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## Polycystic Ovary Syndrome and Cardiovascular Disease

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### 1. Introduction

Young women have an inferior risk of cardiac events, but this benefit fades after menopause, leaving them at risk to develop a cardiovascular disease (CVD) (Stramba-Badiale, Fox et al. 2006). Endocrine and gynecologic diseases may have impact on this pattern. Ever since the classical notice of Stein and Leventhal in 1935 (Stein and Leventhal. 1935), interest in polycystic ovaries (PCO) and its accompanying syndrome (PCOS) has grown from a “gynecological curiosity to a multisystem endocrinopathy” (Homburg 1996). Actually, polycystic ovary syndrome (PCOS), is the most common female endocrinopathy in up to 10% in reproductive age and appears to be related with an increased cardiovascular risk (Talbot, Guzick et al. 1995; Cibula, Cifkova et al. 2000). The syndrome is characterized by chronic anovulation and hyperandrogenism (Franks 1995; Scarpitta and Sinagra 2000). Cardiovascular disease and type 2 diabetes are two potential major long-term sequelae of this condition that is worth of examination.

Even though the first description occurred almost 70 years ago, there has not been agreement about its definition. At a recent collective European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM) consensus meeting, a refined definition of PCOS was agreed: particularly, the presence of two out of the following three criteria:

- i. oligo- and/or anovulation
- ii. hyperandrogenism (clinical and/or biochemical)
- iii. polycystic ovaries, with the exclusion of other etiologies (2004).

It is widely accepted that polycystic ovary syndrome (PCOS) is correlated with an increased risk of cardiovascular disease. Dyslipidaemia (Legro, Kunesman et al. 2001; Pirwany, Fleming et al. 2001), hypertension (Dahlgren, Janson et al. 1992; Luque-Ramirez, Alvarez-Blasco et al. 2007) and diabetes (Ehrmann, Barnes et al. 1999; Legro, Kunesman et al. 1999) are appeared to be more common in women with PCOS. Obesity, especially central obesity, is a pivotal factor for predicting the long-term risk of cardiovascular disease (Franks, Kiddy

et al. 1991; Luque-Ramirez, Alvarez-Blasco et al. 2007). There is substantial convergence among these features found in PCOS and the metabolic syndrome, and it is potential that these are interrelated conditions. Alterations in clotting (Manneras-Holm, Baghaei et al. 2011) and blood vessel function (Paradisi, Steinberg et al. 2001) might describe why cardiovascular disease is a long-term risk in women with PCOS.

However metabolic abnormalities aforementioned and obesity were not recognized until reduced sensitivity to insulin and compensatory hyperinsulinemia were demonstrated in PCOS patients. The metabolic profile well known in women with PCOS, is equivalent to the insulin resistance syndrome, a clustering within an individual with hyperinsulinemia, mild glucose intolerance, dyslipidemia, and hypertension. The insulin resistance syndrome (or syndrome X) has been recognized as a risk factor for developing type 2 diabetes and CVD (Legro, Kunselman et al. 1999; Korhonen, Hippelainen et al. 2001).

There is also a strong association between hyperandrogenemia and insulin resistance in PCOS (Bremer and Miller 2008). This may mainly consider the stimulatory effect of hyperinsulinemia on ovarian androgen production, although hyperandrogenemia may finally contribute to insulin resistance (Baptiste, Battista et al. 2010). This may also underlie the association between hyperandrogenemia and impaired vascular function and reported in some studies involving PCOS subjects (Wu and von Eckardstein 2003). Nevertheless, even though insulin resistance per se has been associated with endothelial dysfunction and increased cardiovascular risk, there is no stable proof that hyperandrogenemia is a risk factor for cardiovascular disease in women (Gorgels, v d Graaf et al. 1997).

Notwithstanding the fact that PCOS is increasingly recognized as being associated with a cluster of cardiovascular risk factors, there is no final evidence for increased cardiovascular events in PCOS. Nor is there, evidently, data show that PCOS alone imparts increased risk independent of associated risk factors. This article intends to review the spectrum of cardiovascular risk factors, the cardiovascular epidemiology and especially the most recent studies of subclinical cardiovascular disease in PCOS, investigating cardiovascular structure and function. Although, these latter sets of studies have, in particular, further elucidated the causal links between PCOS and cardiovascular disease.

## **2. Cardiovascular risk factors in PCOS**

### **2.1 Biochemical**

#### **2.1.1 Hyperinsulinemia and insulin resistance**

Insulin resistance, described as a reduced glucose response to a given amount of insulin, is a typical metabolic disturbance related with PCOS. Resistance to the activity of insulin in target tissues is a main pathogenic factor in metabolic syndrome and type 2 diabetes. Association of PCOS with insulin resistance was known nearly three decades ago (Burghen, Givens et al. 1980). Hyperinsulinemic euglycemic clamp measurements have shown that insulin-mediated glucose uptake have decreased by 35-40% in both lean and obese women with PCOS, similar to the degree of insulin resistance seen in patients with type 2 diabetes (Dunaif, Segal et al. 1989). Insulin resistance causes compensatory hyperinsulinemia, which is related to many of the phenotypic features of PCOS (menstrual disturbances, evolvment of ovarian cysts, hirsutism and other associated disorders) through multiple mechanisms, involving ovarian steroidogenesis, gonadotrophin secretion, and sex hormone binding

globulin production (Ehrmann 2005). Insulin can enhance ovarian steroidogenesis and enhance directly, independently and/or augment LH-mediated androgen production (Barbieri, Makris et al. 1984; Poretsky, Cataldo et al. 1999; Bremer and Miller 2008). Hence, hyperinsulinemia and hyperandrogenemia are two essential characteristics of PCOS. Their cause and effect relationship is still debated (Dunaif 1997; Poretsky, Cataldo et al. 1999; Legro, Gnatuk et al. 2005; Bremer and Miller 2008). However, several evidences suggest that hyperinsulinemia may be the principal cause leading to the ovarian hyperandrogenemia. Insulin level reduction pharmacologically, has been ameliorating hyperinsulinemia as well as hyperandrogenemia and restore ovulation in the women with PCOS. Even though, a decrease in androgen levels by bilateral oophorectomy, administration of GnRH agonist (Bremer and Miller 2008), or antiandrogenic combinations (Dunaif 1997) had no impact on IR or hyperinsulinemia in the PCOS women, which would have been expected if hyperandrogenemia was the factor of hyperinsulinemia. Besides, the peripheral insulin resistance in PCOS was related to defective pancreatic  $\beta$ -cell function (Ehrmann, Sturis et al. 1995). Additionally, insulin resistance increases the risk for evolvement of glucose intolerance, type 2 diabetes mellitus (T2DM), hypertension, dyslipidemia and cardiovascular abnormalities in these patients (Maitra, Pingle et al. 2001; Legro, Gnatuk et al. 2005).

PCOS patients have a higher incidence of insulin resistance and hyperinsulinemia than age-matched controls in both obese and nonobese patients. Nonetheless, obese women with PCOS have significantly decreased insulin sensitivity compared with nonobese women who have PCOS. Insulin resistance has been known to lead to the progression of type 2 diabetes mellitus. PCOS patients have progress to impaired glucose tolerance in 30% to 40% of the cases, and as many as 10% of them develop type 2 diabetes mellitus by the age of 40 (Clayton, Ogden et al. 1992; Guzick 2004; Tsilchorozidou, Overton et al. 2004). Strong association between insulin resistance and hyperandrogenemia has been shown by several studies. This association was first reported by Achard and Thiers in 1921 in a bearded woman who was also a diabetic (Guzick 2004). Androgen production is magnified synergistically with LH and insulin action in the ovarian theca cells. In addition insulin decreases hepatic synthesis and release of sex hormone-binding globulin, the hormone that binds testosterone in the blood flow, hence increasing the amount of free testosterone that is biologically attainable (Tsilchorozidou, Overton et al. 2004). Free testosterone levels typically have been increased in hyperinsulinemic PCOS patients. Although the total testosterone concentration may be at the upper range of normal or only moderately elevated (Tsilchorozidou, Overton et al. 2004). The exact cellular and molecular mechanisms of insulin resistance in PCOS remain elusive in spite of the crucial role of insulin resistance in the pathogenesis of this syndrome. Together intrinsic and acquired defects in insulin signaling, have been known as mediators of insulin resistance in women with PCOS.

