Cardiometabolic aspects of polycystic ovarian syndrome

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Abstract: It is estimated that 6%–7% of women of reproductive age have polycystic ovarian syndrome (PCOS). Women with this condition exhibit an adverse cardiovascular risk profile, characteristic of the cardiometabolic syndrome and given the high prevalence of PCOS in the female population, this condition may contribute towards the acceleration of cardiovascular disease among young women. This article summarizes the recent development and findings in the cardiometabolic abnormalities in patients with PCOS. Patients with PCOS have the clinical features of oligomenorrhoea, hirsutism and infertility; however, they also exhibit hyperinsulinemia, obesity, hypertension, dyslipidemia, and an increased pro-thrombotic state. They have an increased risk of type 2 diabetes and impaired glucose tolerance, and sleep apnea is also found more commonly in this population. However, despite the presence of cardiovascular risk factors and increased surrogate markers of cardiovascular disease it is unclear if they have accelerated atherosclerosis. End point studies are currently lacking and the available evidence are conflicting. Adipose tissue has emerged as an important endocrine organ over the last decade and gained recognition in having an important role in the cardiometabolic syndrome. Adiponectin that is secreted exclusively by adipocytes has recently been recognized as an important marker of cardiometabolic syndrome, obesity, type 2 diabetes, and coronary artery disease. Other adipocytokines like leptin and resistin have also recently been recognized. This article will address the current evidence for the adverse cardiovascular risk in PCOS and the other factors that may be implicated. Finally the therapeutic options for treatment will be discussed.

Keywords: cardiometabolic syndrome, polycystic ovarian syndrome, cardiovascular disease

Introduction

Polycystic ovarian syndrome (PCOS) is a common endocrine disorder affecting 6%–7% of the population (Knochenhauer et al 1998; Diamanti-Kandarakis et al 1999; Asuncion et al 2000; Azziz et al 2004). It is characterized by chronic anovulation and hyperandrogenism with the clinical manifestation of oligomenorrhoea, hirsutism, and acne (Franks 1995). In January 2004, the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) co-sponsored the Rotterdam polycystic ovary syndrome consensus workshop that published diagnostic guidelines, building on the consensus statement of the National Institutes of Health 1990 (ESHRE/ASRM-Sponsored_PCOS_Consensus_Workshop_Group 2004). The Rotterdam criteria for the diagnosis of PCOS states 2 of the 3 features needs to be present to make the diagnosis and with the exclusion of other etiologies (congenital adrenal hyperplasia, androgen-secreting tumors, Cushing's syndrome). These features includes (1) Oligo- or anovulation (2) Clinical and/or biochemical signs of hyperandrogenism and (3) Polycystic ovaries (either 12 or more follicles measuring 2–9 mm in diameter, or an ovarian volume of >10 cm^3) (Balen et al 2003).

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It has now been recognized that the diagnosis of metabolic syndrome identifies patients at increased risk of developing cardiovascular disease, and attempts have been made to develop the most convenient and useful criteria for the diagnosis of this condition in clinical practice. With the pathogenesis of metabolic syndrome not well understood, central obesity and insulin resistance are acknowledged as important causative factors (Anderson et al 2001; Carr et al 2004; Nesto 2003). The most recent International Diabetes Federation consensus, however, has developed a new definition emphasizing the importance of central obesity with modifications according to ethnic groups (Alberti et al 2006). Previous definitions from the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III), USA (NCEP/ATPIII 2001) and the World Health Organization (WHO) had emphasized insulin resistance (Alberti and Zimmet 1998; Grundy et al 2004).

It would appear that many women with PCOS fulfil the criteria for the metabolic syndrome in view of a higher reported incidence of hypertension, dyslipidemia, visceral obesity, insulin resistance and hyperinsulinemia in this population (Glueck et al 2003). It is recognized that insulin resistance and compensatory hyperinsulinemia not only contribute to hyperglycemia, but they also have a pathophysiological role in the development of the cardio-metabolic state (Mather et al 2000).

