9. https://doi.org/10.1186/s13048-022-01091-0