Cardio-metabolic risk factors in polycystic ovary syndrome

Tehrani, F. R. & Behboudi-Gandevani, S.

Published in: Cardiometabolic Diseases and Risk Factors

Available online: July 2020

Citation:
Tehrani, F. R. & Behboudi-Gandevani, S. (2020). Cardio-metabolic risk factors in polycystic ovary syndrome. In Ralston, P. (Ed.), Cardiometabolic diseases and risk factors (p. 43-85). Nova Science Publishers.

Chapter

CARDIO-METABOLIC RISK FACTORS IN POLYCYSTIC OVARY SYNDROME

Fahimeh Ramezani Tehrani[1,*] MD
and Samira Behboudi-Gandevani[2], PhD

[1]Reproductive Endocrinology Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[2]Faculty of Nursing and Health Sciences, Nord University, Bodø, Norway

ABSTRACT

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders with an estimated prevalence of 7% to14% among reproductive-aged women. Although the exact underlying etiology of PCOS is not entirely clear, however, evidence has shown that insulin resistance, hyperandrogenemia and adipose tissue dysregulation play key roles on its pathogenesis. The syndrome is recognized as a cardio-metabolic disorder. Data have shown that traditional cardiovascular and

[*] Corresponding Author's Email: fah.tehrani@gmail.com; ramezani@endocrine.ac.ir.

metabolic risk factors including hypertension, dyslipidemia, metabolic syndrome, obesity and central obesity, glucose intolerance and diabetes are more prevalent among PCOS patients. In addition, subclinical cardiovascular markers such as coronary artery calcium scores, C-reactive protein, carotid intima-media thickness and endothelial dysfunction are more likely to be increased in women with PCOS. Nevertheless, there is much more controversy regarding whether cardio-metabolic events are increased in PCOS in later life, leaving many issues regarding cardiovascular and metabolic events unresolved. This chapter will discuss the literature on PCOS and cardio-metabolic risk factors and provides recommendations that would be helpful for healthcare provider and policy makers in the monitoring and management of these risk factors in PCOS population. Treatment options are beyond the scope of this chapter.

Keywords: cardio-metabolic risk factors, polycystic ovary syndrome (PCOS), cardio vascular diseases (CVD)

1. INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder, with an estimated prevalence of 7% to 20% among women of reproductive age [1-3]. Heterogeneous by nature, the syndrome is characterized by a combination of signs and symptoms of ovarian dysfunction (including oligo/anovulation, and/or polycystic ovarian morphology (PCOM)) and androgen excess (including hyperandrogenemia and/or hyperandrogenism), after the exclusion of other related disorders [4, 5].

The exact underlying etiology and pathogenesis of PCOS remains largely unknown, but it seems to be a complex interactions between multifactorial components of genetic, epigenetic, environmental and lifestyle factors [6, 7]. The imbalance in sex hormones and insulin resistance (IR) are considered to be a main factor of the reproductive and metabolic abnormalities in PCOS [8, 9]. Insulin resistance with compensatory increased insulin production contributes to hyperandro-genemia due to the augmentation of ovarian androgen production and the inhibition of hepatic sex hormone-binding globulin secretion [5]. Moreover, PCOS is closely

linked to adipose tissue dysregulation [10], which is characterized by hypertrophic adipocytes and impairments in lipolysis and insulin action [11, 12]. Further, chronic low grade inflammation [13, 14] and excessive formation of oxidative stress [15, 16] have been actively implicated in the etiology of the syndrome.

Data have shown that traditional cardiovascular/metabolic risk factors such as obesity and central obesity [17, 18], increased carotid intima media thickness [19, 20] and coronary artery calcifications [21] are more common among women with PCOS compared with the age-matched women without the syndrome.

However, despite the presence of cardiovascular risk factors and increased surrogate markers of cardiovascular disease, it is not clearly understood whether PCOS patients have accelerated atherosclerosis or other cardiovascular events and also greater mortality, the latter mainly because of a lack of long term endpoint studies.

This chapter addresses, summarizes, and discusses salient data from the existing literature, including gaps and uncertainties, aspects, and mechanisms related to the spectrum of adverse cardiometabolic profile factors in women with PCOS.

This chapter outlines, summarizes, and discusses salient data from the existing literature, including gaps and uncertainties, latest advances and current limitations and mechanisms related to the spectrum of cardiometabolic aspects in PCOS.

1.1. Definition of PCOS

Some sets of criteria for diagnosis have been proposed for PCOS. At the first time, National Institutes of Health (NIH) in 1990 introduce the PCOS diagnosis criteria including only presence of clinical and/or biochemical hyperandrogenism and oligo/anovulation [22]. Later, two international consensus have developed adult diagnostic criteria that broaden the definition beyond NIH criteria by incorporating the presence of polycystic ovary morphology [23, 24] as a diagnostic criterion for PCOS. Rotterdam

criteria in 2003 are the broadest and encompass all combinations and require two of three features including oligo/anovulation, clinical and/or biochemical hyperandrogenism and PCOM in ultrasound assessment [25]. Androgen Excess-PCOS (AE-PCOS) Society criteria in 2006 encompass otherwise unexplained hyperandrogenism with either oligo/anovulation or PCOM [23].

In addition, the presentation of PCOS reflects at least four possible phenotypes (Phenotypes A–D) depending on the presence or absence of three general features of oligo-anovulation, androgen excess and polycystic ovarian morphology) [26]

- Phenotype A: Hirsutism/hyperandrogenemia + Ovulatory dysfunction + Polycystic ovaries (classic combination of all the reproductive endocrine features)
- Phenotype B: Hirsutism/hyperandrogenemia + Ovulatory dysfunction
- Phenotype C: Hirsutism/hyperandrogenemia + Polycystic ovaries
- Phenotype D: Ovulatory dysfunction + Polycystic ovaries

Whether these phenotypes represent a continuum of the same condition, but PCOS phenotypes with hyperandrogenism and oligo/ anovulation had the worst metabolic presentations in terms of insulin resistance, diabetes, obesity, metabolic syndrome and cardiovascular disease [27-29]. However, further characterization of PCOS phenotypic differences is an important area for ongoing research.

The diagnosis of PCOS in adolescent female populations is complicating, since adolescence is a transitional stage of physical and psychological development and functional variations in the hypothalamic-pituitary-ovarian axis during normal puberty leads to changes in reproductive hormones and menstrual patterns that mimic some of the features of PCOS. Moreover, many of the PCOS features may evolve over time and change during the first few years after menarche. There is no consensus on precise diagnosis of PCOS in adolescents [30] Therefore, international consensus have endorsed more stringent criteria including

using all three components of the Rotterdam criteria [31] or using NIH criteria for diagnosis of PCOS in adolescents [32]. However, precise definition of PCOS in adolescent is essential, since associated cardiometabolic morbidity such as obesity, insulin resistance and dyslipidemia may benefit from early intervention approaches.

1.2. Pathogenesis of Polycystic Ovary Syndrome

PCOS is a multifactorial disease. The interaction between genetic predisposition, intra-uterine (prenatal) and postnatal environmental factors may comprise in development of PCOS [6, 7, 33].

Although, the genes that are involved in the etiology of the syndrome have not been fully understood yet, the role of genetic factors in PCOS is strongly supported [34-38]. Studies of twins in which women with monozygotic twin sisters affected by PCOS and also first-degree relatives of women with PCOS were shown to have higher the risk of developing PCOS features and metabolic disturbances, which suggests a genetic background effect and familial condition. Although there are low external validity, gene variants of lots of coding genes associated with the clinical and laboratory features of PCOS have been demonstrated in these populations [39]. In addition, some genes have shown altered expression indicating that the genetic abnormality in PCOS affects signal transduction pathways regulating insulin, gonadotrophin and steroid hormones action and production as well as energy homeostasis, chronic inflammation and others [40].

In addition, environmental factors potentially could involve in PCOS development which are classified as prenatal intra-uterine developmental programming and postnatal factors [41-43]. Evidence suggests that environmental stimuli can both mimic hormonal actions and activate pre-existing, predisposing factors that trigger the endocrine activity characteristic of PCOS [6]. Glucocorticoids excess during critical period of fetal development, either by the fetal origin (resulting from fetal hypoxia and IUGR) [44, 45] or maternal source (resulting from elevation of endogenous

or exogenous maternal androgen levels during pregnancy) [46, 47] may related to PCOS developmental programming. It may lead to functional changes in organs, endocrine pathways and subsequently clinical, metabolic and reproductive changes during postnatal life [48]. In this respect, it is demonstrated that sexual function of women whose mothers also had PCOS and therefore potentially may had prenatal androgen exposure, was significantly decreased compared to women whose mothers did not [49]. In addition, postnatal factors including diet and nutrition, obesity, sedentary lifestyle, environmental toxins, medications and social and economic factors may play a role in development of PCOS [42].

1.3. PCOS and Traditional Cardio-Metabolic Risk Factors

1.3.1. Insulin Resistance, Glucose Intolerance and Diabetes Mellitus

Insulin resistance play a key role in the metabolic manifestations among women with PCOS which is independent of BMI and obesity [50]. The prevalence of IR among women with PCOS is estimated around 30% and 70%, based on the women's age, obesity status and ethnicity [51]. In this respect, older age, higher BMI and Hispanic ethnicity exacerbates IR to a greater extent in women with than those without PCOS, irrespective of the definition used [8, 50, 52]. However, it is well documented that high testosterone and low sex hormone-binding globulin (SHBG) concentrations are independently associated with IR [53-55]. It has been shown that the PCOS phenotypes with hyperandrogenism are strongly associated with insulin resistant, irrespective of BMI or central adiposity [9, 56, 57]. Additionally, it seems that despite common genetic variations at the diabetes related loci in PCOS and non PCOS women, the association between IR and diabetogenic polymorphisms may be affected by PCOS status [58]

There are several underlying mechanisms have been proposed for the development of IR in PCOS including (i) an increase in serine phosphorylation that causes post-binding defects in insulin signalling [59], and disturbances in the tyrosine phosphorylation of insulin receptors and insulin receptor substrate-1 that affects metabolic pathways in classic insulin

targets mainly adipocytes, skeletal muscles and ovaries [59], (ii) reduced insulin receptor-β abundance in omental adipose tissue, reduced glucose transporter 4 (GLUT4) in subcutaneous adipocytes, both leading to reduction in glucose uptake, (iii) reduced hepatic clearance of insulin, (iv) mitochondrial dysfunction, constitutive activation of serine kinases in the mitogen-activated protein kinase/extracellular signal-regulated kinases pathway [59], (v) genetic disruption of insulin signalling in the central nervous system (vi) chronic low-grade inflammation with increased tumor necrosis factor-alpha (TNF-α) secretion from mononuclear cells [60, 61] (vii) increased iron tissue depots due to chronic oligo/anovulation that lead to impair insulin secretion by oxidative damage of β cells and decrease insulin clearance and muscle glucose uptake [62, 63]. However, increased level of insulin due to the both increased insulin production and reduced insulin clearance in liver, could induce higher androgen secretion. Hyperandrogenemia *per se* could change insulin action in the target tissues leading to increase visceral adiposity in PCOS women [64].