In PCOS the “central paradox” is characterized by responsive ovaries to insulin effect to produce androgens in spite of systemic insulin resistant state; nonetheless, classical target organs of insulin as well as ovary remains resistant to its metabolic activity. Distinct insulin target tissues and ovary have comprised optimal number and affinity of insulin receptors, and as well as no structural and mutational abnormalities could be detected in the PCOS women (Dunaif 1997; Ciaraldi, Morales et al. 1998; Book and Dunaif 1999; Poretsky, Cataldo et al. 1999). Therefore, a post-receptor binding defect in the insulin signaling pathway appears to play a consequential function in the etiology of selective IR. Notwithstanding the fact that several in vitro and in vivo researches have been carried out in various tissues to

illuminate the possible mechanism of IR and hyperandrogenemia (ovarian cells) (Ovarian cells, adipocytes, fibroblasts, myocytes) (Dunaif 1997; Poretsky, Cataldo et al. 1999; Pessin and Saltiel 2000; Nelson-Degrave, Wickenheisser et al. 2005; Diamanti-Kandarakis and Papavassiliou 2006) in PCOS patients, however the data has not been yet conclusive.

Pancreatic  $\beta$ -cell dysfunction has been described in women with PCOS, whereby there is augmented basal secretion of insulin in spite of an insufficient postprandial response (Ehrmann, Sturis et al. 1995). This imperfection remains even after weight loss, despite an amelioration in glucose tolerance (Holte, Bergh et al. 1995). Insulin performs its effects via insulin receptor to begin a cascade of post-receptor events within the target cell. Phosphorylation stimulates insulin receptor substrates (IRS1-4) to promote glucose uptake through the transmembrane glucose transporter (GLUT4) and additionally intracellular protein synthesis. Tyrosine phosphorylation increments the tyrosine kinase activity of the insulin receptor, while serine phosphorylation inhibits it, and it appears that at least 50% of PCOS patients have excessive serine phosphorylation and inhibition of normal signaling (Tsilchorozidou, Overton et al. 2004). This influences merely glucose homeostasis and not the other pleiotropic activity of insulin, so that cell growth and protein synthesis continue. In addition, serine phosphorylation boosts activity of P450c17 in both the ovary and adrenal gland, hence promoting androgen synthesis, and this may be a reason for both insulin resistance and hyperandrogenism in some PCOS patients (Zhang, Rodriguez et al. 1995).

The source of hyperinsulinemia in patients with PCOS also remains unknown. The post receptor insulin signaling pathway and/or defective insulin secretion may be associated with an intrinsic abnormality (Holte, Bergh et al. 1995; Dunaif 1997). Probably, the metabolic abnormalities in PCOS begin very early in life, during the prenatal or prepubertal period, and an early exposure to androgens during growth may affect the body fat distribution and insulin action (Abbott, Dumesic et al. 2002; Eisner, Barnett et al. 2002). These observations have shown convincing proof that PCOS patients have insulin resistance and/or hyperinsulinemia, especially when they are anovulatory and obese with central fat distribution. Given that insulin resistance is an independent risk factor for metabolic abnormalities, the presence of insulin resistance in PCOS women implies the future possibility of cardiovascular disease and type 2 diabetes. Moreover, applying a cardiovascular risk score, insulin resistance in PCOS was established to be an important independent determining factor of cardiovascular risk in women with PCOS (Mather, Kwan et al. 2000).

The 2003 Rotterdam Consensus Conference (at least two of three features: oligo/anovulation, clinical and/or biochemical hyperandrogenism, polycystic ovaries) (2004) revised the 1990 US National Institutes of Health (NIH) definition of PCOS (hyperandrogenism and/or hyperandrogenemia plus oligo-ovulation, with the exclusion of other causes) (Zawadzki and Dunaif 1992), started a great debate. The majority of the studies investigating the metabolic associations of PCOS have used the 1990 NIH definition. Existing proofs support an increased risk of metabolic dysfunction in patients with clinical and/or biochemical hyperandrogenism and oligoovulation, and also in women with hyperandrogenism and normoovulation with polycystic ovaries (Azziz, Carmina et al. 2006). Women with or without oligoovulation with polycystic ovaries have nil or very subtle metabolic characteristics that makes it difficult for their involvement as a syndrome (Azziz, Carmina et al. 2006; Barber, Wass et al. 2007).



### 2.1.2 Dyslipidemia

Dyslipidemia is one of the most verified independent risk factors for the development of atherosclerotic cardiovascular disease, especially elevated low-density lipoprotein (LDL) and triglyceride (TG) levels. The most common metabolic abnormality in PCOS may be dyslipidemia, with a prevalence of up to 70% according to National Cholesterol Education Program criteria (Dunaif, Segal et al. 1989; Talbott, Clerici et al. 1998; Legro, Kuneselman et al. 1999).

Insulin resistance, and its common, but not constant companion, compensatory hyperinsulinemia, have been linked with other different patterns of dyslipidemia. These include low levels of high-density lipoprotein(HDL)-cholesterol (HDL-C), increased values of triglycerides and total and low-density lipoprotein (LDL)-cholesterol (LDL-C), as well as varied LDL quality (Talbott, Clerici et al. 1998; Legro, Kuneselman et al. 2001; Pirwany, Fleming et al. 2001; Essah, Nestler et al. 2008; Valkenburg, Steegers-Theunissen et al. 2008). However, lower HDL levels, higher low-density lipoprotein (LDL)/HDL ratios and higher triglyceride levels are seen most often in both lean and obese women with PCOS (Wild, Painter et al. 1985). This lipid pattern is similar to that found in T2DM. And it is mostly the result of IR that impairs the capability of insulin to suppress lipolysis, thereby expanding mobilization of free fatty acids from adipose stores. As a result, raised hepatic delivery of free fatty acids impairs insulin inhibition of hepatic very low-density lipoprotein 1 synthesis, causing altered catabolism of very low-density lipoprotein (Brunzell and Ayyobi 2003). Excessive adipose tissue increase insulin resistance, and this pattern is more common in obese patients with PCOS. These different patterns may be linked to the accompanying effects of IR and hyperandrogenism that merge with environmental (diet, physical exercise) and genetic factors (Dunaif 1997).

LDL subclasses are consequential predictors of CVD (Gardner, Fortmann et al. 1996). LDL particles are diverse in magnitude, density, and structure. CAD has been associated with small dense LDL particles and increased relative risk of CAD, that ranges from 3- to 7-fold (Austin, Breslow et al. 1988). Numerous studies have revealed a high prevalence of small LDL size in PCOS patients (Wild, Pierpoint et al. 2000; Dejager, Pichard et al. 2001). The differences in lipid profile are sharper at earlier ages and minor divergence is notable beyond the age of 40 years among to PCOS and control women, suggesting an increased risk for atherosclerosis at an earlier age (Talbott, Guzick et al. 1995; Talbott, Clerici et al. 1998). Existence of hormonal discordance may cause an earlier occurrence of atherosclerosis. Obesity and intraabdominal fat distribution in PCOS patients or may reflect the LDL-C increment with age among controls.

Recently, several studies have shown that similar changes of plasma lipids, distinct alterations of Lp and apoB substantially increase the cardiovascular risk (2002; Wierzbicki 2008). ApoB is the principal constitutional component of LDL and a true indicator of the number of particles promoting arteriosclerosis (2002). Some studies found no differences in apoB levels between women with PCOS and the controls (Valkenburg, Steegers-Theunissen et al. 2008). However, the others have shown significant increments in PCOS patients than the controls (Demirel, Bideci et al. 2007). Almost certainly, genetic and environmental influences may cause different lipid patterns. Based on these present data the determination of apoB levels is not advisable in women with PCOS.

Lipoprotein(a) is a miscellaneous class of lipoproteins constructed of an apo(a) molecule connected to an apoB-100 and a lipid. Lp(a) levels are determined genetically, and its metabolic characteristics are different from LDL. The concentration of Lp(a) is remaining stable during the life of a subject (Scanu 1992). Elevated Lp(a) concentrations represent an independent risk factor for cardiovascular events, associated to a raised risk of myocardium infarction, stroke and coronary heart disease (Sandkamp, Funke et al. 1990; Nagayama, Shinohara et al. 1994). Many studies and metaanalysis suggest that Lp(a) levels are increased in women with PCOS (Rizzo, Berneis et al. 2009; Toulis, Goulis et al. 2011).