Metabolic abnormalities of PCOS

Hyperinsulinemia and insulin resistance

Insulin binds to its receptor on the cell membrane facilitating the delivery of glucose across the membrane by enhancing the expression of GLUT transporters (Stephens and Pilch 1995). Disturbance in insulin's ability to bind to its receptor, or the transport mechanism across the cell membrane may lead to a state of reduced sensitivity to insulin, or insulin resistance. Studies suggest that insulin induced receptor autophosphorylation is markedly diminished in approximately 50% of PCOS women. In those PCOS women who have normal receptor autophosphorylation, it remains likely that signalling mechanism downstream of the receptor are abnormal (Dunaif 1995). In addition to decreased insulin sensitivity, pancreatic β-cell secretory dysfunction has also been reported (Ehrmann et al 1995; Dunaif and Finegood 1996). Furthermore, a reduction in hepatic insulin extraction resulting in a reduction of insulin clearance rate may also contribute to the high insulin levels (Mahabeer et al 1989; O'Meara et al 1993).

Insulin stimulates lipogenesis in arterial tissue and adipose tissue via an increased production of acetyl-Co A, and the entry of glucose and triglycerides (Pekala et al 1983). Dyslipidemia associated with high levels of triglycerides and low levels of HDL cholesterol in cardiometabolic syndrome are attributed to the effect of insulin on cholesterol ester transfer protein that promotes the transfer of cholesterol from HDL to VLDL and resultant catabolism of Apo lipoprotein A (Swenson 1991; Chen et al 1991). As insulin increases the levels of HMG Co A reductase, the rate-limiting enzyme in the synthesis of cholesterol, it may contribute to the raised cholesterol level that is also a feature of hyperinsulinemia (Dietschy and Brown 1974).

Loss of peroxisome proliferator activated nuclear receptor (PPAR) gamma has been linked to the development of severe insulin resistance, diabetes, and hypertension (Celi and Shuldiner 2002). Although both metformin and the thiazolidinediones act as insulin sensitizers, one recent study suggested that only rosiglitazone, but not metformin, increased the expression of PPAR gamma in peripheral tissue (Tiikkainen et al 2004) thereby increasing peripheral insulin sensitivity. This may suggest that the thiazolidinediones may have additional peripheral benefits compared with metformin.

Visceral obesity

The prevalence of obesity in PCOS varies widely, between approximately 10–50% (Balen et al 1995; Carmina et al 1992). Obese PCOS have lower levels of luteinizing hormone (LH), sex hormone binding globulin (SHBG), dehydroepiandrosterone (DHEAS), dihydrotestosterone, free insulin-like growth Factor (IGF)-I, high-density lipoprotein, and higher low-density lipoprotein, compared with the nonobese PCOS group (Silfen et al 2003). However, the situation is complex; not all obese people are insulin resistant and not all who are insulin resistant are obese. Gluteo-femoral obesity is less associated with insulin resistance than is central or android obesity (Basdevant et al 1987). A state of hyperinsulinemia may itself contribute to obesity by the anabolic effect on fat metabolism through adipogenesis with increased uptake of glucose into adipocytes, the production of triglycerides and inhibition of hormone sensitive lipase (Arner 2005).

Hypertension

Hyperinsulinemia may contribute to the hypertension of the cardiometabolic syndrome by enhanced sodium retention (Zavaroni et al 1995), causing an increased intracellular sodium and calcium (Resnick 1992), and stimulation of the

sympathetic nervous system (Muller-Wieland et al 1998; Sechi and Bartoli 1996).

Insulin also stimulates the release of IGF-1 that may contribute to the development of hypertension by causing vascular smooth muscle hypertrophy. Current evidence on prevalence of hypertension in patients with PCOS are conflicting at present with some studies suggesting a higher prevalence in this population (Vrbikova et al 2003; Elting et al 2001; Orbetzova et al 2003; Holte et al 1996), but not by others (Cibula et al 2000; Zimmermann et al 1992; Sampson et al 1996). A large long-term follow-up study by Wild et al (2000a) suggested an increased prevalence of hypertension in patients with PCOS, but with no increased risk of mortality and morbidity from coronary heart disease.