It should be noted that IR and hyperinsulinemia may play further important roles in the modulation of cardiovascular risk. Insulin resistance may lead to disturbance in natriuretic peptides (NP) which are secreted from cardiomyocytes and directly influence blood pressure, body fluid homeostasis, and various metabolic functions including lipolytic activity [65, 66]. Insulin increases the expression of NP clearance receptor in adipose tissue, independent of glycemia [67-69].

Although there is some variability in reports of the prevalence of prediabetes and DM among women with PCOS, most studies agree that women with PCOS have a higher prevalence of impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and DM, especially among the obese. [3, 70-73]. In a prospective study of 254 PCOS women, it is showed that that 31% of PCOS patients had impaired glucose intolerance, and 7.5% had diabetes; a 3- to 7-fold higher than the age-comparable population, and around a 2-fold higher risk compared with age- and BMI-comparable women with normal cycles [74]. In another long term population based prospective study among 178 women with PCOS and 1524 eumenorrheic, non-hirsute, healthy women, it is showed that the risk of developing diabetes

and prediabetes in young women with PCOS is 4.9 and 1.7 times higher, respectively, than in the general female population after adjustment for potential related confounders. In contrast, those hazard differences between PCOS and controls disappeared in their late reproductive years [70]. A recent systematic review and meta-analysis of 40 quality studies found women with PCOS had an increased prevalence of impaired glucose tolerance (IGT) (OR = 3.26, 95% CI: 2.17-4.90) and T2DM (OR = 2.87, 95% CI: 1.44-5.72), which differed by ethnicity (for IGT, Asia: 5-fold, the Americas: 4-fold and Europe: 3-fold), was higher with obesity [73].

Taken together, the findings support close monitoring, with screening for T2DM in women with PCOS [75]. In this respect, the Endocrine Society [32] and ESHRE/ASRM [25] recommended the use of OGTT in all adolescents and adult women with PCOS. Nevertheless, there is no evidence on the optimal time for serial screening, but it has been arbitrarily suggested every three to five years, except for an earlier worsening in clinical symptomatology [32]. Reciprocally, the European Society of Endocrinology (ESE) in 2014 endorsed an oral glucose tolerance test (OGTT) in all obese and lean women with PCOS older than 40 years, with a positive history of GDM or family history of T2DM [76].

1.3.2. Dyslipidemia

There are many studies showed that dyslipidemia is one of the common feature of metabolic disturbances among women with PCOS [59, 77]. A meta-analysis in 2011 reported that PCOS patients had 26.39 (95% CI 17.24, 35.54) mg/dl higher TG levels, 6.41 (95% CI 3.69, 9.14) mg/dl lower HDL-C and 18.82 (95% CI 15.53, 22.11) mg/dl higher non- HDL-C levels compared with age matched controls. LDL-C levels were also higher even in studies with BMI matching [8.32 mg/dl, 95% CI (5.82,10.81] [78].

The exact underlying mechanisms that involved to developing dyslipidemia in PCOS are not clearly described, but it has been hypothesized that the intertwined effects of obesity, insulin resistance and hyperandrogenism induce dyslipidemia among women with PCOS [79-81].

The mechanisms by which obesity is associated with dyslipidemia in women with PCOS include insulin resistance, overproduction of VLDL,

abnormal lipoprotein lipase-mediated lipolysis and a defect in the insulin-signaling pathway mediated by an overexpression of PI3KR1 gene [81]. Androgens decrease catabolic removal of LDL by attenuating estrogen receptor-mediated induction of LDL receptor activity and also upregulate of genes responsible for catabolism of HDL [81, 82]. In addition, IR leads to hepatic overproduction of apolipoprotein B-containing VLDL and hypertriglyceridemia [81, 82]. In particular, IR increases the production of VLDL, decreases the elimination of VLDL and chilomicrons from the circulation and increases the clearance of apolipoprotein A, the major component of HDL-C [83, 84].

Those lipid metabolic dysfunction in women with PCOS definitely exaggerates the risk for cardiovascular disease (CVD) with aging [79].

Although various patterns of dyslipidemia have been described, the most common profile mong women with PCOS is generally characterized by increased serum concentration of low density lipoprotein cholesterol (LDL-C) and very-low density lipoprotein cholesterol (VLDL-C), triglyceride (TG) and free fatty acid, as well as decreased serum level of high density lipoprotein cholesterol (HDL-C), particularly HDL2-C, due to reduced apolipoprotein A-I (apoA-I) [59, 85] and higher level of oxidized LDL-C, independent of BMI, [86]. However, this atherogenic profile is exacerbated by increased BMI and IR. However, the lipoprotein profile in PCOS is therefore similar to that seen in T2DM patients [51]. Therefore, it is worth noting that lipid pattern in women with PCOS is only modestly more atherogenic compared with healthy women with similar BMI [51].

However, there are some concerns that most of those available evidence usually derived from clinical-based studies with small sample sizes, lacked appropriate control groups, used heterogeneous diagnostic criteria, and did not adjust potential confounders. Moreover, clinical-based studies might be misleading; they present severe phenotypes of PCOS women referred for treatment. On the other hand, a population-based study might include younger, lower BMI women with less severe phenotypes that might have never been referred.

However, long-term population-based cohort study, did not confirmed the higher risk of dyslipidemia compared to general population [4].

However, population based studies with larger sample sizes and long term follow up are still recommended to show whether these risks reemerge later in life.

1.3.3. Hypertension

There are some evidence showed that blood pressure, particularly systolic blood pressure may increase in PCOS patients [51]. In this respect, Obesity and insulin resistance are considered key factors for the alteration of blood pressure in women with PCOS [87]. Insulin resistance and compensatory hyperinsulinemia in PCOS leads to an imbalance in the autonomic nervous system, increased renal sodium reabsorption, as well as a reduction in the production of nitric oxide [88, 89]. As well, it could interfere with the endothelium-dependent vasodilatation mechanisms causing vascular muscle wall hypertrophy [90, 91]. Obesity and central obesity as most prevalent feature in PCOS, lead to metabolic, endothelial and vascular dysfunction, neuroendocrine imbalances, sodium retention, glomerular hyperfiltration, proteinuria, and maladaptive immune and inflammatory responses; all associated with hypertension [92] among women with PCOS. Endothelial dysfunction is a major forerunner of obesity-related hypertension by impairing control of the vascular tone and by promoting structural changes of the vessel wall [61, 93]. Furthermore, renin-angiotensin system activation [94] due to hyperandrogenism and endothelial dysfunction due to increased endothelin-1 levels in women with PCOS regardless of BMI [87, 95] may play a role in developing of hypertension in the syndrome.

However, the studies addressing the prevalence of HTN in PCOS had conflicting results. Observational studies reported that the prevalence of hypertension, mainly systolic blood pressure in PCOS women is estimated at 9–25.7%, higher than the general population [96-99]. However, other cohort studies did not confirm a higher incidence of hypertension [4, 100]. A results of meta-analysis confirmed a greater risk of HTN in PCOS patients but demonstrates that this risk is increased only in reproductive age women with PCOS, indicating that after menopause, having a history of PCOS may not be as an important predisposing factor for developing HTN [101].

In conclusion, evidence about whether or not rates of hypertension increase differently over time in women with PCOS is inconclusive. There might be a predisposition of these women to hypertension in later life that may set the milieu for potential accelerated progression of cardiovascular events irrespective of BMI and centripetal obesity [102], the assumption need to be further clarified.

1.3.4. Obesity

Obesity is a key contributor to the clinical and metabolic manifestations of PCOS patients. However, there is little debate about the association between obesity, especially central obesity, and cardiovascular risk factors. Several methods are used to assess the content and distribution of body fat. BMI assessment is commonly used for evaluation of obesity and prediction of adverse cardio-metabolic outcomes as strong predictor for IR and metabolic syndrome [103]. Recently some metabolic parameters of lipids were added to adiposity indices for better prognostic evaluation of cardio-metabolic adverse events. However, less is known regarding the complex adiposity indexes, in women with PCOS. However, there are some studies showed that lipid accumulation product (LAP) [104], visceral adiposity index (VAI) [105] and a body shape index (ABSI) [103] were a good tool for assessing cardiometabolic risk in among PCOS patients.

In this respect, it is well recognized that a large proportion of women with PCOS are suffering from overweight, obesity and central obesity compared with age-matched controls [8, 18, 51, 103]. In a meta-analysis, women with PCOS had two fold higher risk of overweight (RR: 1.95; 95% CI:1.52, 2.50), three fold higher risk of obesity (RR: 2.77; 95% CI: 1.88, 4.10) and two fold central obesity (RR:1.73; 95% CI: 1.31, 2.30) compared to healthy women [106]. Although, magnetic resonance imaging (MRI) in women with PCOS and health controls matched for BMI and fat mass showed no difference in body fat distribution [107, 108], however, increased waist to hip ratio affects between 50-70% of those patients, independent to BMI [10, 109].

In general, Adipose tissue in PCOS is characterized by aberrant cellularity, which probably alters adipose tissue function and most likely

contributes to metabolic disturbances in women with the syndrome. Adipocyte size reflects the balance between triglyceride storage and mobilization [110]. Overweight or obesity in PCOS may be attributable to IR, which leads to hyperinsulinemia that stimulates ovarian steroidogenesis and subsequent reduction in sex hormone-binding globulin (SHBG) [111]. Obesity could also increase the androgens, particularly total testosterone and free androgen index that can lead to the accumulation of visceral fat causing central obesity [80, 112]. In addition, obesity through obesity-related haemodynamic and metabolic abnormalities, leads to increased circulating blood volume, systemic vascular resistance, and activation of SNS and the renin-angiotensin system, that could potentially increase the risk of hypertension and CVD [113, 114]. Moreover, visceral obesity is associated with low-grade inflammation and raised inflammatory cytokines and proinflammatory factors such as TNF-α, interleukin-6 (IL-6) and interleukin-18 (IL-18), which are secreted by activated tissue marcophages infiltrated in adipose tissue, both of which are associated with CVD in patients with PCOS [115-117]. However, all of those alteration are related to metabolic and reproductive disturbances in PCOS patients and strongly influences the severity of its clinical, cardiometabolic, and endocrine disturbances in these women.

1.3.5. Adipokines

PCOS is closely associated with adipose tissue dysfunction [11]. Androgen excess, as experienced by women with PCOS, is often associated with adipocyte hypertrophy and both adipose tissue hypertrophy and hyperandrogenism are strongly associated with IR [11]. As well, Chronic low-grade inflammation in PCOS is also associated with androgen excess and to the hypertrophy of adipocytes, leading to adipose tissue dysfunction and altered secretion of cytokines [118].