Lipid disorders in PCOS appear to be connected to hyperinsulinemia (Mather, Kwan et al. 2000) and central obesity (Pirwany, Fleming et al. 2001). Some of the researchers suggested that androgen levels were associated with triglyceride levels, and lipids did not have any association (Legro, Kunselman et al. 2001). Nevertheless, others found no association between androgen levels and dyslipidemia (Pirwany, Fleming et al. 2001).

The current data suggest that distinct lipid profiles may be present in women with PCOS. Furthermore, distinctions among diverse racial and geographical characteristics cannot be entirely explained with body weight variations solely (Essah, Nestler et al. 2008; Valkenburg, Steegers-Theunissen et al. 2008). These distinctions may depend on the combination of genetic, environmental, and hormonal influences. In support of this issue, nonobese women with PCOS also can have raised levels of lipoprotein (a), a steady, genetically and racially determined, lipid-rich, LDL-like lipoprotein that is metabolically different from LDL-C (Scanu 1992; Rizzo, Berneis et al. 2009).

### 2.1.3 Hyperandrogenism

Hyperandrogenism is a dominant characteristic of PCOS with rises of ovarian androgens, testosterone, and androstenedione. Sex hormone binding globulin (SHBG) is usually low in PCOS, principally due to obesity, leading to higher free testosterone levels (Carmina 2002). Hyperandrogenism in PCOS patients, is an indefinite diagnosis of "androgen excess" that does not virilize. However, goes beyond the normal limits. Some depend on the clinical presentation of peripheral androgen excess in women, involving midline hirsutism, acne, and androgenic alopecia to make the diagnosis of hyperandrogenism as part of the PCOS phenotype (Hatch, Rosenfield et al. 1981; Lookingbill, Demers et al. 1991). Hirsutism is quite more common than the PCOS in the populations. Biochemical criteria, in contrast to clinical criteria, are more often used to report hyperandrogenism (Azziz, Ehrmann et al. 2001). Generally, it is concluded with serum tests to document increase in circulating androgen levels. In many multicenter clinical trials of women with PCOS, testosterone and/or some measurements of bioavailable testosterone has been frequently used to determine hyperandrogenism (Hines, Moran et al. 2001).

The gender distinction in vulnerability to cardiovascular disorder has been referred to the difference in sex steroids with oestrogen being seen as cardioprotective and androgens as a potential for exacerbating cardiovascular risk factors (Wu and von Eckardstein 2003). Clinical signs of hyperandrogenism, hirsutism and acne have been recognized as common characteristics of women suffering catheterization for coronary artery disease and were related with more serious disease (Wild, Grubb et al. 1990). There is little proof of an association among androgenic alopecia and raised cardiovascular risk in men, and there is

even less in women (Rebora 2001). Iatrogenic hyperandrogenism in female-to-male transsexuals does not cause increased cardiovascular mortality (van Kesteren, Asscheman et al. 1997). Nevertheless, in an experimental model, testosterone management in female primates was related with raised premature atherogenesis, independent of lipid property (Adams, Williams et al. 1995). Equivalent trials in animal models of PCOS have not been reported to date.

The CVD is very low in premenopausal women and there was no evidence about correlation with increased androgens in circulation or urinary excretion with subsequently developed CVD (Gorgels, v d Graaf et al. 1997). Furthermore, prospective researches of postmenopausal populations, circulating androgen levels did not correlate with cardiovascular events (Price, Lee et al. 1997). The few studies that examined the correlation between endogenous androgens and the evolvement of cardiovascular disorder have not shown that androgen level performs a significant role in women with PCOS (Barrett-Connor and Goodman-Gruen 1995). The carotid intima-medial thickness (CIMT) has been shown to be inversely correlated with endogenous dehydroepiandrosterone sulphate (DHEAS) and testosterone in premenopausal and postmenopausal women (Bernini, Sgro et al. 1999).

It looks likely that in spite of the accepted consistent gender disproportion in the prevalence of cardiovascular disease, nonhormonal, genetic and environmental circumstances may play a greater role than that of androgens. In summary, the evidence for a association between hyperandrogenism per se and CVD in women is faint.

#### 2.1.4 Novel risk factors

Recent cardiovascular studies have identified new biochemical markers for early atherosclerosis, and many of these have been found to be elevated in women with PCOS. Preliminary investigations suggest that serum biomarkers of cardiovascular disease, such as C-reactive protein (Kelly, Lyall et al. 2001; Mohlig, Spranger et al. 2004), adiponectin (Panidis, Kourtis et al. 2003; Spranger, Mohlig et al. 2004), plasminogen activator-1 (Sampson, Kong et al. 1996), endothelin-1 (Diamanti-Kandarakis, Spina et al. 2001), Von Willebrand factor (Dahlgren, Janson et al. 1994), homocysteine (Loverro, Lorusso et al. 2002) and markers of oxidative stress (Sabuncu, Vural et al. 2001) were abnormal in women with PCOS.

Whilst hyperhomocysteinemia is a risk factor for cardiovascular diseases, it has been assumed that homocysteine levels are higher in women with PCOS than controls. Homocysteine is an amino acid created by the transformation of methionine to cysteine. Homocysteine is metabolized by one of two mechanisms: trans-sulfuration and remethylation. This procedure needs vitamin B as a cofactor (Dahlgren, Janson et al. 1992; Talbott, Guzick et al. 1995; Wild, Pierpoint et al. 2000).

Potential pathophysiologic mechanisms of the impact of homocysteine comprise intensified peroxidation injury, proliferation of the smooth vessel, initiative of monocytic chemotaxis, enhanced cytotoxicity and inflammation, promotion of clotting, inhibition of anticoagulation, through effects on endothelial cells, and activation of platelet aggregation (Fermo, Vigano' D'Angelo et al. 1995; Mayer, Jacobsen et al. 1996; D'Angelo and Selhub 1997).

Numerous epidemiological reports have established hyperhomocysteinemia as an independent risk factor for cardiovascular disease, cerebrovascular disease, recurrent



venous thromboembolism. It may arise from genetic defects in the enzymes within homocysteine pathways such as a methylene tetrahydrofolate reductase (MTHFR), imperfections in vitamin cofactors, or other causes, which contain drugs, such as fibrates and nicotinic acid and several chronic medical conditions (D'Angelo, Coppola et al. 2000; Orio, Palomba et al. 2003; Dierkes, Westphal et al. 2004; Baccarelli, Zanobetti et al. 2007). Many studies have evaluated homocysteine levels in women with PCOS. Most have revealed that women with PCOS have increased homocysteine levels when compared with controls (de la Calle, Gallardo et al. 2007; Atamer, Demir et al. 2008; Yilmaz, Pektaş et al. 2008; Oktem, Ozcimen et al. 2009).

The role of inflammation in the evolvement of atherosclerosis has been well clarified. Epidemiological researches to have displayed that markers of inflammation, such as C-reactive protein (CRP) and white cell count, are independent predictors of cardiovascular disease odds. Several studies have been displayed elevated levels of high sensitivity CRP (Kelly, Lyall et al. 2001; Boulman, Levy et al. 2004), but not all (Mohlig, Spranger et al. 2004), in women with PCOS, independent of BMI. Recently, a higher white cell count was found to be correlated with a degree of insulin resistance in women with PCOS independent of BMI (Orio, Palomba et al. 2005). Predictors of vascular endothelial activation and damage, and oxidative stress has also been associated to a raised incidence of cardiovascular hazard, and peculiarities of these have been reported in women with PCOS. This issue is controversial if these correlations are independent of co-existent causes such as age, obesity, insulin resistance, blood pressure, serum glucose and lipid levels.

The circulating levels of tumour necrosis factor- $\alpha$  (TNF  $\alpha$ ), interleukin (IL)-6, as well as white blood count (WBC) and neutrophil count have been found to be elevated in PCOS patients compared with age- and /body mass index- (BMI-) matched controls (Alexander 1994; Kelly, Lyall et al. 2001; Amato, Conte et al. 2003). However, it has been revealed that obesity, and not PCOS status per se, was a major determinant of the circulating inflammatory markers TNF  $\alpha$ , soluble type 2 TNF receptor, IL-6, and hs-CRP (Escobar-Morreale, Villuendas et al. 2003; Mohlig, Spranger et al. 2004). Increment in both low-grade chronic inflammation and insulin resistance in women with PCOS is related with raised central fat excess rather than PCOS status (Puder, Varga et al. 2005). Furthermore, TNF  $\alpha$  is over expressed in adipose tissue and induces insulin resistance throughout acute and chronic effects on insulin-sensitive tissues (Hotamisligil, Shargill et al. 1993). The origin of redundant TNF  $\alpha$  in PCOS is likely to be adipose tissue in the obese but remain obscure in lean women with PCOS. Nevertheless, increased visceral obesity could be a origin of redundant TNF  $\alpha$  in lean women with PCOS. Other proinflammatory cytokine is IL-18, which was showed to be raised in PCOS patients (Stephens, Butts et al. 1992). IL-18 causes the production of TNF  $\alpha$  which promotes the synthesis of IL-6, which is also thought about a strong risk marker for cardiovascular disease (Blankenberg, Tiret et al. 2002). Collectively, the above findings reveal that low-grade chronic inflammation could be a novel mechanism contributing to increased risk of coronary heart disease in PCOS.