Dyslipidemia

Data are conflicting on whether women with PCOS have a characteristic dyslipidemia. Studies have reported decreased levels of the cardioprotective high-density cholesterol lipoprotein (HDL-C), and elevated levels of triglycerides (Reaven 1988; Robinson et al 1996; Conway et al 1992; Holte et al 1994; Wild et al 1985; Legro et al 1999), although in one study HDL was elevated (Legro et al 2001). Of concern, dyslipidemia has been found at puberty in studies on adolescent girls with a history of premature pubarche (Kent and Legro 2002) and the metabolic disturbances can often be detected in the prepubertal period and throughout puberty (Ibanez et al 1998). This dyslipidemia is seen in both lean and obese PCOS (Yildirim et al 2003)

Pro-thrombotic state

Hyperinsulinemia contributes to the prothrombotic state by reducing fibrinolysis and raising the level of plasminogen activator inhibitor (PAI-1) (Potter van Loon et al 1993). In patients with PCOS, the level of PAI-1 was found to be elevated (Atiomo et al 1998; Sampson et al 1996; Yildiz et al 2002), and it decreased with improvement in insulin sensitivity, either through weight loss (Andersen et al 1995) or the use of insulin sensitizing agents (Ehrmann et al 1997; Velazquez et al 1997). The increase in PAI-1 activity in PCOS was thought to be independent of body mass index since elevated levels were also observed in lean PCOS women. Moreover, the increased level of PAI activity in PCOS was directly correlated with insulin resistance, thus implicating it as a contributing cardiovascular risk factor (Tarkun et al 2004). However, other studies disagree (Atiomo et al 2000; Dahlgren et al 1994).

Risk of type 2 diabetes

PCOS is commonly detected in a younger age group and is associated with a high risk of progression to type 2 diabetes and impaired glucose tolerance. For example, in one study, 35% of patients with PCOS had impaired glucose tolerance and 10% had type 2 diabetes by the age of 40 (Ehrmann et al 1999). A history of type 2 diabetes in a first-degree relative appears to define a subset of PCOS subjects with a greater prevalence of insulin secretory defects. The risk of developing type 2 diabetes through increased insulin resistance in PCOS may be enhanced by the defects described in insulin secretion (Ehrmann et al 1995).

A unique defect in serine phosphorylation of the insulin receptor that resulted in decreased activation of the receptor has been identified in about 50% of women with PCOS (Zhang et al 1995). Furthermore, serine phosphorylation of *CYP17* (Cytochrome P450, subfamily XVII), may also be part of the mechanism of increased adrenal androgen synthesis implicating serine phosphorylation an important process in the PCOS phenotype. The *CYP17* gene encodes the cytochrome *P450c17* enzyme which mediates the 17α-hydroxylation of pregnenolone and progesterone, and subsequent conversion of these 17-hydroxylated products to the estradiol precursors DHEA and androstenedione. In addition, familial PCOS has been linked to an insulin regulatory locus on chromosome 11 (Waterworth et al 1997). Whether this represents a common genetic defect in PCOS and diabetes or whether it reflects co-segregation of diabetes with PCOS in the tested families, remains to be determined.

Sleep apnea

Sleep apnea is an independent cardiovascular risk factor that has been found to be more common in PCOS, the difference remained significant even when controlled for body mass index (BMI) (Gopal et al 2002; Fogel et al 2001). It was reported that the strongest predictors for sleep apnoea were fasting plasma insulin and glucose-to-insulin ratios (Vgontzas et al 2001).