Adipose tissue is an active endocrine organ and release a large number of bioactive peptides, involving in the regulation of energy homeostasis, reproduction, insulin action, lipid metabolism and systemic inflammation [119] that is generally called adipokines. Emerging evidence suggest that abnormal production, release or function of adipokines are one of the

important underlying potential mechanisms associated with the increased risk of cardio-metabolic risk factors and IR in PCOS [11, 120-122]. The two main important and well-known of adipokines are adiponectin and leptin.

Adiponectin, as an anti-inflammatory cytokine, is exclusively produced by adipose tissue and plays a role in a variety of functions including the anti-inflammatory, anti-atherogenic mediator, and insulin-sensitizing effects [123]. This peptide, is adversely associated with the adipocyte mass and visceral adiposity [124, 125]. There are some evidence reporting that the serum level of adiponectin was significantly decreased in disorders with IR including obesity, metabolic syndrome, diabetes, and obesity-related cardiovascular diseases [123, 126-128].

In a meta-analysis, it is showed that women with PCOS had significantly lower adiponectin level compared to healthy counterparts regardless of the degree of obesity [123]. Obesity, as a prevalent manifestation of PCOS, can downregulate adiponectin through alterations in the expression of adiponectin receptors and reduces the adiponectin sensitivity. It leads to insulin resistance that in turn aggravates hyperinsulinemia in women with PCOS [129]. In addition, some adiponectin gene polymorphism is more expressed in PCOS, which may be related to the reduced secretion of adiponectin [130].

In contrast to adiponectin, leptin has a central and peripheral regulatory role in energy expenditure regulation, based on to the levels of energy stored as body fat [131]. As such, insulin indirectly regulates the secretion of leptin through its trophic effect on adipocytes by stimulates leptin gene expression [132, 133]. Leptin may also contribute to increased level of androgens by inducing steroidogenesis and inhibiting neuropeptide Y, which leads to increasing serum level of gonadotropin releasing hormone (GnRH) and lutenizing hormone (LH) [59, 134]. Moreover, increased serum level of leptin is associated with systemic inflammation, IR and high risk of atherosclerosis [135, 136]. In a meta-analysis involving 991 women with PCOS and 898 controls, it is revealed the higher leptin concentration in patients with PCOS compared to healthy women (standardized mean difference: 1.62, 95% CI: 1.01-2.23) and obesity exacerbated the increased level of leptin in PCOS patients [137].

However, the profile of most adipokines in PCOS is not still understood and the studies focusing the role on other adipokines are insufficient and controversial. However, exact underlying physiological and pathophysiological function of adipokines in the regulation of obesity and PCOS needs to study the dynamic interaction between adipokines and other potential pathways. In this respect, some adipokines such as adiponectin, leptin, omentin, resistin, irisin, apelin, vaspin, and visfatin are more dependent on obesity and insulin pathways [10, 11, 131, 133, 138-143] and some such as chemerin are more involved in low-grade inflammatory responses [141, 144], even some may participate in both pathways.

However, there is a long way a head to understand the role of adipokines in PCOS, which may act as a link between obesity and PCOS.

1.3.6. Metabolic Syndrome

Metabolic syndrome (MetS) is a cluster of endocrinopathy and metabolic disturbances including hyperglycemia/insulin resistance, central obesity, dyslipidemia and hypertension [145]. Among women, it is diagnosed by the presence of any three of the following criteria including (i) increased waist circumference of ≥90 cm, (ii) increased triglycerides of ≥150 mg/dL, (iii) decreased HDL-C of < 50 mg/dL, (iv) increased blood pressure including ≥130 mmHg for systolic and/or ≥85 mmHg for diastolic and (v) increased fasting glucose ≥100 mg/dL [146].

Women with PCOS potentially have an elevated risk of the individual components of MetS including dyslipidemia, hyperglycemia and hypertension [147-149]. These patients also have increased novel and nontraditional cardiovascular risk factors including elevated carotid intima media wall thickness and coronary artery calcification, increased inflammatory cytokines, endothelial dysfunction, arterial stiffness, carotid or aortic plaque [21, 111, 150-153]. It is suggested that IR in PCOS plays a major role in the pathway of potential pathological mechanisms responsible for the development of MetS in women with PCOS [111, 154, 155]. The potential underlying of clinical manifestations of MetS is debated in this chapter.

However, the results of studies about the risk of MetS in PCOS is controversial. In a meta-analysis, women with PCOS had a higher prevalence of MetS (OR 3.35, 95% CI 2.44, 4.59), particularly in overweight or obese PCOS patients (OR 1.88, 95% 1.16, 3.04) but not in lean women (OR 1.45, 95% CI 0.35, 6.12) [111]. In contrast, in another recent meta-analysis, the odds of MetS had no differences between adults with PCOS compared to healthy controls in population-based studies. These results were confirmed by the subgroup meta- analysis of some studies using age and BMI adjustment/matching [156], indicating that age, BMI and study design can affect the risk of MetS in PCOS.

1.4. PCOS and Non-Traditional Cardio-Metabolic Risk Factors

1.4.1. Hyperandrogenism and Severe PCOS Phenotypes

It is well documented that androgen excess as the most prominent feature in PCOS, *per se*, is also correlated with CVD in female [157]. Hyperandrogenism is closely associated with aggravation of central obesity, IR, atherogenic lipid profile including lowering HDL-C and increasing LDL-C [158, 159] which are the metabolic core for the development of CVD. Although obesity may play a role, but it is demonstrated that testosterone could increase angiotensinogen and renin gene expression which contribute to hypertension [160-162]. Moreover, it have been found to increase the appetite [163], chronic inflammation, and oxidative stress associated with PCOS [164-166]and also involve in anxious and depressed mood states [167, 168]. Along with metabolic effects, androgens directly have adverse effect on vasculature, promoting endothelial dysfunction [169-172] and accelerating atherosclerotic alterations [20, 173].

Women with severe phenotypes PCOS, mainly phenotype A and B who have, seems to have a more adverse cardio-metabolic profile, particularly increased prevalence of glucose intolerance and metabolic syndrome and also worse lipid profile with higher LDL and non-HDL cholesterols compared to milder phenotypes [78, 158, 174, 175]. However, it appear to

be generally related to androgen excess, adiposity and central adiposity in those subPCOS population [158].

1.4.2. Chronic Inflammation

Evidence in support of the presence of chronic low-grade systemic inflammation a as a key contributor to the underlying pathogenesis of PCOS is incontrovertible. There is a genetic basis for the inflammation reported in PCOS [176]. It is demonstrated that women with PCOS have decreased anti-inflammatory agents, such as adiponectin and omentin [105], and increased proinflammatory cytokines such as C-reactive protein (CRP), TNF-α [177-179], interleukin-18, monocyte chemoattractant protein-1, oxidative stress and white blood count are increasing in women with PCOS [13, 179-181], independent of obesity and BMI, consistent with a chronic low-grade inflammatory state. However, chronic inflammation is strongly associated with development, progression, and prognosis of endothelial dysfunction and CV events in PCOS patients [179, 182]. As such, Inflammation is also likely to be associated with other prominent aspects of PCOS including insulin resistance and hyperandrogenism [180, 183]. However, further studies required to clear the role of inflammation in developing CVD in PCOS.

1.4.3. Oxidative Stress

Oxidants are chemical products that tend to gain electrons losing positive charge. They include products of normal cellular metabolism including reactive oxygen species (ROS) and reactive nitrogen species that derive from nitric oxide (RNS). ROS derive from molecular oxygen, and include oxygen ions, free radicals (chemical species with unpaired electrons) and peroxides [184]. Oxidative stress is characterized by as the imbalance between production and scavenging of oxidants and antioxidants [185]. Oxidants excess leads to DNA, cellular lipids and proteins damage, and could disturb their physiological function. Therefore, oxidative stress may involves in many underlying pathophysiology of human pathologic situation as well as in the physiologic process of ageing [186].

Emerging evidence revealed that oxidative circulating markers are significantly increased in patients with PCOS compared to healthy women [187]. In this respect, homocysteine, asymmetric dimethylarginine, and malondialdehyde as a promoters and by-products of oxidative stress are increased in women with PCOS, contrary, glutathione and paraoxonase-1 as antioxidants are decreased in women with PCOS independent of age and BMI [184, 188] which may shows that oxidative stress play an important role in pathophysiology of PCOS.

Obesity, androgen excess, insulin resistance and dyslipidemia in PCOS could induce inflammatory response oxidative stress by increased ROS-related oxidative stress, muscle activity to carry excessive weight, hyperleptinemia, chronic inflammation and inadequate antioxidant defences in PCOS, [189] even in the absence of excess adiposity [190)]. Circulating and molecular markers of oxidative stress and inflammation are also highly correlated with circulating androgens [116, 117]. Nevertheless, the effect of the abnormalities in oxidative stress is relatively small, and their clinical significance as cardiovascular risk factors needs to be precisely defined in future.

1.4.4. Haemostasis and Fibrinolysis Imbalance

There is no doubt that haemostatic system abnormalities could increase arterial and venous thromboembolism as important cardiovascular risk factors [191]. However, there is relatively strong literature suggesting that PCOS is associated with increased platelet aggregation and impaired plasma fibrinolytic activity with increased plasminogen activator inhibitor-1 and plasminogen [192, 193]. Those risks are exacerbated by oral contraceptive use, as a common PCOS treatment strategy [194]. Although those abnormalities are likely to increase cardiovascular disease in PCOS population, however further studies are warranted.

1.4.5. Vitamin D Deficiency

Vitamin D is a fat-soluble vitamin that is synthesized endogenously by sunlight-stimulated photochemical conversion of cholesterol to 7-dehydrocholesterol in the skin or obtained from the diet [195]. Vitamin D is

known for its primary role in bone and mineral homeostasis. However recent evidence demonstrates its vitamin D deficiency contributes in a spectrum of pathologic process of metabolic disturbances and CVD [196]. Evidence has demonstrated that vitamin D receptor complex regulates genes contributed in glucose and lipid metabolism and also in blood pressure regulation, thereby indicating a role of vitamin D deficiency in the underlying pathogenesis of cardiovascular disease [197]. In this respect, vitamin D deficiency increases both insulin resistance and activation of proinflammatory process leading to glucose intolerance by β-cell damage and death. Moreover, it may activate the epigenetic alterations by hypermethylation in many diabetes-related genes as a feature of diabetes [198, 199]. It is showed that vitamin D deficiency has a negative effect on lipid profile particularly on total cholesterol and LDL cholesterol, apolipoprotein AI and HDL cholesterol levels [200, 201]. Moreover, Calcitriol is a pro-inflammatory and anti-inflammatory cellular cytokines modulator [202]. There is some evidence that vitamin D deficiency is negatively correlated with inflammatory markers such as CRP concentrations [203]. As well, Vitamin D also imply a crucial role in the modulation of innate and adaptive immune response in various inflammatory and autoimmune disorders. It is now recognized that active metabolite vitamin D receptors are expressed in cells of the immune system [204, 205].