Adiponectin, leptin and resistin, are bioactive peptides that are known as adipocytokines secreted by adipocytes, can affect insulin sensitivity and energy balance. Whether or not they have a function in the pathogenesis of PCOS is mysterious. Still the peculiarities in the plasma concentrations of adipocytokines independent of obesity and insulin resistance in PCOS have

not been consistently demonstrated (Panidis, Kourtis et al. 2003; Spranger, Mohlig et al. 2004). The low plasma adiponectin levels have been related with an increased risk of the development of type 2 diabetes (Lindsay, Funahashi et al. 2002). Low adiponectin levels have also been connected with endothelial dysfunction (Tan, Xu et al. 2004), inflammation (Ouchi, Kihara et al. 2003) and coronary artery disease (Kumada, Kihara et al. 2003).

## **2.2 Clinical factors**

### **2.2.1 Obesity**

Obesity is a well defined independent risk factor for the development of type 2 diabetes and cardiovascular disorder. The western lifestyle is a major cause that increased the obesity prevalence (Kuczmarski, Flegal et al. 1994). The hyperinsulinemia appears to be the principal metabolic characteristic in normoglycemic normotensive obese subjects, while insulin resistance is not as extensive as formerly thought (Ferrannini, Natali et al. 1997). Most momentously, cardiovascular morbidity and mortality are raised in obese women independently of other hazardous influences (Manson, Colditz et al. 1990).

The PCOS patients are usually more obese than age matched controls, and have a rise of both BMI and waist/hip ratio (Talbot, Guzick et al. 1995). The appearance of obesity in women with PCOS diverges according to geographic location and the obese phenotype being remarkably common in the United States of America (Knochenhauer, Key et al. 1998). The UK researches showed the prevalence of obesity in PCO women was 35–38% (Kiddy, Sharp et al. 1990; Balen, Conway et al. 1995). The prevalence of PCOS was 10–38% in Mediterranean countries (Diamanti-Kandarakis, Kouli et al. 1999; Asuncion, Calvo et al. 2000) and Norman et al. found a prevalence as high as 63% in Australia (Norman, Masters et al. 1995).

Obesity is related with the insulin resistance, hypertension, dyslipidemia, subclinical inflammation and increased platelet activation, which are risk factors for atherosclerosis (Despres, Moorjani et al. 1990; Davi, Guagnano et al. 2002; Dalton, Cameron et al. 2003). A central obesity, which is demonstrated with an elevated waist/hip ratio, is an important and independent cardiovascular risk factor (Norman, Masters et al. 2001). The correlation between central obesity and cardiovascular disease in PCOS may be relatively linked to low plasma adiponectin levels, even though this postulate has not yet been seriously evaluated (Nishizawa, Shimomura et al. 2002).

### **2.2.2 Hypertension**

Whether the prevalence of hypertension is increased in women with PCOS is obscure. Relevant researches to have utilized varying definitions of PCOS, and a wide diversity of techniques to evaluate blood pressure. Furthermore, studies, including those utilizing 24-h ambulatory blood pressure monitoring procedures, have stated inconsistent consequences (Dahlgren, Janson et al. 1992; Mather, Kwan et al. 2000; Wild, Pierpoint et al. 2000). Obese PCOS patients were found to have raised systolic but not diastolic BP compared to weight matched control women, although there was no divergence in blood pressure degrees between the non-obese group (Legro, Kusanman et al. 2001). Women with oligomenorrhea and hirsutism had increased levels of systolic and diastolic blood pressures compared to control women (Taponen, Martikainen et al. 2004). Additionally, some research indicated that an increased risk of having prehypertension (SBP 120 to 139 mm Hg or DBP 80 to 89 mm Hg) in

women with PCOS (Lo, Feigenbaum et al. 2006), a condition related with a two-times an increased risk of death from a cardiovascular disease (Masi, Feigenbaum et al. 1995).

However, existing data need to be assessed with caution, since small differences in blood pressure could have a great effect on the population cardiovascular risk (Rose 1981). The absence of momentous association with hypertension is surprising while considering the close link between PCOS and the metabolic syndrome. Pertinent studies have, however, utilized variable definitions of PCOS and employed a wide variety of techniques to assess blood pressure.

### 2.2.3 Metabolic syndrome

Metabolic syndrome, or the insulin resistance syndrome which has been known as a constellation of endocrine and biochemical markers that places affected individuals at important cardiovascular risk. The metabolic syndrome is described by the presence of three out of the five following criteria: fasting serum glucose of 100 mg/dL or greater, blood pressure higher than 130/85 mmHg, fasting triglyceride level greater than 150 mg/dL; serum high density lipoprotein cholesterol less than 50 mg/dL in females and a woman's waist circumference equal to or greater than 35 inches (88 cm) (2002).

Individuals with the metabolic syndrome have a raised likelihood of having CVD and increased all-cause mortality, nevertheless, in the absence of diabetes or cardiovascular disease at baseline (Korytkowski, Mookan et al. 1995). PCOS patients have been found to have an increased incidence of the metabolic syndrome (Dahlgren, Landin et al. 1998; Baillargeon, Jakubowicz et al. 2004). The prevalence has been stated to be as high as 43% in these patients, which is twofold more than the age-adjusted prevalence rate of 24% nationally, displayed in the NHANES III survey data analysis (Morin-Papunen, Vauhkonen et al. 2000). Dokras et al. revealed the age- and BMI-adjusted prevalence of the metabolic syndrome to be 47% in women with PCOS compare to 4.3% in controls, which renders to an eleven-fold increased risk (Elter, Imir et al. 2002).

A waist circumference >88 cm (35 in) or >85 cm defined a central obesity, as proposed by the International Diabetes Foundation, appears to be the most common element of the metabolic syndrome in PCOS. Unexpectedly, Dokras et al. also displayed a 23% prevalence of the metabolic syndrome in those women with PCOS under 30 years of age, compared to 0% for their counterparts without PCOS and 6.7% prevalence among the same demographic values in women in the NHANES study (Elter, Imir et al. 2002; Shroff, Kerchner et al. 2007). Consequently, these researchers suggested that all women with PCOS be screened for the metabolic syndrome. Other experts related to this area also agreed with this suggestion.

Furthermore, the important issue is that the usefulness of the metabolic syndrome as a predictor of cardiovascular disease and type 2 diabetes was recently elucidated when compared with established alternative, more specific risk prediction models. The Diabetes Predicting Model and the Framingham cardiovascular risk score estimate the future risk of developing type 2 diabetes and cardiovascular disease respectively. They take into consideration several risk factors such as ethnicity, age, gender, fasting blood glucose, blood pressure, lipids, smoking status and family history. When compared with the metabolic syndrome in a population-based cohort study these specific prediction models were found

to have raised the sensitivity and specificity in predicting diabetes and cardiovascular disease respectively (Stern, Williams et al. 2004).

#### **2.2.4 Mood disturbances and reduced quality of life**

Accumulating data indicated that mood disturbances, principally severe depression were independent risk factors for CVD (Ounpuu, Negassa et al. 2001) and prevalent in PCOS (Jones, Hall et al. 2008; Bishop, Basch et al. 2009). Various studies displayed increased prevalence of depression and anxiety in women with PCOS. These mood alterations and impaired quality of life cause tiredness, sleep disturbances, phobia, appetite changes, and binge eating (Hollinrake, Abreu et al. 2007; Bishop, Basch et al. 2009; Jedel, Waern et al. 2010). Consequently, depressed women with PCOS have higher BMI and greater IR as CVD risk factors than nondepressed women with PCOS without discrepancies in androgen status (Hollinrake, Abreu et al. 2007), whereas weight loss by an energy-restricted diet ameliorates their depression and quality of life (Thomson, Buckley et al. 2010). It remains to be resolved how mood disturbances as CVD risk factors are associated with shifted stress responsiveness in PCOS patients, as demonstrated by excessive ACTH and cortisol stress responses, disabled IL-6 reply following stress (Benson, Arck et al. 2009), and raised sympathetic nerve activity (Sverrisdottir, Mogren et al. 2008).