Atherosclerosis

The presence of cardiovascular risk factors of obesity, insulin resistance and dyslipidemia may predispose women with PCOS to coronary heart disease, although this remains controversial:

Angiography

One report evaluated 143 women age less than 60 years old undergoing cardiac catheterization for the investigation of

chest pain. Polycystic ovarian morphology was present in 42% of women, and was associated with hirsutism, lower levels of HDL cholesterol, and higher concentrations of free testosterone, triglyceride, and C-peptide. The women with polycystic ovaries had more extensive coronary disease on angiography than those with normal ovaries (Birdsall et al 1997). However, this study only examined at the association between ultrasound evidence of polycystic ovaries alone (rather than the full Rotterdam consensus definition of PCOS) and the extent of coronary disease on cardiac catheterization.

Carotid ultrasound

A predisposition toward atherosclerosis was suggested in an ultrasonographic study of 16 women with PCOS aged over 40 years, where carotid artery intima-media thickness (IMT) was significantly greater than in normal controls (Guzick et al 1996). However, the mean IMT in the PCOS group was still well below that seen in patients with significant carotid artery disease. In another study with a larger cohort of subjects, the same group of researchers reported that among women aged 45 years or above, patients with PCOS had significantly greater mean carotid IMT than women in the control group (Talbott et al 2000).

Endothelial dysfunction

Endothelial dysfunction is associated with the development of atherosclerosis (Celermajer et al 1992). A positive correlation was demonstrated between abnormal endothelial function and testosterone levels in hyperandrogenic insulin-resistant women with PCOS, an association that was stronger than that of insulin sensitivity (Paradisi et al 2001). Conversely, others have reported no differences in surrogate markers including endothelial function for increased cardiovascular risk in PCOS compared with weight-matched controls (Bickerton et al 2005).

Several mechanisms may be involved in the development of endothelial dysfunction, such as reduced synthesis and release of nitric oxide (NO) (Kawashima and Yokoyama 2004), enhanced inactivation of NO after its release from endothelial cells (Bitar et al 2005) or enhanced synthesis of vasoconstricting agents (Bhagat and Vallance 1999). It has been demonstrated that insulin exerts a direct hypertrophic effect on the vascular endothelium and the smooth muscle cells. It has been found that in the skeletal muscle circulation insulin stimulates both endothelin-1 and NO activity, and an imbalance between the release of these two substances may be involved in the pathophysiology of endothelial dysfunction. Recent studies suggested that CRP directly promotes the atherosclerotic processes and endothelial cell inflammation leading to atherothrombosis (Sjoholm and Nystrom 2005).

Long-term risk

In the Nurses' Health Study, a history of menstrual cycle irregularity was associated with an increased risk of non-fatal and fatal coronary heart disease (Solomon et al 2002). This might be explained by a high rate of PCOS with its associated metabolic disturbances in these women, although no other clinical or biochemical androgen data was available to confirm that menstrual irregularity was due to PCOS.

Despite the increase in cardiovascular risk factors including diabetes, hypertension, raised plasma cholesterol and BMI >30, morbidity and mortality from of coronary heart disease among women with PCOS in a long-term study has not proved to be as high as previously predicted (Wild et al 2000b).

One recent observation showed no difference in surrogate markers of cardiovascular risk between PCOS and weight-matched controls (glucose, lipid, lipoprotein, sialic acid, fibrinogen, CRP, reactive hyperemic forearm blood flow) (Bickerton et al 2005). However, in contrast, in another study patients with PCOS were found to have elevated triglycerides and cholesterol but no differences in CRP or 24 hour BP were observed. In addition, they also demonstrated that patients with PCOS had increased arterial stiffness measured by pulse wave velocity (PWV) and reduced brachial artery flow mediated vasodilatation (FMD), a marker of endothelial function (Meyer et al 2005). Whether these differences could have been accounted for by differing patient selection is unclear.

In summary, cardiovascular disease studies in PCOS have been inconclusive with some suggesting increased cardiac events among women with PCOS whilst other studies suggesting no increase compared with normal cycling women. This could be due to small sample size in the studies and variation in the characteristics of patients recruited. It has been suggested that patients with PCOS as defined by hyperandrogenemia plus either of oligomenorrhoea or polycystic ovaries on ultrasound may have a slight increase in cardiovascular risk profile as compared with those with only oligomenorrhoea and polycystic ovaries without hyperandrogenemia.