However, vitamin D regulates about 3% of the human genome, including genes that are crucial for glucose and lipid metabolism, via its nucleoprotein receptor that binds to vitamin D response elements found in the promoter region of responsive genes [206].

However, studies showed that vitamin D deficiency are so prevalent among women with PCOS and it may play a key role in the development of PCOS [207, 208]. The genetic variant of the VDR was found to have an association with severity of clinical features of PCOS, but none with disease risk [206]. As well a recent meta-analysis showed that lower serum vitamin D levels were related to metabolic and hormonal disorders in women with PCOS, particularly dysglycemia including increased levels of fasting glucose and insulin resistance compared to those without vitamin D

deficiency [209, 210]. However, result of studies focusing on the effect of vitamin D supplementation on metabolic and endocrine parameters in PCOS in insufficient and inconclusive. Therefore, given the heterogeneity of the current available studies, a definite conclusion is difficult to make. Well-designed randomized controlled trials are still needed to clarify the effect vitamin D deficiency treatment on cardio-metabolic disturbances in PCOS population.

1.5. PCOS and Cardiovascular Events

There is much more controversy regarding whether the risk of cardiovascular events are increased among women with PCOS [211, 212]. However, increased cardiovascular risk factors in PCOS is translated into increased risk for cardiovascular events remains to be established, considering that PCOS may improve with aging. In this respect, some studies have shown that hyperinsulinemia and hyperandrogenemia are independently associated with the presence of atherosclerosis and cardiovascular events [159, 213]. However, most probably, PCOS phenomenon and therefore the attributed cardiovascular risks in women with PCOS progressively normalizes with aging. It has been reported that the progressive reduction of ovarian and adrenal androgen secretion in the decade preceding menopause reduces the risk factors [214].

In agreement with this hypothesis, a recent published metanalysis evaluated the prevalence and hazard ratio of cardiovascular events among reproductive and menopausal women with PCOS, compared to healthy controls. However, 16 studies were included for final meta-analysis. Results showed that the pooled hazard of CV events in PCOS patients in both subgroups of reproductive and menopausal age were significantly 1.5 fold higher than healthy controls. However, sub group analysis among studies with population-based design, which may show the general PCOS population characteristics, revealed that the HR of CV events increased only in reproductive age PCOS patients, whereas the difference was not statistically significant when comparing menopausal PCOS patients to

healthy controls [215]. It may suggested that history of PCOS during reproductive ages may not be a great risk factor for developing cardiovascular events in later life. At present, well designed, long term population based prospective studies, initiated in the reproductive period, are needed to clarify it.

CONCLUSION

PCOS is a common heterogeneous endocrinopathy among reproductive-aged women with significant adverse health impacts. Both traditional and non-traditional cardiometabolic risk factors may interact in PCOS, contributing to increased cardiometabolic risks, which are further exacerbated by high rates of concomitant obesity. Nevertheless, there is much more controversy regarding whether cardio-metabolic disease are increased in PCOS in later life, leaving many issues regarding cardiovascular and metabolic events unresolved. Overall, at present methodological heterogenicity, failure to control of confounders and also absence of long term follow up of PCOS population have hampered progress in understanding cardiometabolic aspects in PCOS. Larger-scale studies that address these gaps are needed to better characterize mechanisms and interrelationships between those factors that are intrinsic to PCOS.

REFERENCES

[1] Sirmans SM, Pate KA. Epidemiology, diagnosis, and management of polycystic ovary syndrome. *Clinical epidemiology.* 2014;6:1.

[2] Tehrani FR, Simbar M, Tohidi M, Hosseinpanah F, Azizi F. The prevalence of polycystic ovary syndrome in a community sample of Iranian population: Iranian PCOS prevalence study. *Reproductive Biology and Endocrinology.* 2011;9(1):39.

[3] Yildiz BO, Bozdag G, Yapici Z, Esinler I, Yarali H. Prevalence, phenotype and cardiometabolic risk of polycystic ovary syndrome under different diagnostic criteria. *Human reproduction.* 2012;27(10):3067-73.

[4] Behboudi-Gandevani S, Tehrani FR, Hosseinpanah F, Khalili D, Cheraghi L, Kazemijaliseh H, et al. Cardiometabolic risks in polycystic ovary syndrome: long-term population-based follow-up study. *Fertility and sterility.* 2018;110(7):1377-86.

[5] Escobar-Morreale HF. Polycystic ovary syndrome: definition, aetiology, diagnosis and treatment. *Nature Reviews Endocrinology.* 2018;14(5):270.

[6] de Melo AS, Dias SV, de Carvalho Cavalli R, Cardoso VC, Bettiol H, Barbieri MA, et al. Pathogenesis of polycystic ovary syndrome: multifactorial assessment from the foetal stage to menopause. *Reproduction.* 2015;150(1):R11-R24.

[7] Noroozzadeh M, Behboudi-Gandevani S, Zadeh-Vakili A, Tehrani FR. Hormone-induced rat model of polycystic ovary syndrome: A systematic review. *Life sciences.* 2017;191:259-72.

[8] Behboudi-Gandevani S, Ramezani Tehrani F, Rostami Dovom M, Farahmand M, Bahri Khomami M, Noroozzadeh M, et al. Insulin resistance in obesity and polycystic ovary syndrome: systematic review and meta-analysis of observational studies. *Gynecological Endocrinology.* 2016;32(5):343-53.

[9] Panidis D, Tziomalos K, Misichronis G, Papadakis E, Betsas G, Katsikis I, et al. Insulin resistance and endocrine characteristics of the different phenotypes of polycystic ovary syndrome: a prospective study. *Human reproduction.* 2012;27(2):541-9.

[10] Behboudi-Gandevani S, Tehrani FR, Yarandi RB, Noroozzadeh M, Hedayati M, Azizi F. The association between polycystic ovary syndrome, obesity, and the serum concentration of adipokines. *Journal of endocrinological investigation.* 2017;40(8):859-66.

[11] Spritzer PM, Lecke SB, Satler F, Morsch DM. Adipose tissue dysfunction, adipokines, and low-grade chronic inflammation in polycystic ovary syndrome. *Reproduction.* 2015;149(5):R219-R27.

[12] Villa J, Pratley RE. Adipose tissue dysfunction in polycystic ovary syndrome. *Current diabetes reports.* 2011;11(3):179.

[13] Duleba AJ, Dokras A. Is PCOS an inflammatory process? *Fertility and sterility*. 2012;97(1):7-12.

[14] Shorakae S, Teede H, de Courten B, Lambert G, Boyle J, Moran LJ, editors. *The emerging role of chronic low-grade inflammation in the pathophysiology of polycystic ovary syndrome. Seminars in reproductive medicine;* 2015: Thieme Medical Publishers.

[15] Hyderali BN, Mala K. Oxidative stress and cardiovascular complications in polycystic ovarian syndrome. *European Journal of Obstetrics & Gynecology and Reproductive Biology*. 2015;191:15-22.

[16] Papalou O, M Victor V, Diamanti-Kandarakis E. Oxidative stress in polycystic ovary syndrome. *Current pharmaceutical design.* 2016;22(18):2709-22.

[17] Legro RS, editor. *Obesity and PCOS: implications for diagnosis and treatment. Seminars in reproductive medicine;* 2012: Thieme Medical Publishers.

[18] Lim S, Norman RJ, Davies M, Moran L. The effect of obesity on polycystic ovary syndrome: a systematic review and meta-analysis. *Obesity Reviews.* 2013;14(2):95-109.

[19] Allameh Z, Rouholamin S, Adibi A, Mehdipour M, Adeli M. Does carotid intima-media thickness have relationship with polycystic ovary syndrome? *International journal of preventive medicine.* 2013;4(11):1266.

[20] Meyer ML, Malek AM, Wild RA, Korytkowski MT, Talbott EO. Carotid artery intima-media thickness in polycystic ovary syndrome: a systematic review and meta-analysis. *Human reproduction update.* 2012;18(2):112-26.

[21] Calderon-Margalit R, Siscovick D, Merkin SS, Wang E, Daviglus ML, Schreiner PJ, et al. Prospective association of polycystic ovary syndrome with coronary artery calcification and carotid-intima-media thickness: the Coronary Artery Risk Development in Young Adults Women's study. *Arteriosclerosis, thrombosis, and vascular biology*. 2014;34(12):2688-94.

[22] Carmina E. Diagnosis of polycystic ovary syndrome: from NIH criteria to ESHRE-ASRM guidelines. *Minerva ginecologica.* 2004;56(1):1-6.

[23] Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, et al. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. *Fertility and sterility.* 2009;91(2):456-88.

[24] Balen AH, Laven JS, Tan SL, Dewailly D. Ultrasound assessment of the polycystic ovary: international consensus definitions. *Human reproduction update.* 2003;9(6):505-14.

[25] Eshre TR, Group A-SPCW. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertility and sterility.* 2004;81(1):19-25.

[26] Azziz R, Kintziger K, Li R, Laven J, Morin-Papunen L, Merkin SS, et al. Recommendations for epidemiologic and phenotypic research in polycystic ovary syndrome: an androgen excess and PCOS society resource. *Human Reproduction.* 2019;34(11):2254-65.

[27] Moran C, Arriaga M, Rodriguez G, Moran S. Obesity differentially affects phenotypes of polycystic ovary syndrome. *International journal of endocrinology.* 2012;2012.

[28] Tehrani FR, Rashidi H, Khomami MB, Tohidi M, Azizi F. The prevalence of metabolic disorders in various phenotypes of polycystic ovary syndrome: a community based study in Southwest of Iran. *Reproductive biology and endocrinology.* 2014;12(1):89.

[29] Tziomalos K. Cardiovascular Risk in the Different Phenotypes of Polycystic Ovary Syndrome. *Current pharmaceutical design.* 2016;22(36):5547-53.

[30] Ramezani Tehrani F, Amiri M. Polycystic Ovary Syndrome in Adolescents: Challenges in Diagnosis and Treatment. *International journal of endocrinology and metabolism.* 2019;17(3):e91554.

[31] Fauser BC, Tarlatzis BC, Rebar RW, Legro RS, Balen AH, Lobo R, et al. Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd

PCOS Consensus Workshop Group. *Fertility and sterility.* 2012;97(1):28-38. e25.

[32] Legro RS, Arslanian SA, Ehrmann DA, Hoeger KM, Murad MH, Pasquali R, et al. Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. *The Journal of Clinical Endocrinology & Metabolism.* 2013; 98(12):4565-92.

[33] Noroozzadeh M, Tehrani FR, Sedaghat K, Godini A, Azizi F. The impact of prenatal exposure to a single dose of testosterone on insulin resistance, glucose tolerance and lipid profile of female rat's offspring in adulthood. *Journal of endocrinological investigation.* 2015;38(5):489-95.