#### **2.2.5 Obstructive sleep apnea**

Reports in recent years have revealed on another comorbidity connected with PCOS, obstructive sleep apnea (OSA). OSA has significant clinical consequences, involving raised daytime sleepiness, decreased quality of life, and lessened cognitive performance. Serious cardiovascular effects have also been shown to consequences from OSA, comprising hypertension (Brooks, Horner et al. 1997; Lavie, Herer et al. 2000), stroke (Dyken, Somers et al. 1996), and myocardial infarction (Hung, Whitford et al. 1990). Fogel et al. was shown that obese women with PCOS had substantially raised Apnea-Hypopnea Index (AHI) when compared to age- and weight-matched controls. Moreover, this research demonstrated that PCOS patients were also nine times as more likely to suffer from OSA when compared to the control group (Fogel, Malhotra et al. 2001). Another study performed by Vgontzas et al. displayed sleep-disturbed breathing prevalence 30 times more in PCOS patients than the control group (Vgontzas, Legro et al. 2001).

The high prevalence of OSA has been regarded to be a role of both increased levels of testosterone as well as the obesity that prevalently accompanies PCOS. Nevertheless, it looks that the high commonness of OSA in PCOS cannot be completely explained for based on these two causes solely (Nitsche and Ehrmann 2010). Insulin resistance was found to be a sharper predictor of sleep disordered breathing than was age, circulating testosterone concentrations and BMI (Vgontzas, Legro et al. 2001). It also revealed that women with PCOS taking oral contraceptives were reduced probability to have sleep disordered breathing, uniform with new consequences from the Sleep Heart Health Study Research Group in which hormone-replacement treatment was related with an inferior possibility of sleep disordered breathing among post-menopausal women (Shahar, Redline et al. 2003).

Obese PCOS patients are more likely to suffer from OSA compared to lean patients. The important morbidity and mortality, associated with this condition. PCOS patients should be



screened meticulously with regard to characteristics of daytime sleepiness, morning headaches, snoring, and other symptoms of OSA and directed for proper studies to verify this diagnosis.

### **3. Subclinical atherosclerosis**

Even though the epidemiologic data on cardiovascular events are sparse in women with PCOS, the evaluation of cardiovascular structure and function is providing proof that PCOS and its related clinical phenotype clearly affects the arterial wall and/or myocardium.

#### **3.1 Carotid intima media thickness**

The CIMT has been displayed in numerous studies to predict cardiovascular events, with increasing CIMT correlated with an elevated age-adjusted cardiovascular risk (Bots, Dijk et al. 2002). Increased carotid intima media thickness (IMT), reminiscent of a raised risk for atherosclerosis, was displayed in a small group of PCOS patients over 40 years of age. However, there were no important discrepancies in the prevalence of carotid plaque amongst cases and controls (Guzick, Talbott et al. 1996). This result was independent of dyslipidemia but not plasma insulin levels and obesity. Nevertheless, Talbott et al. stated that CIMT measurements were only distinctive in older PCOS patients compared with controls, and after adjusting for coexistent cardiovascular risk factors PCOS was not a significant predictor of CIMT. This study additionally reported a substantially greater carotid plaque index in the PCOS subjects compared with controls. These results imply that in women with PCOS, subclinical atherosclerosis may not be obvious up to the time of the perimenopause (Talbott, Guzick et al. 2000).

Recently, two researches have displayed a significant difference in CIMT among young, normal weight PCOS patients compared with controls (Orio, Palomba et al. 2004; Vural, Caliskan et al. 2005). Vural et al. demonstrated that PCOS, BMI and a reduced sex hormone binding globulin were all independent predictors of CIMT (Vural, Caliskan et al. 2005). However, the report by Orio et al., showed a strong association between CIMT and the free androgen index that suggests a contribution of hyperandrogenemia to evolvement of atherosclerosis in PCOS (Orio, Palomba et al. 2004). Contrarily, in a larger study raised CIMT was conversely correlated with plasma DHEAS and androstenedione concentrations, proposing a fascinating vasculoprotective influence of hyperandrogenemia in PCOS (Vryonidou, Papatheodorou et al. 2005). Meyer et al. also found a similar vasculoprotective effect of DHEAS in a study involving 80 obese women with PCOS, where higher DHEAS corresponded to notably lower CIMT (Meyer, McGrath et al. 2005). Whether the DHEAS has actually beneficial effects on atherogenesis in PCOS obscure and needs further studies to elucidate this issue.

#### **3.2 Coronary artery calcification**

Coronary artery calcification (CAC) demonstrates the grade of atherosclerosis and is early marker for clinical events. The electron beam computer tomography, has been employed to show raised arterial calcification in the coronary circulation in PCOS women compared with controls (Christian, Dumesic et al. 2003). Since adjusting for BMI, dyslipidemia remained a useful prognosticator of coronary calcification. The research of Mayo Clinic found a 3-fold



rise in CAC in non-diabetic PCOS cases than population controls (Christian, Dumesic et al. 2003). Moreover, when these same participants were compared to obese control women, the participants with PCOS had 2-fold higher degrees of CAC. The intriguing prospective, case-control research with over a nine year follow-up period in PCOS reported by Talbott et al. display an increased incidence of coronary and aortic arterial calcification (Talbott, Zborowski et al. 2004). Young obese PCOS patients have been shown to have a five times raised prevalence of subclinical CAD with the presence of momentous CAC as contrasted to age- and weight matched women (Shroff, Kerchner et al. 2007). The features of metabolic syndrome affect the grade of calcification, comprising central obesity, elevated blood pressure and dyslipidemia, and as a consequence insulin resistance. In that study, the degree of aortic calcification was also positively associated with plasma testosterone concentrations, questioning a presumed atheroprotective nature of hyperandrogenemia in PCOS. These reports, accompanied with angiographic statistics in women displayed a correlation among coronary artery disease and polycystic ovaries (Birdsall, Farquhar et al. 1997).

### 3.3 Endothelial dysfunction

Endothelial dysfunction is recognized to be an early characteristic in the progression of atherosclerosis, and the greater part of researches of macro- and micro-vascular endothelial function in women with PCOS has displayed significant peculiarities. The findings of the studies revealed that arterial dilatatory function was a sign for the presence of endothelial dysfunction in distinct arterial beds in women with PCOS and was related to endothelial dysfunction among insulin resistance and less consistently to hyperandrogenemia. Related mechanisms almost certainly account for the effect of insulin resistance on the biology of NO in both conduit and resistance arteries in PCOS patients (Paradisi, Steinberg et al. 2001; Kelly, Speirs et al. 2002; Orio, Palomba et al. 2004). These studies collectively confirmed that increased arterial stiffness, myocardial and endothelial dysfunction showed solid pathophysiological proof for arterial atherosclerosis in women with PCOS. Many of these studies have shown a correlation between insulin resistance and cardiovascular abnormalities, and supported the hypothesis that insulin resistance remains at the vascular level in women with PCOS. However, still needs further proof for the associate with the clinical cardiovascular events.

### 3.4 Ventricular function

One of the early manifestations of diabetic cardiomyopathy is left ventricular (LV) diastolic dysfunction which has been recognized as a predictor for cardiovascular events in hypertensive patients (Schannwell, Schneppenheim et al. 2002; Schillaci, Pasqualini et al. 2002). Its etiology is multifactorial and refers to hypertension, coronary artery disease, insulin resistance, autonomic neuropathy, microangiopathy, dyslipidemia, endothelial dysfunction and oxidative stress (Brutsaert, Sys et al. 1993). The case control prospective studies that utilize echocardiographic methods demonstrated that women with PCOS were found to have a raised isovolumetric relaxation time (IVRT), an indicator of the early LV diastolic dysfunction, and lower ejection fraction in contrast to weight matched controls. In addition, an important clear connection among plasma insulin levels and IVRT was displayed in PCOS patients (Tiras, Yalcin et al. 1999). These results were consistent with another study which demonstrated an independent association between hyperinsulinemia and LV mass (Orio, Palomba et al. 2004).

The postulate that insulin resistance may contribute to myocardial dysfunction in PCOS has been supported with these studies' findings.