The role of adipocyte in cardiometabolic syndrome

Adipose tissue has traditionally been considered an energy storage organ, but over the last decade a novel role of the

adipose tissue as an endocrine organ has emerged (Mohamed-Ali et al 1998; Spiegelman and Flier 1996; Fruhbeck 2004). Adipocytes are metabolically active cells which secrete tumor necrosis factor alpha, interleukin 6, plasminogen activator inhibitor-1, leptin, resistin, adiponectin, and angiotensinogen (Rondinone 2006; Yu and Ginsberg 2005).

Leptin is secreted mainly by adipose tissue and deficiency in leptin results in hyperphagia, decreased energy expenditure and morbid obesity (Friedman and Halaas 1998). However, in terms of human obesity, leptin deficiency is rare. It has been postulated that leptin activates the sympathetic nervous system and is involved in blood pressure regulation, brain and bone development, hematopoiesis and wound healing (Ahima and Flier 2000).

It has been suggested that the function of leptin is to control the deposition of fat and this modulates its harmful accumulation in tissues such as heart, liver and kidneys. Leptin is involved in the control of vascular tone by stimutaneously producing a pressor action and opposing the nitric oxide mediated relaxing function (Fruhbeck and Gomez-Ambrosi 2001). This may contribute to the hypertension associated with cardiometabolic syndrome. A positive relationship between insulin resistant PCOS women (both obese and non-obese) and hyperleptinemia, regardless of the BMI has been suggested in one study (Calvar et al 2003).

Increasing adipose tissue mass is associated with increasing levels of angiotensin II from the increased secretion of angiotensinogen by adipose tissue. Increase in angiotensin II could contribute to hypertension and aggravate insulin resistance (Engeli et al 2003).

IL-6 inhibits liproprotein lipase activity, enhances aromatase activity and increases the hepatic production of triglycerides (Nonogaki et al 1995). IL-6 is stimulated by TNF-alpha: TNF stimulates C-reactive protein that has been found to be correlated with obesity, insulin resistance, endothelial dysfunction, and therefore cardiovascular risk, and patients with PCOS have been shown to have a higher level of CRP (Kelly et al 2001; Bahceci et al 2004). TNF-alpha also suppresses lipoprotein lipase and its release is inhibited by the thiazolidinediones and in PCOS, serum TNF-alpha is increased irrespective of obesity (Gonzalez et al 1999). Elevation of these inflammatory markers are in accord with the hypothesis that atheroma formation is primarily an inflammatory condition.

Adiponectin is secreted exclusively by adipocytes and levels are reduced in obesity, type 2 diabetes and coronary heart disease. Studies suggest an important link with insulin resistance (Steppan et al 2001) and adiponectin also inhibits vascular smooth muscle proliferation and the expression of adhesion molecules. Levels of adiponectin are increased by weight reduction and by thiazoledinediones (Yu et al 2002). It has recently been shown that a significant reciprocal correlation exists between adiponectin and resistin independent of insulin resistance in women with PCOS (Lewandowski et al 2005). Resistin is implicated in the pathogenesis of Type 2 diabetes and obesity (Seow et al 2004) where circulating resistin levels and resistin expression in adipocytes are increased. However, the role of resistin in patients with PCOS and thus cardiovascular risk in this group is still debatable. In one study, serum resistin level in patients with PCOS were no different to matched controls but resistin mRNA levels were 2-fold higher in omental adipocytes from PCOS patients (Seow et al 2004). Others have reported that there is an increase in serum resistin level in patients with PCOS (Munir et al 2005), although it has been suggested that this increase is dependent on BMI (Panidis et al 2004). Against this argument is that in BMI matched patients, serum resistin was found not to be different compared with controls (Carmina et al 2005, 2006). Therefore more studies will be required to determine its importance in patients with PCOS.