[34] Ajmal N, Khan SZ, Shaikh R. Polycystic ovary syndrome (PCOS) and genetic predisposition: A review article. *European journal of obstetrics & gynecology and reproductive biology:* X. 2019:100060.

[35] Panda PK, Rane R, Ravichandran R, Singh S, Panchal H. Genetics of PCOS: a systematic bioinformatics approach to unveil the proteins responsible for PCOS. *Genomics data.* 2016;8:52-60.

[36] Salehi Jahromi M, Hill JW, Ramezani Tehrani F, Zadeh-Vakili A. Hypomethylation of specific CpG sites in the promoter region of steroidogeneic genes (GATA6 and StAR) in prenatally androgenized rats. *Life sciences.* 2018;207:105-9.

[37] Salehi Jahromi M, Ramezani Tehrani F, Hill JW, Noroozzadeh M, Zarkesh M, Ghasemi A, et al. Alteration in follistatin gene expression detected in prenatally androgenized rats. *Gynecological endocrinology : The official journal of the International Society of Gynecological Endocrinology.* 2017;33(6):433-7.

[38] Zadeh-Vakili A, Ramezani Tehrani F, Daneshpour MS, Zarkesh M, Saadat N, Azizi F. Genetic polymorphism of vitamin D receptor gene affects the phenotype of PCOS. *Gene.* 2013;515(1):193-6.

[39] Escobar-Morreale HF, Luque-Ramírez M, San Millán JL. The molecular-genetic basis of functional hyperandrogenism and the polycystic ovary syndrome. *Endocrine reviews.* 2005;26(2):251-82.

[40] Prapas N, Karkanaki A, Prapas I, Kalogiannidis I, Katsikis I, Panidis D. Genetics of polycystic ovary syndrome. *Hippokratia.* 2009;13(4):216.

[41] Diamanti-Kandarakis E, Kandarakis H, Legro RS. The role of genes and environment in the etiology of PCOS. *Endocrine.* 2006; 30(1):19-26.

[42] Merkin SS, Phy JL, Sites CK, Yang D. Environmental determinants of polycystic ovary syndrome. *Fertility and sterility.* 2016; 106(1):16-24.

[43] Zhang J, Liu X, Liu Y, Xu L, Zhou L, Tang L, et al. Environmental risk factors for women with polycystic ovary syndrome in china: a population-based case-control study. *Journal of biological regulators and homeostatic agents.* 2014;28(2):203-11.

[44] Longo S, Bollani L, Decembrino L, Di Comite A, Angelini M, Stronati M. Short-term and long-term sequelae in intrauterine growth retardation (IUGR). *The Journal of Maternal-Fetal & Neonatal Medicine.* 2013;26(3):222-5.

[45] Wells JC. The thrifty phenotype: an adaptation in growth or metabolism? *American Journal of Human Biology.* 2011;23(1):65-75.

[46] Escobar-Morreale HF, Álvarez-Blasco F, Botella-Carretero JI, Luque-Ramírez M. The striking similarities in the metabolic associations of female androgen excess and male androgen deficiency. *Human Reproduction.* 2014;29(10):2083-91.

[47] Hakim C, Padmanabhan V, Vyas AK. Gestational hyperandrogenism in developmental programming. *Endocrinology.* 2017;158(2):199-212.

[48] Gur EB, Karadeniz M, Turan GA. Fetal programming of polycystic ovary syndrome. *World journal of diabetes.* 2015;6(7):936.

[49] Noroozzadeh M, Tehrani FR, Khomami MB, Azizi F. A comparison of sexual function in women with polycystic ovary syndrome (PCOS) whose mothers had PCOS during their pregnancy period with those without PCOS. *Archives of sexual behavior.* 2017;46(7):2033-42.

[50] Cassar S, Misso ML, Hopkins WG, Shaw CS, Teede HJ, Stepto NK. Insulin resistance in polycystic ovary syndrome: a systematic review

and meta-analysis of euglycaemic–hyperinsulinaemic clamp studies. *Human reproduction.* 2016;31(11):2619-31.

[51] Randeva HS, Tan BK, Weickert MO, Lois K, Nestler JE, Sattar N, et al. Cardiometabolic aspects of the polycystic ovary syndrome. *Endocrine reviews.* 2012;33(5):812-41.

[52] Engmann L, Jin S, Sun F, Legro RS, Polotsky AJ, Hansen KR, et al. Racial and ethnic differences in the polycystic ovary syndrome metabolic phenotype. *American journal of obstetrics and gynecology.* 2017;216(5):493. e1-. e13.

[53] Jayagopal V, Kilpatrick E, Jennings P, Hepburn D, Atkin S. The biological variation of testosterone and sex hormone-binding globulin (SHBG) in polycystic ovarian syndrome: implications for SHBG as a surrogate marker of insulin resistance. *The Journal of Clinical Endocrinology & Metabolism.* 2003;88(4):1528-33.

[54] Luotola K, Piltonen TT, Puurunen J, Morin-Papunen LC, Tapanainen JS. Testosterone is associated with insulin resistance index independently of adiposity in women with polycystic ovary syndrome. *Gynecological Endocrinology.* 2018;34(1):40-4.

[55] Zhang B, Wang J, Shen S, Liu J, Sun J, Gu T, et al. Association of androgen excess with glucose intolerance in women with polycystic ovary syndrome. *BioMed research international.* 2018;2018.

[56] Diamanti-Kandarakis E, Panidis D. Unravelling the phenotypic map of polycystic ovary syndrome (PCOS): a prospective study of 634 women with PCOS. *Clinical endocrinology.* 2007;67(5):735-42.

[57] Paschou SA, Palioura E, Ioannidis D, Anagnostis P, Panagiotakou A, Loi V, et al. Adrenal hyperandrogenism does not deteriorate insulin resistance and lipid profile in women with PCOS. *Endocrine connections.* 2017;6(8):601-6.

[58] Tehrani FR, Zarkesh M, Tohidi M, Azizi F, Zadeh-Vakili A. Is the association between insulin resistance and diabetogenic haematopoietically expressed homeobox (HHEX) polymorphism (rs1111875) affected by polycystic ovary syndrome status? *Reproduction, fertility, and development.* 2017;29(4):670-8.

[59] Anagnostis P, Tarlatzis BC, Kauffman RP. Polycystic ovarian syndrome (PCOS): Long-term metabolic consequences. *Metabolism.* 2018;86:33-43.

[60] González F, Sia CL, Bearson DM, Blair HE. Hyperandrogenism induces a proinflammatory TNFα response to glucose ingestion in a receptor-dependent fashion. *The Journal of Clinical Endocrinology & Metabolism.* 2014;99(5):E848-E54.

[61] Luque-Ramírez M, Escobar-Morreale HF. Polycystic ovary syndrome as a paradigm for prehypertension, prediabetes, and preobesity. *Current hypertension reports.* 2014;16(12):500.

[62] Behboudi-Gandevani S, Abtahi H, Saadat N, Tohidi M, Tehrani FR. Effect of phlebotomy versus oral contraceptives containing cyproterone acetate on the clinical and biochemical parameters in women with polycystic ovary syndrome: a randomized controlled trial. *Journal of ovarian research.* 2019;12(1):78.

[63] Escobar-Morreale HF. Iron metabolism and the polycystic ovary syndrome. *Trends in Endocrinology & Metabolism.* 2012;23(10):509-15.

[64] Diamanti-Kandarakis E, Dunaif A. Insulin resistance and the polycystic ovary syndrome revisited: an update on mechanisms and implications. *Endocrine reviews.* 2012;33(6):981-1030.

[65] Moro C, Pasarica M, Elkind-Hirsch K, Redman LM. Aerobic exercise training improves atrial natriuretic peptide and catecholamine-mediated lipolysis in obese women with polycystic ovary syndrome. *The Journal of Clinical Endocrinology & Metabolism.* 2009;94(7):2579-86.

[66] Potter LR, Abbey-Hosch S, Dickey DM. Natriuretic peptides, their receptors, and cyclic guanosine monophosphate-dependent signaling functions. *Endocrine reviews.* 2006;27(1):47-72.

[67] Pivovarova O. Gogebakan O Kloting N Sparwasser A Weickert MO Haddad I Nikiforova VJ Bergmann A Kruse M Seltmann AC. Insulin up-regulates natriuretic peptide clearance receptor expression in the subcutaneous fat depot in obese subjects: a missing link between CVD

risk and obesity. *Journal of Clinical Endocrinology and Metabolism.* 2012;97:E731-E9.

[68] Frøssing S, Nylander M, Kistorp C, Skouby SO, Faber J. Effect of liraglutide on atrial natriuretic peptide, adrenomedullin, and copeptin in PCOS. *Endocrine connections.* 2018;7(1):115-23.

[69] Pereira VM, Honorato-Sampaio K, Martins AS, Reis FM, Reis AM. Downregulation of natriuretic peptide system and increased steroidogenesis in rat polycystic ovary. *Peptides.* 2014;60:80-5.

[70] Jaliseh HK, Tehrani FR, Behboudi-Gandevani S, Hosseinpanah F, Khalili D, Cheraghi L, et al. Polycystic ovary syndrome is a risk factor for diabetes and prediabetes in middle-aged but not elderly women: a long-term population-based follow-up study. *Fertility and sterility.* 2017;108(6):1078-84.

[71] Vrbikova J, Cifkova R, Jirkovska A, Lanska V, Platilova H, Zamrazil V, et al. Cardiovascular risk factors in young Czech females with polycystic ovary syndrome. *Human Reproduction.* 2003;18(5):980-4.

[72] Moran LJ, Misso ML, Wild RA, Norman RJ. Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: a systematic review and meta-analysis. *Human reproduction update.* 2010;16(4):347-63.

[73] Kakoly N, Khomami M, Joham A, Cooray S, Misso M, Norman R, et al. Ethnicity, obesity and the prevalence of impaired glucose tolerance and type 2 diabetes in PCOS: a systematic review and meta-regression. *Human reproduction update.* 2018;24(4):455-67.

[74] Legro RS, Kunselman AR, Dodson WC, Dunaif A. Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. *The journal of clinical endocrinology & metabolism.* 1999;84(1):165-9.

[75] Kakoly NS, Earnest A, Teede HJ, Moran LJ, Joham AE. The impact of obesity on the incidence of type 2 diabetes among women with polycystic ovary syndrome. *Diabetes care.* 2019;42(4):560-7.

[76] Conway G, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Franks S, Gambineri A, et al. The polycystic ovary syndrome: a

position statement from the European Society of Endocrinology. *European Journal of Endocrinology.* 2014;171(4):P1-P29.

[77] Yilmaz M, Bi˙ ri˙ A, Bukan N, Karakoç A, Sancak B, Törüner F, et al. Levels of lipoprotein and homocysteine in non-obese and obese patients with polycystic ovary syndrome. *Gynecological endocrinology.* 2005;20(5):258-63.