### 3.5 Aortic stiffness

The peripheral circulation arterial stiffness is related to raised systolic blood pressure, pulse pressure and ventricular load, as well as to decreased diastolic perfusion of the coronary blood flow. Arterial stiffness may be assessed by two approaches. One is the ultrasonographic evaluation of carotid artery distensibility by measuring pulse wave velocity (PWV) and the other one analysis of the diastolic part of the radial waveform (Bots, Dijk et al. 2002). Arterial stiffness is increased in other diseases such as in renal failure it has been indicated to have prognostic value for cardiovascular events (London, Marchais et al. 2004). Kelly et al. found increased pulse wave velocity of the brachial artery, but not of the aorta, in PCOS patients in a small case control study (Kelly, Speirs et al. 2002). Likewise, Lakhani et al. showed raised stiffness of both internal and external carotid arteries in women with both PCOS and PCO (ultrasonographic polycystic ovaries alone) compared with controls. Multivariate analysis implied independent influences of PCOS and PCO on arterial stiffness (Lakhani, Constantinovici et al. 2000).

## 4. Cardiovascular events

In spite of the fact that cardiovascular risk factors are more frequently found in PCOS patients, reliable proof for a raised prevalence of cardiovascular disease is lacking. The predicted relative risk of myocardial infarction was found 7,4 by the calculated risk factor profile in a small group of women (n = 33) with histopathological verification of polycystic ovaries (PCO) compared with aged-matched controls (Dahlgren, Janson et al. 1992).

A subsequent study that included 142 women undergoing coronary angiography revealed that polycystic ovaries were independently correlated with the presence of an extent of coronary atherosclerosis determined during catheterization. The examination of pelvic ultrasonography imaging showed that forty two percent of these women had polycystic ovaries. Moreover, these patients had more extensive coronary artery disease than the group without polycystic ovaries, established on a number of segments by more than 50% stenosis (Fogel, Malhotra et al. 2001).

Nevertheless, a larger retrospective cohort found that PCOS patients (n = 345) diagnosed primarily with ovarian morphology, had further cardiovascular risk factors, comprising obesity, diabetes, hypertension and hyperlipidemia. Their mortality and morbidity from coronary heart disease didn't show a disparity from age-matched controls (n = 1060) (Wild, Pierpoint et al. 2000). This remarkable result could be explained with the ascertainment bias, to application of a non-standard description of PCOS, or perhaps to a cardiovascular defensive impact of hyperandrogenemia. Even though, after adjusting for BMI, the odd's ratios for developing diabetes and cerebrovascular disease in this analysis were raised considerably at 2.3 and 2.8, respectively.

The Women's Ischemia Syndrome Evaluation (WISE) is the most important study that evaluated both cardiovascular risk and consequences in women with PCOS. WISE is a multicenter research that intends to ameliorate diagnostic testing for ischemic heart disease

in women and to study pathophysiology and prognosis in women with symptoms and proof of myocardial ischemia in the absence or presence of obstructive coronary artery disease (CAD). The researchers included 390 postmenopausal women and diagnosed PCOS with the rise in blood serum androgen concentrations integrated with a premenopausal history of irregular menses ( $n = 104$ ). Notably, the prevalence (27%) of PCOS was considerably higher than the population anticipation (5%–8%). However, women with ischemia may represent a refined pool for women with PCOS. Clinically most significant consequence is the cumulative 5-year cardiovascular event-free survival was 78.9% for 104 women with PCOS and 88.7% for 286 women without PCOS (Shaw, Bairey Merz et al. 2008).

Two more studies provided further support to the link between PCOS and CVD. One of them is a cross-sectional study, which included 713 postmenopausal women (mean age, 73.8 yr) and found in nondiabetic women with intact ovaries, a step-by-step categorized association between CVD and quantities of features of assumed PCOS, as described by premenopausal menstrual irregularity, hirsutism, or present biochemical hyperandrogenism (Krentz, von Muhlen et al. 2007). The other case-control study recruited 414 postmenopausal women (mean age, 60.4 yr), used premenopausal menstrual irregularity as a putative sign of PCOS, and found an increased odd's ratio for coronary vascular disorder (Azevedo, Duarte et al. 2006).

Since the majority of studies centered on surrogate results and there are weak at detecting true discrepancies in these consequences, we need extended-course of data to evaluate real risk.

## 5. Management of CVD risk factors

The PCOS treatment aims at amelioration of ovarian function, involving regulating and averting anovulatory uterine hemorrhagia, diminishing obesity, controlling cardiovascular risk factors such as insulin resistance, diabetes, hypertension, hyperlipidemia. Nevertheless, there is no better treatment alternative distinct from lifestyle modification. Numerous researches indicated that improving insulin sensitivity with lifestyle modifications or pharmacological treatment can diminish circulating androgen levels, and increase spontaneous ovulation and pregnancy.

### 5.1 Lifestyle modification

The most valuable approaches for improving insulin sensitivity in overweight, obese PCOS patients are diet, weight reduction, and physical activity. Obesity has changed into an epidemic in most parts of the world and has a marked on reproductive and metabolic peculiarities in women with PCOS. Regrettably there are no optimized medical therapies at this point that causes a permanent weight loss. Moreover, it was reported that 90–95% of subjects who achieved a weight loss will generally relapse (Rosenbaum, Leibel et al. 1997). The efficacious surgical alternative for the morbidly obese PCOS patients may be a bariatric surgery. However, there has been a few reports of this intervention in this special group.

The lifestyle modification for overweight/ obese patients, comprising diet, exercise, termination of smoking, and behavioral modification (Norman, Davies et al. 2002), may have beneficial effects to decrease CVD risk (De Backer, Ambrosioni et al. 2003). The researches revealed that short-period weight-loss intervention in PCOS patients lowers abdominal fat (Andersen, Seljeflot et al. 1995; Holte, Bergh et al. 1995), lessens androgen

levels (Holte, Bergh et al. 1995), IR and in addition ameliorates dyslipidemia, depression, and quality of life, even though long-term weight loss is improbable (Andersen, Seljeflot et al. 1995; Thomson, Buckley et al. 2010).

Numerous studies in PCOS patients have demonstrated, that weight reduction can ameliorate the main characteristics of the endocrine syndrome of PCOS. Weight reduction decrease circulating androgen levels and restart the menstrual cycle (Guzick, Wing et al. 1994; Okajima, Koyanagi et al. 1994; Clark, Ledger et al. 1995). These alterations can be obtained with a weight loss as small as 5% of the initial weight (Franks, Kiddy et al. 1991; Kiddy, Hamilton-Fairley et al. 1992). Additional advantages that have been reported to have lowered circulating insulin levels (Kiddy, Hamilton-Fairley et al. 1989; Kiddy, Hamilton-Fairley et al. 1992). The reduction of free testosterone concentrations, subsequent weight loss mostly mediated through increases by SHBG (Franks, Kiddy et al. 1991; Kiddy, Hamilton-Fairley et al. 1992).

The hypocaloric, low saturated fat, increased mono- and polyunsaturated fat nutrition is advocated, simultaneously with at least 30 min of intermediate-strength physical activity every day to maintain weight. Together both decrease BMI and ameliorate IR and cardiopulmonary function in overweight/obese PCOS patients (Vigorito, Giallauria et al. 2007) and performed greater decreases in fat mass in PCOS women (Bruner, Chad et al. 2006). Altering a dietary macronutrient constitution does not offer a benefit for weight loss over prevalent dietetic approaches solely (Moran, Pasquali et al. 2009).

However, the majority of PCOS patients difficult to achieve desirable weight loss, despite a caloric reduction and modification to healthier diets and physical activity. It may be even harder for these subjects to maintain weight loss, especially whether they are insulin resistant. As well as 10-30% of women with PCOS are lean, weight loss is not a choice for their management.

## 5.2 Insulin sensitizers

Medications developed to treat type 2 diabetes that have insulin sensitizing properties (ie, metformin and thiazolidinediones) have been utilized to treat PCOS, because both diseases are thought to be developed based on impaired insulin action. This class of medication enhance insulin sensitivity and transform impaired to normal glucose tolerance in non-diabetic women with PCOS. These drugs, additionally improve metabolic predictors of cardiovascular risk in PCOS patients, comprising serum triglycerides, PAI-I, and lower blood pressure (Diamanti-Kandarakis, Kouli et al. 1998; Moghetti, Castello et al. 2000). The data provided from the UKPDS, a research of diabetic men and women, showed that there may be lesser cardiovascular events in insulin-resistant individuals treated with insulin-sensitizing drugs (1998).