Therapy of PCOS

The effective treatment of patients with PCOS requires that the specific goal(s) of the therapy be first established. Individual goals may include fertility, treatment for hirsutism and/or acne, achieving a regular menstrual cycle, weight reduction, and the prevention of the long-term consequences associated with PCOS (type 2 diabetes, dyslipidemia, and possibly cardiovascular disease) or all of the above!

Treatments discussed here will focus on those aimed at modifying the cardiometabolic aspects of PCOS.

Exercise and diet

Although obesity is not thought to be the cause for PCOS, it may exacerbate this dysfunction (Holte 1996). Loss of significant weight has been reported to result in spontaneous resumption of ovulation (Crosignani et al 2003), improvement in fertility (Norman et al 2004), increased SHBG, and reduced basal level of insulin (Huber-Buchholz et al 1999; Tolino et al 2005).

Data from the Diabetes Prevention Program (DPP) showed the importance of weight reduction in patients with impaired glucose tolerance that were at high risk of developing diabetes This study showed that both metformin therapy and intensive lifestyle intervention reduced the risk of developing diabetes (by 31% and 58%, respectively, in comparison with placebo), and both interventions were

suggested to be cost-effective on the basis of computer projected lifetime risk (Ratner 2006). In accord with that is the observation that significant weight loss, ie, >15% of body weight, has been found to improve the metabolic profile of PCOS women (Kiddy et al 1989).

Insulin sensitizers

Metformin

Metformin is effective in the treatment of metabolic syndrome and modestly increases menstrual regularity and ovulation, and may improve hirsutism in patients with PCOS (Harborne et al 2003). Metformin treatment in lean women with PCOS also improves insulin resistance and hyperandrogenism without a change in BMI (Nestler and Jakubowicz 1997). Whilst metformin appears to induce cardio-protective effects on serum insulin (Sahin et al 2004), serum lipids (Ibanez et al 2004), and PAI-1 (Song et al 2002), the actual protection from long-term mortality and morbidity of cardiovascular disease has yet to be demonstrated. In addition, it has been suggested that metformin has a beneficial effect on endothelial function in patients with polycystic ovarian syndrome (Orio et al 2005).

Thiazolidinediones

Pioglitazone and rosiglitazone have also shown positive cardiometabolic effects, reducing hyperandrogenemia, and hirsutism as well as regulating the menstrual cycle in women with PCOS (Brettenthaler et al 2004; Sepilian and Nagamani 2005; Cataldo et al 2006). Rosiglitazone was found to markedly reduce liver fat, increase insulin clearance, double adiponectin concentrations, and unlike metformin, it also increases peripheral insulin sensitivity (Tiikkainen et al 2004). However, thiazolidinediones causes weight gain that may not be a desireable effect in this population of young women whose initial presenting complaint may well be the inability to lose weight.

Orlistat

Orlistat, a pancreatic lipase inhibitor, limits the absorption of dietary fat. We have recently shown that it significantly reduced body weight and that there was a reduction in total testosterone levels in PCOS women equal to that of metformin (Jayagopal et al 2005). In women with PCOS, weight loss is associated with an improvement in insulin sensitivity and a reduction of the insulin concentration in the plasma (Ajossa et al 2004). Therefore weight reduction with orlistat would be a suitable adjunct to insulin sensitizers in the treatment of patients with PCOS.

Sibutamine

Sibutramine, a selective serotonin and adrenergic reuptake inhibitor, has shown positive effects on hyperandrogenemia, and clinical metabolic risk factors for cardiovascular disease in obese women with PCOS (Sabuncu et al 2003). However, sibutramine has to be prescribed with care in patients with hypertension, and in patients with PCOS, metformin may be a more effective treatment in the prompt restoration of ovarian function as compared with sibutramine (Lazurova et al 2004).

In summary, cardiovascular disease studies in PCOS have been inconclusive, with some suggesting an increased in cardiac events among women with PCOS whilst others showed no difference. The mainstay of treatment is the encouragement of diet and exercise augmented by weight reducing medication and use of insulin sensitizers like metformin. Insulin sensitisers have beneficial effects on menstrual regularity, but their use specifically for potential cardio-protection needs to be clarified.

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