[78] Wild RA, Rizzo M, Clifton S, Carmina E. Lipid levels in polycystic ovary syndrome: systematic review and meta-analysis. *Fertility and sterility.* 2011;95(3):1073-9. e11.

[79] Wild RA. *Dyslipidemia in PCOS. Steroids.* 2012;77(4):295-9.

[80] Osibogun O, Ogunmoroti O, Michos ED. *Polycystic ovary syndrome and cardiometabolic risk: Opportunities for cardiovascular disease prevention.* Trends in cardiovascular medicine. 2019.

[81] Diamanti-Kandarakis E, Papavassiliou AG, Kandarakis SA, Chrousos GP. Pathophysiology and types of dyslipidemia in PCOS. *Trends in Endocrinology & Metabolism.* 2007;18(7):280-5.

[82] Macut D, Bjekić-Macut J, Savić-Radojević A. Dyslipidemia and oxidative stress in PCOS. *Polycystic Ovary Syndrome*. 40: Karger Publishers; 2013. p. 51-63.

[83] Sidhwani S, Scoccia B, Sunghay S, Stephens-Archer CN, Mazzone T, Sam S. Polycystic ovary syndrome is associated with atherogenic changes in lipoprotein particle number and size independent of body weight. *Clinical endocrinology.* 2011;75(1):76-82.

[84] Savage DB, Petersen KF, Shulman GI. Disordered lipid metabolism and the pathogenesis of insulin resistance. *Physiological reviews.* 2007;87(2):507-20.

[85] Hoffman LK, Ehrmann DA. Cardiometabolic features of polycystic ovary syndrome. *Nature clinical practice Endocrinology & metabolism.* 2008;4(4):215-22.

[86] Macut D, Damjanovic S, Panidis D, Spanos N, Glišić B, Petakov M, et al. Oxidised low-density lipoprotein concentration–early marker of an altered lipid metabolism in young women with PCOS. *European Journal of Endocrinology.* 2006;155(1):131-6.

[87] Macut D, Mladenović V, Bjekić-Macut J, Livadas S, Stanojlović O, Hrnčić D, et al. Hypertension in polycystic ovary syndrome: Novel insights. *Current hypertension reviews.* 2020;16(1):55-60.

[88] Marchesan LB, Spritzer PM. ACC/AHA 2017 definition of high blood pressure: implications for women with polycystic ovary syndrome. *Fertility and sterility.* 2019;111(3):579-87. e1.

[89] Marchesan LB, Spritzer PM. *Blood pressure: implications for women with polycystic ovary syndrome.* 2019.

[90] Zhou M-S, Wang A, Yu H. Link between insulin resistance and hypertension: What is the evidence from evolutionary biology? *Diabetology & metabolic syndrome*. 2014;6(1):12.

[91] Cascella T, Palomba S, Tauchmanovà L, Manguso F, Di Biase S, Labella D, et al. Serum aldosterone concentration and cardiovascular risk in women with polycystic ovarian syndrome. *The Journal of Clinical Endocrinology & Metabolism*. 2006;91(11):4395-400.

[92] DeMarco VG, Aroor AR, Sowers JR. The pathophysiology of hypertension in patients with obesity. *Nature Reviews Endocrinology.* 2014;10(6):364.

[93] Sprung V, Cuthbertson D, Pugh C, Daousi C, Atkinson G, Aziz N, et al. Nitric oxide-mediated cutaneous microvascular function is impaired in polycystic ovary sydrome but can be improved by exercise training. *The Journal of physiology.* 2013;591(6):1475-87.

[94] Alphan Z, Berberoglu Z, Gorar S, Candan Z, Aktas A, Aral Y, et al. Increased total Renin levels but not Angiotensin-converting enzyme activity in obese patients with polycystic ovary syndrome. *Medical Principles and Practice*. 2013;22(5):475-9.

[95] Diamanti-Kandarakis E, Spina G, Kouli C, Migdalis I. Increased endothelin-1 levels in women with polycystic ovary syndrome and the beneficial effect of metformin therapy. *The Journal of Clinical Endocrinology & Metabolism.* 2001;86(10):4666-73.

[96] Shi Y, Cui Y, Sun X, Ma G, Ma Z, Gao Q, et al. Hypertension in women with polycystic ovary syndrome: prevalence and associated cardiovascular risk factors. *European Journal of Obstetrics & Gynecology and Reproductive Biology.* 2014;173:66-70.

[97] Elting M, Korsen T, Bezemer P, Schoemaker J. Prevalence of diabetes mellitus, hypertension and cardiac complaints in a follow-up study of a Dutch PCOS population. *Human Reproduction.* 2001;16(3):556-60.

[98] Orbetzova M, Shigarminova R, Genchev G, Milcheva B, Lozanov L, Genov N, et al. Role of 24-hour monitoring in assessing blood pressure changes in polycystic ovary syndrome. *Folia medica.* 2003;45(3):21-5.

[99] Holte J, Gennarelli G, Berne C, Bergh T, Lithell H. Elevated ambulatory day-time blood pressure in women with polycystic ovary syndrome: a sign of a pre-hypertensive state? *Human reproduction.* 1996;11(1):23-8.

[100] Wild S, Pierpoint T, McKeigue P, Jacobs H. Cardiovascular disease in women with polycystic ovary syndrome at long-term follow-up: a retrospective cohort study. *Clinical endocrinology.* 2000;52(5):595-600.

[101] Amiri M, Ramezani Tehrani F, Behboudi-Gandevani S, Razieh B-Y, Carmina E. Risk of hypertension in women with polycystic ovary syndrome: a systematic review, meta-analysis and meta-regression. *Reproductive Biology and Endocrinology.* 2020;in press.

[102] Glueck CJ, Morrison JA, Goldenberg N, Wang P. Coronary heart disease risk factors in adult premenopausal white women with polycystic ovary syndrome compared with a healthy female population. *Metabolism.* 2009;58(5):714-21.

[103] Behboudi-Gandevani S, Tehrani FR, Cheraghi L, Azizi F. Could "a body shape index" and "waist to height ratio" predict insulin resistance and metabolic syndrome in polycystic ovary syndrome? *European Journal of Obstetrics & Gynecology and Reproductive Biology.* 2016;205:110-4.

[104] Wehr E, Gruber H-J, Giuliani A, Möller R, Pieber TR, Obermayer-Pietsch B. The lipid accumulation product is associated with impaired glucose tolerance in PCOS women. *The Journal of Clinical Endocrinology & Metabolism.* 2011;96(6):E986-E90.

[105] Agrawal H, Aggarwal K, Jain A. Visceral adiposity index: Simple Tool for assessing cardiometabolic risk in women with polycystic

ovary syndrome. *Indian journal of endocrinology and metabolism.* 2019;23(2):232.

[106] Lim SS, Davies M, Norman RJ, Moran L. Overweight, obesity and central obesity in women with polycystic ovary syndrome: a systematic review and meta-analysis. *Human reproduction update.* 2012;18(6):618-37.

[107] Mannerås-Holm L, Leonhardt H, Kullberg J, Jennische E, Odén A, Holm G, et al. Adipose tissue has aberrant morphology and function in PCOS: enlarged adipocytes and low serum adiponectin, but not circulating sex steroids, are strongly associated with insulin resistance. *The Journal of Clinical Endocrinology & Metabolism.* 2011;96(2):E304-E11.

[108] Barber TM, Golding SJ, Alvey C, Wass JA, Karpe F, Franks S, et al. Global adiposity rather than abnormal regional fat distribution characterizes women with polycystic ovary syndrome. *The Journal of Clinical Endocrinology & Metabolism.* 2008;93(3):999-1004.

[109] Horejsi R, Möller R, Rackl S, Giuliani A, Freytag U, Crailsheim K, et al. Android subcutaneous adipose tissue topography in lean and obese women suffering from PCOS: comparison with type 2 diabetic women. *American Journal of Physical Anthropology: The Official Publication of the American Association of Physical Anthropologists.* 2004;124(3):275-81.

[110] Blouin K, Nadeau M, Perreault M, Veilleux A, Drolet R, Marceau P, et al. Effects of androgens on adipocyte differentiation and adipose tissue explant metabolism in men and women. *Clinical endocrinology.* 2010;72(2):176-88.

[111] Lim S, Kakoly N, Tan J, Fitzgerald G, Bahri Khomami M, Joham A, et al. Metabolic syndrome in polycystic ovary syndrome: a systematic review, meta-analysis and meta-regression. *Obesity reviews.* 2019;20(2):339-52.

[112] Rachoń D, Teede H. Ovarian function and obesity—interrelationship, impact on women's reproductive lifespan and treatment options. *Molecular and cellular endocrinology.* 2010;316(2):172-9.

[113] Rahmouni K, Correia ML, Haynes WG, Mark AL. Obesity-associated hypertension: new insights into mechanisms. *Hypertension.* 2005;45(1):9-14.

[114] Artham SM, Lavie CJ, Milani RV, Ventura HO. Obesity and hypertension, heart failure, and coronary heart disease—risk factor, paradox, and recommendations for weight loss. *Ochsner Journal.* 2009;9(3):124-32.

[115] Sathyapalan T, Atkin SL. Mediators of inflammation in polycystic ovary syndrome in relation to adiposity. *Mediators of inflammation.* 2010;2010.

[116] Lumeng CN, Saltiel AR. Inflammatory links between obesity and metabolic disease. *The Journal of clinical investigation.* 2011;121(6):2111-7.

[117] Bañuls C, Rovira-Llopis S, de Marañon AM, Veses S, Jover A, Gomez M, et al. Metabolic syndrome enhances endoplasmic reticulum, oxidative stress and leukocyte–endothelium interactions in PCOS. *Metabolism.* 2017;71:153-62.

[118] Schiffer L, Arlt W, O'Reilly MW. Understanding the role of androgen action in female adipose tissue. *Hyperandrogenism in Women.* 53: Karger Publishers; 2019. p. 33-49.

[119] Durmus U, Duran C, Ecirli S. Visceral adiposity index levels in overweight and/or obese, and non-obese patients with polycystic ovary syndrome and its relationship with metabolic and inflammatory parameters. J*ournal of endocrinological investigation.* 2017;40(5):487-97.

[120] K Dimitriadis G, Kyrou I, S Randeva H. Polycystic ovary syndrome as a proinflammatory state: The role of adipokines. *Current pharmaceutical design.* 2016;22(36):5535-46.

[121] Chen X, Jia X, Qiao J, Guan Y, Kang J. Adipokines in reproductive function: a link between obesity and polycystic ovary syndrome. *J Mol Endocrinol.* 2013;50(2):R21-37.

[122] Delitala AP, Capobianco G, Delitala G, Cherchi PL, Dessole S. Polycystic ovary syndrome, adipose tissue and metabolic syndrome. *Archives of gynecology and obstetrics.* 2017;296(3):405-19.