### 5.2.1 Metformin

Metformin is one of the most frequently prescribed drugs to treat PCOS. Metformin has constantly shown an insulin lowering effect, and that may be its prime mechanism of action. Metformin was certified for the usage of type 2 diabetes by the FDA in 1994, although has been used clinically for approximately to 20 years formerly in other parts of the world (Coetzee and Jackson 1979).



Study results regarding the effects of metformin on primary prevention of CVD are not coherent (Moggetti, Castello et al. 2000; Diamanti-Kandarakis, Alexandraki et al. 2005; Rautio, Tapanainen et al. 2005). Metformin has a little influence on body weight (less than 2–3% of BMI) (Moggetti, Castello et al. 2000; Rautio, Tapanainen et al. 2005; Nieuwenhuis-Ruifrok, Kuchenbecker et al. 2009) and may ameliorate atherogenic dyslipidemia, raising HDL-C and lowering triglycerides (Rautio, Tapanainen et al. 2005; Trolle, Flyvbjerg et al. 2007). Nevertheless, no alterations in HDL-C or triglycerides were seen in some studies (Banaszewska, Pawelczyk et al. 2009). Metformin cannot improve LDL-C or non-HDL-C (Rautio, Tapanainen et al. 2005; Trolle, Flyvbjerg et al. 2007; Banaszewska, Pawelczyk et al. 2009). Furthermore, several studies with metformin have shown that, it lessens of circulating C-reactive protein, PAI-1 (Velazquez, Acosta et al. 1997; Morin-Papunen, Rautio et al. 2003) and may ameliorate premature atherosclerosis, decrease carotid IMT and enhance endothelial function (Diamanti-Kandarakis, Alexandraki et al. 2005; Agarwal, Rice et al. 2010).

The research of Sharma et al. investigated the efficacy of metformin in averting progression to type 2 diabetes, particularly in PCOS patients. During 43.3 months of treatment with metformin, 5% (N.=2) of the 39 patients with normal glucose tolerance at baseline transformed to impaired glucose tolerance, bearing an annual conversion rate of 1.4%. The published article's stated a 16–19% annual conversion rate for PCOS women, therefore, rendering a 11-fold decrease in the annual conversion to impaired glucose tolerance in this metformin given PCOS women. Moreover, none of the fifty PCOS women developed diabetes throughout the study period (Sharma, Wickham et al. 2007).

### 5.2.2 Thiazolidinediones

Thiazolidinediones (TZDs) have been proposed as a treatment option for many of the metabolic aspects of PCOS. These drugs act by increasing insulin stimulated glucose uptake, principally in adipose and skeletal muscle tissues. The activation of  $\gamma$ -peroxisome proliferation activator receptors (PPAR- $\gamma$ ) activates the genes that encode insulin. Troglitazone was the first to be used in this class. Troglitazone treatment improved endothelial function in obese PCOS patients when compared to age and weight matched controls (Paradisi, Steinberg et al. 2003). The same result was obtained with rosiglitazone (Tarkun, Cetinarslan et al. 2005) and pioglitazone (Romualdi, Guido et al. 2003). Troglitazone additionally lowered circulating insulin levels, improved hirsutism, and increased the ovulation rates of PCOS patients (Paradisi, Steinberg et al. 2003)(Dunaif, Scott et al. 1996). A study examined the effects of metformin, rosiglitazone, and a combination of these drugs in non-obese PCOS patients with no clinical or biochemical proof of insulin resistance. Together with other findings, measures of insulin sensitivity was ameliorated meaningfully with metformin and combination therapy, but not with rosiglitazone solely (Baillargeon, Jakubowicz et al. 2004).

Troglitazone and rosiglitazone, at present, are not available due to liver toxicity and cardiovascular side effects respectively. Pioglitazone is the only available molecule in this class and to date did not have the hepatic side effects of their predecessors. A new study closely assessed cardiovascular risk factors in women with PCOS randomized to pioglitazone or placebo for 16 weeks (Glintborg, Hojlund et al. 2008). Enhancement of insulin sensitivity determined with clamp technique, however a serum marker of atherosclerosis sCD36 and hs-CRP significantly diminished. Insignificant alterations were measured in body weight or body composition in the treatment patients, which was



unexpected, given the tendency to weight gain with thiazolidinedione remedies. Another recent analysis randomized 60 women with PCOS for 24 weeks to exenatide (a glucagon-like peptide-1 [GLP-1] analogue in the incretin class of drugs), metformin, or a combination of both (Elkind-Hirsch, Marrioneaux et al. 2008). The research revealed greater weight loss with exenatide than with metformin and found an additive effect of both. Even though no serious side effects (ie, pancreatitis with exenatide) were noted although the knowledge with incretins in women with PCOS is very limited.

### 5.3 Cholesterol lowering drugs

The HMG-CoA reductase inhibitors are a class of cholesterol- lowering agents, also recognized as statins, are blocking the rate limiting step of cholesterol synthesis. Restriction of mevalonate production may furthermore cause diminished maturation of insulin receptors, inhibition of steroidogenesis (via restricting the substrate cholesterol), and change of signal transduction pathways that mediate cellular proliferation (Kodaman and Duleba 2008). They are thought to have a favorable influence on cardiovascular risk independent of their lipid-lowering effect as well, expectedly by pleiotropic activity on systemic inflammation and oxidative stress, the mechanism of which is still to be determined. Stress and inflammation are also thought to play a role in the progression of ovarian theca cell hyperplasia, lead to anovulation and hyperandrogenism in PCOS.

Even though several lipid-lowering medications have been tried (Rizzo, Berneis et al. 2008; Rosenzweig, Ferrannini et al. 2008), only statins have been adequately studied in women with PCOS and have efficiently lowered LDL-C levels (Banaszewska, Pawelczyk et al. 2009; Sathyapalan, Kilpatrick et al. 2009). Several studies found that, statins decrease IR and inflammation, reduce serum total and free testosterone concentrations, and ameliorate endothelial dysfunction in PCOS patients (Duleba, Banaszewska et al. 2006; Banaszewska, Pawelczyk et al. 2009; Sathyapalan, Kilpatrick et al. 2009). Nevertheless, their usage in gestation is contraindicated, and contraception is needed.

Patients with serious dyslipidemia that is not adequately corrected by lifestyle modification and statins may need double pharmacotherapy. It has been found that the addition of metformin does not ameliorate lipid levels furthermore (Banaszewska, Pawelczyk et al. 2009). Statins combined with a fibrate may be required when hypertriglyceridemia and low HDL levels coexist. Fenofibrate is favored because of less drug interactions and the diminished possibility of myopathy (Zambon and Cusi 2007; Rosenzweig, Ferrannini et al. 2008). Nicotinic acid causes a beneficial effect on lipoproteins however needs cautious monitoring for deterioration of glycemic control (Rosenzweig, Ferrannini et al. 2008).

### 5.4 Hypertension therapy

Antihypertensive drug medication is recommended for blood pressure of more than 140 mmHg systolic or 90 mmHg diastolic. Since milder elevation of BP (or prehypertension), increase CVD risk, diminishing BP to 120/80 mm Hg is desirable for longtime CVD protection (Rosenzweig, Ferrannini et al. 2008). Most of the researchers recommend merging pharmacotherapy accompanied by lifestyle modification for incessant hypertension in PCOS patients. Even though some investigators favor angiotensin-converting enzyme inhibitors and angiotensin receptor blockers over diuretics and beta-blockers, utilization of

angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics and beta-blockers is contraindicated in pregnancy and requires contraception.

### 5.5 Antiobesity medications

Phenteramine, sibutramine, and orlistat are FDA-approved weight loss medicines. A number of researches have found that sibutramine combined with a hypocaloric diet enhances weight loss, improves IR, and hypertriglyceridemia, decrease serum free testosterone concentrations, to a greater extent than hypocaloric diet alone. However, this drug may raise diastolic BP and heart rate and is not approved in the course of gestation. Orlistat causes a smaller degree of weight loss. Since the clinical experience with these agents is limited in PCOS and unexpected side effects may happen, authorities do not advocate the utilization of weight loss medicines in women with PCOS.

## 6. Conclusion and future aspects

Although the epidemiologic data is uncertain, current study results strongly support a correlation between PCOS and cardiovascular risk factors, which are represented in Figure 1. Discrepancies among some of the reports reviewed in this chapter, may be due to small sample sizes, bias in case-control designs and the non-standard delineations of PCOS criteria.

Data accumulated to date, indicate that insulin resistance, and obesity may be responsible for early ventricular functional abnormalities, arterial stiffness, endothelial dysfunction and both carotid and coronary atherosclerosis. These abnormalities may be detrimental consequences of insulin resistance per se, such as dyslipoproteinemia, hypertension, low grade inflammation, raised oxidative stress, changed hemostasis and coagulation system alterations. The diminished synthesis of nitric oxide (NO) and excess production of peroxynitrite are apparently principal factors to initiate endothelial dysfunction and atherothrombosis.

The function of hyperandrogenemia in subscribing to the cardiovascular abnormalities surveyed remains obscure and debatable. Most researches detected androgens as a cardiovascular risk in women with PCOS. Even though the minority of reports examined indicated an independent correlation of androgens with impaired cardiovascular structure or function. This additionally strengthens the thought that cardiovascular risk in PCOS resides to insulin resistance rather than hyperandrogenemia. Furthermore, some studies showed that in PCOS patients, androgens, particularly DHEAS, have been a negative association with CIMT.

Weight loss is realizable with lifestyle alterations, bariatric surgery, and pharmaceutical treatment, involving antiobesity and antidiabetic medications. Insulin sensitizers and statins, particularly in combination with hormonal remedies such as OCPs, oral contraceptives seem to have beneficial properties. Nonetheless, greater and longer trials are required previously to elucidate, which is the best treatment to impede cardiovascular events in women with PCOS can be advocated.

The postulation for the development of cardiovascular disease in PCOS founded on the studies surveyed and permitting the illustration in Figure 1. It summarizes possible pathways throughout the cardiovascular risk factors to CVD. However, the presence of these cardiovascular risk factors in women with PCOS, at this time sufficient prospective results that supporting the actual prevalence of cardiovascular events in PCOS patients are lacking.

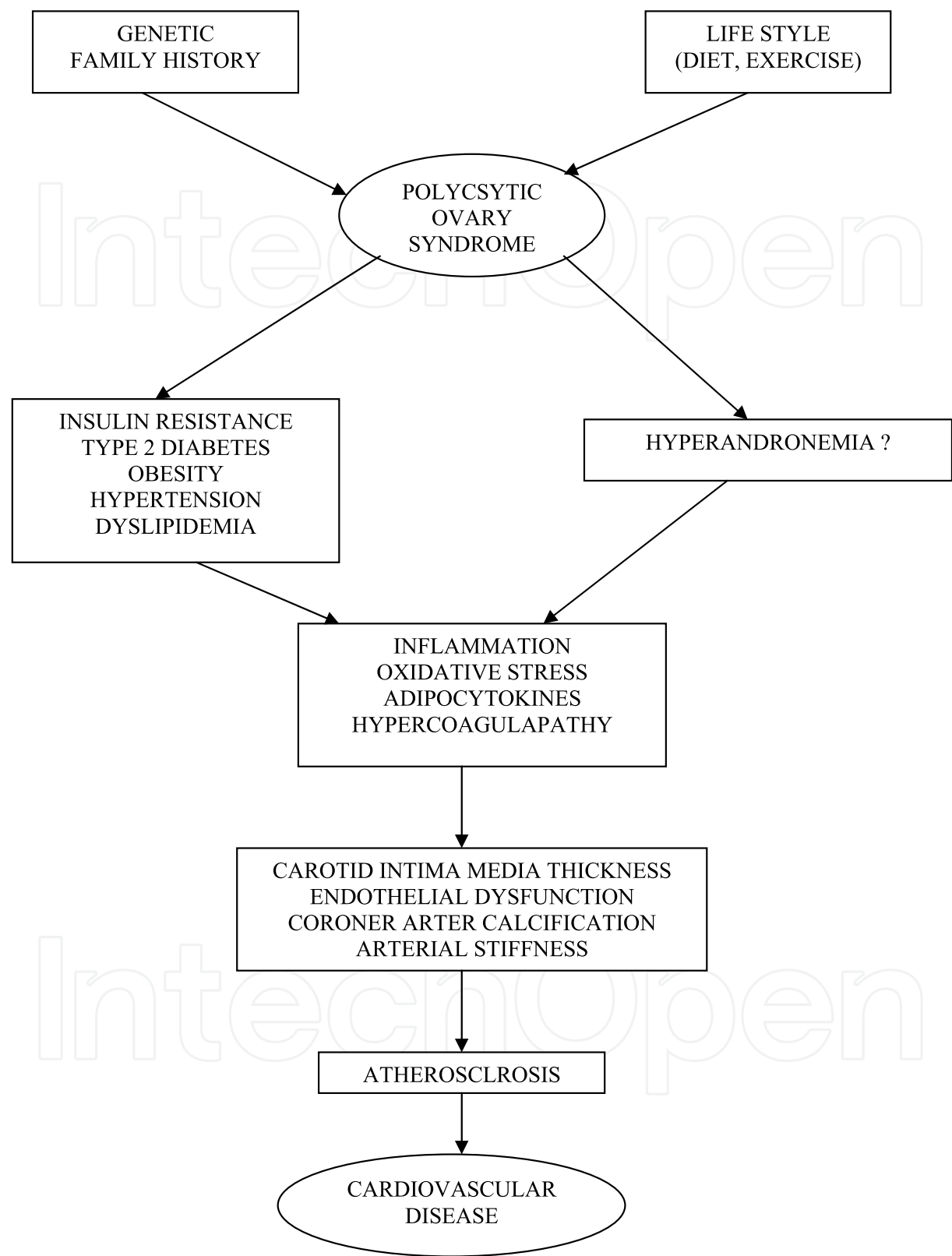


Fig. 1. Postulation for the pathogenesis of cardiovascular disease in PCOS. This figure outlines possible pathways which cardiovascular risk factors associated with PCOS may render into manifest cardiovascular disease.

Definitive prospective data to support a rise in adverse cardiovascular events in women with PCOS is non-existent. However, the most recent studies have firmed up the connection among women with PCOS and CVD events, even though they tend to present in menopause and not in reproductive-age women. Former prediction models have appraised a proportional risk of myocardial infarction of 7.4 PCOS patients. Nevertheless, a large retrospective report of PCOS women showed elevated ratios of diabetes and cerebrovascular disease but not cardiovascular disease, proposing that the earlier estimate of cardiovascular risk may have been extreme. Consequently, that researches perform hereafter have to analyses cardiovascular health results and endeavour to clarify those subgroups that are sharper risk for cardiovascular disease in women with PCOS.

From a clinical aspect, the current statistics imply that management should focus on the designation and treatment of peculiar cardiovascular risk factors recognized to occur more frequently PCOS patients. In particular, lifestyle modification, the avoidance of weight gain and obesity, and the long-term surveillance for evolvement of type 2 diabetes should be accented. After menopause conventional cardiovascular risk accelerates in women, have to be evaluated with precisely mentioning to PCOS. The consequences of interferences such as exogenous oestrogens and anti-androgen treatment on cardiovascular risk in PCOS also required to be investigated further. The high prevalence of this disease in reproductive age women, and the possible correlation with cardiovascular disease, cause future examinations in this issue a priority importance from both a public health and clinical aspect.

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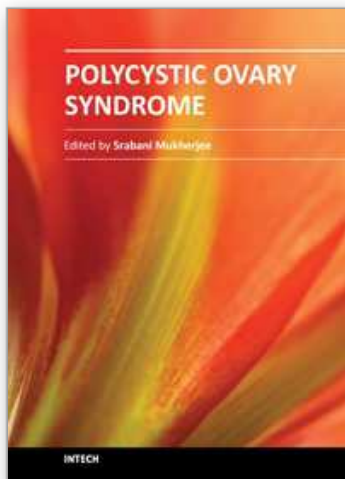
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Brought into the limelight many decades ago, Polycystic Ovary Syndrome (PCOS) is still, to date, surrounded by controversy and mystery. Much attention has been attracted to various topics associated with PCOS research and there has been a healthy advance towards bettering the understanding of the many implications of this complex syndrome. A variety of topics have been dealt with by a panel of authors and compiled in this book. They span methods of diagnosis, reproductive anomalies, metabolic consequences, psychological mindset and ameliorative effects of various lifestyle and medical management options. These books are designed to update all associated professionals on the recent developments in this fast-growing field and to encourage further research into this thought-provoking subject.

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