[123] Toulis KA, Goulis D, Farmakiotis D, Georgopoulos N, Katsikis I, Tarlatzis B, et al. Adiponectin levels in women with polycystic ovary syndrome: a systematic review and a meta-analysis. *Human reproduction update.* 2009;15(3):297-307.

[124] Groth SW. Adiponectin and polycystic ovary syndrome. *Biological research for nursing.* 2010;12(1):62-72.

[125] Mirza SS, Shafique K, Shaikh AR, Khan NA, Qureshi MA. Association between circulating adiponectin levels and polycystic ovarian syndrome. *Journal of ovarian research.* 2014;7(1):18.

[126] Fasshauer M, Paschke R, Stumvoll M. Adiponectin, obesity, and cardiovascular disease. *Biochimie.* 2004;86(11):779-84.

[127] Antoniades C, Antonopoulos A, Tousoulis D, Stefanadis C. Adiponectin: from obesity to cardiovascular disease. *Obesity reviews.* 2009;10(3):269-79.

[128] Lee S, Kwak H-B. Role of adiponectin in metabolic and cardiovascular disease. *Journal of exercise rehabilitation.* 2014;10(2):54.

[129] Drolet R, Bélanger C, Fortier M, Huot C, Mailloux J, Légaré D, et al. Fat depot-specific impact of visceral obesity on adipocyte adiponectin release in women. *Obesity.* 2009;17(3):424-30.

[130] Xita N, Georgiou I, Chatzikyriakidou A, Vounatsou M, Papassotiriou G-P, Papassotiriou I, et al. Effect of adiponectin gene polymorphisms on circulating adiponectin and insulin resistance indexes in women with polycystic ovary syndrome. *Clinical chemistry.* 2005;51(2):416-23.

[131] Athyros VG, Tziomalos K, Karagiannis A, Anagnostis P, Mikhailidis DP. Should adipokines be considered in the choice of the treatment of obesity-related health problems? *Current drug targets.* 2010;11(1):122-35.

[132] Mendonça H, Montenegro Junior R, Foss MC, Silva de Sá M, Ferriani RA. Positive correlation of serum leptin with estradiol levels in patients with polycystic ovary syndrome. *Brazilian journal of medical and biological research.* 2004;37(5):729-36.

[133] Polak K, Czyzyk A, Simoncini T, Meczekalski B. New markers of insulin resistance in polycystic ovary syndrome. *Journal of endocrinological investigation.* 2017;40(1):1-8.

[134] Veldhuis JD, Pincus S, Garcia-Rudaz M, Ropelato M, Escobar M, Barontini M. Disruption of the synchronous secretion of leptin, LH, and ovarian androgens in nonobese adolescents with the polycystic ovarian syndrome. *The Journal of Clinical Endocrinology & Metabolism*. 2001;86(8):3772-8.

[135] Freitas Lima LC, Braga VdA, do Socorro de França Silva M, Cruz JdC, Sousa Santos SH, de Oliveira Monteiro MM, et al. Adipokines, diabetes and atherosclerosis: an inflammatory association. *Frontiers in physiology*. 2015;6:304.

[136] Hou N, Luo JD. Leptin and cardiovascular diseases. *Clinical and Experimental Pharmacology and Physiology.* 2011;38(12):905-13.

[137] Zheng S-H, Du D-F, Li X-L. Leptin levels in women with polycystic ovary syndrome: a systematic review and a meta-analysis. *Reproductive sciences.* 2017;24(5):656-70.

[138] Seow KM, Juan CC, Wu LY, Hsu YP, Yang WM, Tsai YL, et al. Serum and adipocyte resistin in polycystic ovary syndrome with insulin resistance. *Human Reproduction.* 2004;19(1):48-53.

[139] Kim JJ, Choi YM, Hong MA, Kim MJ, Chae SJ, Kim SM, et al. Serum visfatin levels in non-obese women with polycystic ovary syndrome and matched controls. *Obstetrics & gynecology science.* 2018;61(2):253-60.

[140] Sun X, Wu X, Zhou Y, Yu X, Zhang W. Evaluation of apelin and insulin resistance in patients with PCOS and therapeutic effect of drospirenone-ethinylestradiol plus metformin. *Medical science monitor: international medical journal of experimental and clinical research.* 2015;21:2547.

[141] Guvenc Y, Var A, Goker A, Kuscu NK. Assessment of serum chemerin, vaspin and omentin-1 levels in patients with polycystic ovary syndrome. *Journal of International Medical Research.* 2016;44(4):796-805.

[142] Yang X, Quan X, Lan Y, Wei Q, Ye J, Yin X, et al. Serum chemerin level in women with PCOS and its relation with the risk of spontaneous abortion. *Gynecological Endocrinology.* 2018;34(10):864-7.

[143] Emekci Ozay O, Ozay AC, Acar B, Cagliyan E, Seçil M, Küme T. Role of kisspeptin in polycystic ovary syndrome (PCOS). *Gynecological Endocrinology.* 2016;32(9):718-22.

[144] Kort DH, Kostolias A, Sullivan C, Lobo RA. Chemerin as a marker of body fat and insulin resistance in women with polycystic ovary syndrome. *Gynecological Endocrinology.* 2015;31(2):152-5.

[145] Huang PL. A comprehensive definition for metabolic syndrome. *Disease models & mechanisms.* 2009;2(5-6):231-7.

[146] Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. *Circulation.* 2005;112(17):2735-52.

[147] Melo AS, Vieira CS, Romano LGM, Ferriani RA, Navarro PA. The frequency of metabolic syndrome is higher among PCOS Brazilian women with menstrual irregularity plus hyperandrogenism. *Reproductive Sciences.* 2011;18(12):1230-6.

[148] Techatraisak K, Wongmeerit K, Dangrat C, Wongwananuruk T, Indhavivadhana S. Measures of body adiposity and visceral adiposity index as predictors of metabolic syndrome among Thai women with PCOS. *Gynecological Endocrinology.* 2016;32(4):276-80.

[149] Zhang J, Fan P, Liu H, Bai H, Wang Y, Zhang F. Apolipoprotein AI and B levels, dyslipidemia and metabolic syndrome in south-west Chinese women with PCOS. *Human reproduction.* 2012;27(8):2484-93.

[150] Samy N, Hashim M, Sayed M, Said M. Clinical significance of inflammatory markers in polycystic ovary syndrome: their relationship to insulin resistance and body mass index. *Disease markers.* 2009;26(4):163-70.

[151] Macut D, Bačević M, Božić-Antić I, Bjekić-Macut J, Čivčić M, Erceg S, et al. Predictors of subclinical cardiovascular disease in women

with polycystic ovary syndrome: interrelationship of dyslipidemia and arterial blood pressure. *International journal of endocrinology.* 2015;2015.

[152] Meyer C, McGrath BP, Teede HJ. Overweight women with polycystic ovary syndrome have evidence of subclinical cardiovascular disease. *The Journal of Clinical Endocrinology & Metabolism.* 2005;90(10):5711-6.

[153] Dokras A. Cardiovascular disease risk in women with PCOS. *Steroids.* 2013;78(8):773-6.

[154] Essah PA, Wickham EP, Nestler JE. The metabolic syndrome in polycystic ovary syndrome. *Clinical obstetrics and gynecology.* 2007;50(1):205-25.

[155] Amiri M, Tehrani FR, Bidhendi-Yarandi R, Behboudi-Gandevani S, Azizi F, Carmina E. Relationships between biochemical markers of hyperandrogenism and metabolic parameters in women with polycystic ovary syndrome: A systematic review and meta-analysis. *Hormone and Metabolic Research.* 2019;51(01):22-34.

[156] Behboudi-Gandevani S, Amiri M, Bidhendi Yarandi R, Noroozzadeh M, Farahmand M, Rostami Dovom M, et al. The risk of metabolic syndrome in polycystic ovary syndrome: A systematic review and meta-analysis. *Clinical endocrinology.* 2018;88(2):169-84.

[157] Macut D, Antić I, Bjekić-Macut J. Cardiovascular risk factors and events in women with androgen excess. *Journal of endocrinological investigation.* 2015;38(3):295-301.

[158] Chiu W-L, Boyle J, Vincent A, Teede H, Moran LJ. Cardiometabolic risks in polycystic ovary syndrome: non-traditional risk factors and the impact of obesity. *Neuroendocrinology.* 2017;104(4):412-24.

[159] Wu FC, von Eckardstein A. Androgens and coronary artery disease. *Endocrine reviews.* 2003;24(2):183-217.

[160] Chen M-J, Yang W-S, Yang J-H, Chen C-L, Ho H-N, Yang Y-S. Relationship between androgen levels and blood pressure in young women with polycystic ovary syndrome. *Hypertension.* 2007;49(6):1442-7.

[161] Chen Y-F, Naftilan AJ, Oparil S. Androgen-dependent angiotensinogen and renin messenger RNA expression in hypertensive rats. *Hypertension.* 1992;19(5):456-63.

[162] Sulaiman MA, Al-Farsi YM, Al-Khaduri MM, Saleh J, Waly MI. Polycystic ovarian syndrome is linked to increased oxidative stress in Omani women. *International journal of women's health.* 2018;10:763.

[163] Krug I, Giles S, Paganini C. Binge eating in patients with polycystic ovary syndrome: prevalence, causes, and management strategies. *Neuropsychiatric disease and treatment.* 2019;15:1273.

[164] Diamanti-Kandarakis E, Alexandraki K, Piperi C, Protogerou A, Katsikis I, Paterakis T, et al. Inflammatory and endothelial markers in women with polycystic ovary syndrome. *European journal of clinical investigation.* 2006;36(10):691-7.

[165] Diamanti-Kandarakis E, Paterakis T, Kandarakis HA. Indices of low-grade inflammation in polycystic ovary syndrome. *Annals of the New York Academy of Sciences.* 2006;1092(1):175-86.

[166] Fenkci V, Fenkci S, Yilmazer M, Serteser M. Decreased total antioxidant status and increased oxidative stress in women with polycystic ovary syndrome may contribute to the risk of cardiovascular disease. *Fertility and sterility.* 2003;80(1):123-7.

[167] Ekholm UB, Turkmen S, Hammarbäck S, Bäckström T. Sexuality and androgens in women with cyclical mood changes and pre-menstrual syndrome. *Acta obstetricia et gynecologica Scandinavica.* 2014;93(3):248-55.

[168] Cooney LG, Lee I, Sammel MD, Dokras A. High prevalence of moderate and severe depressive and anxiety symptoms in polycystic ovary syndrome: a systematic review and meta-analysis. *Human Reproduction.* 2017;32(5):1075-91.

[169] Kravariti M, Naka KK, Kalantaridou SN, Kazakos N, Katsouras CS, Makrigiannakis A, et al. Predictors of endothelial dysfunction in young women with polycystic ovary syndrome. *The journal of clinical endocrinology & metabolism.* 2005;90(9):5088-95.

[170] Paradisi G, Steinberg HO, Hempfling A, Cronin J, Hook G, Shepard MK, et al. Polycystic ovary syndrome is associated with endothelial dysfunction. *Circulation.* 2001;103(10):1410-5.

[171] Lambert EA, Teede H, Sari CI, Jona E, Shorakae S, Woodington K, et al. Sympathetic activation and endothelial dysfunction in polycystic ovary syndrome are not explained by either obesity or insulin resistance. *Clinical endocrinology.* 2015;83(6):812-9.

[172] El-Kannishy G, Kamal S, Mousa A, Saleh O, El Badrawy A, Shokeir T. Endothelial function in young women with polycystic ovary syndrome (PCOS): Implications of body mass index (BMI) and insulin resistance. *Obesity research & clinical practice.* 2010; 4(1):e49-e56.

[173] Karoli R, Fatima J, Siddiqi Z, Vatsal P, Sultania AR, Maini S. Study of early atherosclerotic markers in women with polycystic ovary syndrome. *Indian journal of endocrinology and metabolism.* 2012;16(6):1004.

[174] Pehlivanov B, Orbetzova M. Characteristics of different phenotypes of polycystic ovary syndrome in a Bulgarian population. *Gynecological endocrinology.* 2007;23(10):604-9.

[175] Hosseinpanah F, Barzin M, Keihani S, Ramezani Tehrani F, Azizi F. Metabolic aspects of different phenotypes of polycystic ovary syndrome: Iranian PCOS Prevalence Study. *Clinical endocrinology.* 2014;81(1):93-9.

[176] Escobar-Morreale HF, Botella-Carretero JI, Alvarez-Blasco F, Sancho J, San Millán JL. The polycystic ovary syndrome associated with morbid obesity may resolve after weight loss induced by bariatric surgery. *The Journal of Clinical Endocrinology & Metabolism.* 2005;90(12):6364-9.

[177] Erdogan M, Karadeniz M, Berdeli A, Alper G, Caglayan O, Yilmaz C. *The relationship of the interleukin-6-174 G> C gene polymorphism with oxidative stress markers in Turkish polycystic ovary syndrome patients. Journal of endocrinological investigation.* 2008;31(7):624-9.

[178] Möhlig M, Spranger J, Osterhoff M, Ristow M, Pfeiffer A, Schill T, et al. *CLINICAL STUDY: The polycystic ovary syndrome per se is not associated with increased chronic inflammation.* 2004.

[179] Escobar-Morreale HF, Luque-Ramírez M, González F. Circulating inflammatory markers in polycystic ovary syndrome: a systematic review and metaanalysis. *Fertility and sterility.* 2011;95(3):1048-58. e2.

[180] González F. Inflammation in polycystic ovary syndrome: underpinning of insulin resistance and ovarian dysfunction. *Steroids.* 2012;77(4):300-5.

[181] Blumenfeld Z. *The Possible Practical Implication of High CRP Levels in PCOS.* SAGE Publications Sage UK: London, England; 2019.

[182] Paquissi FC. The role of inflammation in cardiovascular diseases: the predictive value of neutrophil–lymphocyte ratio as a marker in peripheral arterial disease. *Therapeutics and clinical risk management.* 2016;12:851.

[183] Shorakae S, Ranasinha S, Abell S, Lambert G, Lambert E, de Courten B, et al. Inter-related effects of insulin resistance, hyperandrogenism, sympathetic dysfunction and chronic inflamma-tion in PCOS. *Clinical endocrinology.* 2018;89(5):628-33.

[184] Murri M, Luque-Ramírez M, Insenser M, Ojeda-Ojeda M, Escobar-Morreale HF. Circulating markers of oxidative stress and polycystic ovary syndrome (PCOS): a systematic review and meta-analysis. *Human reproduction update.* 2013;19(3):268-88.

[185] Pisoschi AM, Pop A. The role of antioxidants in the chemistry of oxidative stress: A review. *European journal of medicinal chemistry.* 2015;97:55-74.

[186] Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. *The international journal of biochemistry & cell biology.* 2007;39(1):44-84.

[187] Mohammadi M. Oxidative stress and polycystic ovary syndrome: A brief review. *International journal of preventive medicine*. 2019;10.

[188] Turrens JF. Mitochondrial formation of reactive oxygen species. *The Journal of physiology.* 2003;552(2):335-44.

[189] Vincent HK, Taylor AG. Biomarkers and potential mechanisms of obesity-induced oxidant stress in humans. *International journal of obesity*. 2006;30(3):400-18.

[190] González F, Rote NS, Minium J, Kirwan JP. Reactive oxygen species-induced oxidative stress in the development of insulin resistance and hyperandrogenism in polycystic ovary syndrome. *The Journal of Clinical Endocrinology & Metabolism.* 2006;91(1):336-40.

[191] Alexander CJ, Tangchitnob EP, Lepor NE. Polycystic ovary syndrome: a major unrecognized cardiovascular risk factor in women. *Reviews in Obstetrics and Gynecology.* 2009;2(4):232.

[192] Targher G, Zoppini G, Bonora E, Moghetti P, editors. Hemostatic and fibrinolytic abnormalities in polycystic ovary syndrome. *Seminars in thrombosis and hemostasis;* 2014: Thieme Medical Publishers.

[193] Nave AH, Lange KS, Leonards CO, Siegerink B, Doehner W, Landmesser U, et al. Lipoprotein (a) as a risk factor for ischemic stroke: a meta-analysis. *Atherosclerosis.* 2015;242(2):496-503.

[194] Burchall GF, Piva TJ, Linden MD, Gibson-Helm ME, Ranasinha S, Teede HJ, editors. Comprehensive assessment of the hemostatic system in polycystic ovarian syndrome. *Seminars in thrombosis and hemostasis;* 2016: Thieme Medical Publishers.

[195] Krul-Poel Y, Koenders P, Steegers-Theunissen R, Ten Boekel E, ter Wee M, Louwers Y, et al. Vitamin D and metabolic disturbances in polycystic ovary syndrome (PCOS): A cross-sectional study. *PloS one.* 2018;13(12).

[196] Rahimi-Ardabili H, Gargari BP, Farzadi L. Effects of vitamin D on cardiovascular disease risk factors in polycystic ovary syndrome women with vitamin D deficiency. *Journal of endocrinological investigation.* 2013;36(1):28-32.

[197] Bouillon R, Carmeliet G, Verlinden L, van Etten E, Verstuyf A, Luderer HF, et al. Vitamin D and human health: lessons from vitamin D receptor null mice. *Endocrine reviews.* 2008;29(6):726-76.

[198] Berridge MJ. Vitamin D deficiency and diabetes. *Biochemical Journal*. 2017;474(8):1321-32.

[199] Hu Z, Jin'an Chen XS, Wang L, Wang A. Efficacy of vitamin D supplementation on glycemic control in type 2 diabetes patients: a meta-analysis of interventional studies. *Medicine.* 2019;98(14).

[200] Pérez-López FR. Vitamin D metabolism and cardiovascular risk factors in postmenopausal women. *Maturitas.* 2009;62(3):248-62.

[201] Ge H, Sun H, Wang T, Liu X, Li X, Yu F, et al. The association between serum 25-hydroxyvitamin D3 concentration and serum lipids in the rural population of China. *Lipids in health and disease.* 2017;16(1):215.

[202] Talmor-Barkan Y, Bernheim J, Green J, Benchetrit S, Rashid G. Calcitriol counteracts endothelial cell pro-inflammatory processes in a chronic kidney disease-like environment. *The Journal of steroid biochemistry and molecular biology.* 2011;124(1-2):19-24.

[203] Liu W, Zhang L, Xu H-J, Li Y, Hu C-M, Yang J-Y, et al. The anti-inflammatory effects of vitamin D in tumorigenesis. *International journal of molecular sciences.* 2018;19(9):2736.

[204] Tiosano D, Wildbaum G, Gepstein V, Verbitsky O, Weisman Y, Karin N, et al. The Role of vitamin D receptor in innate and adaptive immunity: a study in hereditary vitamin D–resistant rickets patients. *The Journal of Clinical Endocrinology & Metabolism.* 2013; 98(4):1685-93.

[205] Hewison M. Vitamin D and immune function: an overview. Proceedings of the Nutrition Society. 2012;71(1):50-61.

[206] Zadeh-Vakili A, Tehrani FR, Daneshpour MS, Zarkesh M, Saadat N, Azizi F. Genetic polymorphism of vitamin D receptor gene affects the phenotype of PCOS. *Gene.* 2013;515(1):193-6.

[207] Mogili KD, Karuppusami R, Thomas S, Chandy A, Kamath MS, Aleyamma T. Prevalence of vitamin D deficiency in infertile women with polycystic ovarian syndrome and its association with metabolic syndrome–A prospective observational study. *European Journal of Obstetrics & Gynecology and Reproductive Biology.* 2018;229:15-9.

[208] Kensara OA. Prevalence of hypovitaminosis D, and its association with hypoadiponectinemia and hyperfollistatinemia, in Saudi women with naïve polycystic ovary syndrome. *Journal of clinical & translational endocrinology.* 2018;12:20-5.

[209] He C, Lin Z, Robb SW, Ezeamama AE. Serum vitamin D levels and polycystic ovary syndrome: a systematic review and meta-analysis. *Nutrients.* 2015;7(6):4555-77.

[210] Davis EM, Peck JD, Hansen KR, Neas BR, Craig L. Associations between vitamin D levels and polycystic ovary syndrome phenotypes. *Minerva endocrinologica*. 2019;44(2):176-84.

[211] Azziz R. Does the risk of diabetes and heart disease in women with polycystic ovary syndrome lessen with age? *Fertility and sterility.* 2017;108(6):959-60.

[212] Talbott EO, Zborowski JV, Sutton-Tyrrell K, McHugh-Pemu KP, Guzick DS. Cardiovascular risk in women with polycystic ovary syndrome. *Obstetrics and gynecology clinics of North America.* 2001;28(1):111-33.

[213] Mcfarlane SI, Banerji M, Sowers JR. Insulin resistance and cardiovascular disease. *The Journal of Clinical Endocrinology & Metabolism.* 2001;86(2):713-8.

[214] Carmina E, Campagna A, Lobo R. Emergence of ovulatory cycles with aging in women with polycystic ovary syndrome (PCOS) alters the trajectory of cardiovascular and metabolic risk factors. *Human Reproduction.* 2013;28(8):2245-52.

[215] Ramezani Tehrani F, Amiri M, Behboudi-Gandevani S, Bidhendi-Yarandi R, Carmina E. Cardiovascular events among reproductive and menopausal age women with polycystic ovary syndrome: a systematic review and meta-analysis. *Gynecological Endocrinology.* 2020;36(1):12-23.