Polycystic Ovary Syndrome and the Metabolic Syndrome

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Polycystic ovary syndrome (PCOS) is a common endocrinological disorder in female reproductive age. Insulin resistance (IR) and compensatory hyperinsulinemia seem to be the main pathophysiologies of this syndrome. Therefore, PCOS is at risk for abnormal glucose tolerance, dyslipidemia, central obesity and hypertension. Also, plasminogen activator-inhibitor-1 (PAI-1), hemostatic factor, and C-reactive protein (CRP), inflammatory factor have been reported in PCOS women. The metabolic syndrome (MS), a clustering of several metabolic abnormalities, is more prevalent in PCOS. One-third to 46% of PCOS women with MS have been reported. Since these metabolic abnormalities as well as MS are the important risk factors of cardiovascular disease (CVD), PCOS is at risk for CVD.

Keywords : *Abnormal glucose metabolism, Dyslipidemia, The metabolic syndrome, Polycystic ovary syndrome*

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Polycystic ovary syndrome (PCOS) is a common endocrinological disorder during female reproductive age. The prevalence of the syndrome is 5-10%[1,2]. The main clinical features of PCOS are menstrual abnormalities, hyperandrogenism and typical polycystic appearance of ovaries by ultrasound[3,4]. The etiology of PCOS is still unknown. However, evidence has shown that the pathophysiologies of this disorder are composed of abnormal hypersecretion of luteinizing hormone (LH), abnormal production of androgen and insulin resistance (IR). Of these, IR seems to be the main pathophysiology of PCOS[5,6].

PCOS and insulin resistance

In the early 1980's, Burghen, et al[7] first reported a close association between hyperandrogenism and hyperinsulinemia in PCOS women. The following studies have confirmed the conclusion[8-10]. Dunaif et al. demonstrated that both obese and lean PCOS women have IR when compared with the ovulatory women by using an oral glucose tolerance test[9] and by using a hyperinsulinemic euglycemic clamp technique[10].

IR in PCOS women is selective. The study of fibroblast cells in vitro showed that IR affects in the metabolic, but not the mitogenic pathway[11]. Moreover, IR in PCOS varies between the different tissues. Unlike the fibroblast cells, the cultured skeleton muscle cells do not exhibit the IR state like when they are in vivo. The evidence suggests that there are some circulatory factors, free fatty acids and cytokines, for example, affecting IR of the tissue in PCOS[11]. However, in these tissues, IR in PCOS seems to be secondary to a post binding defect in insulin signaling in the insulin target tissue[11].

IR and compensatory hyperinsulinemia play cardinal roles in the pathophysiology of PCOS. The excess circulating insulin causes hyperandrogenemia. In fact, insulin has a direct effect on the ovarian tissues in steroidogenesis through its own receptors and insulin like growth factor-1 (IGF-1) receptors[12]. It can stimulate the theca cells to produce androgen. Moreover, insulin seems to enhance the effect of luteinizing hormone (LH) on the androgen production in the ovary[13].

High insulin levels can inhibit the production of sex hormone binding globulin (SHBG) from the liver[10,14]. Consequently, this increases the free

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androgen levels and their activities. Furthermore, both hepatic and ovarian IGF-binding proteins (IGFBP), IGFBP-1 in particular, are also inhibit and accordingly increase the free portion of IGF-1. This cytokine has an effect, like insulin, on the ovarian androgen synthesis[14].

The metabolic syndrome

The metabolic syndrome (MS) is a disorder which is composed of the clustering of several metabolic abnormalities including glucose abnormalities, dyslipidemia, obesity and hypertension[15,16]. This syndrome was first proposed by Reaven[17] and several studies have been reported in several names, the syndrome X, the insulin resistance syndrome, and the dysmetabolic syndrome, for instance[15,16,18]. The pathophysiology of MS is IR[19]. Normally, IR state results in compensatory hyperinsulinemia. Both IR and hyperinsulinemia have effects on the several aspects of metabolism. It is well-recognized that IR is a cause of type 2 DM and glucose intolerance[20] and dyslipidemia which comprises of high triglyceride and low high density lipoprotein-cholesterol (HDL-C) levels[17,21,22].

More recently, there have been reports that insulin has inducing pressure effects including increased sympathetic activity, renal sodium retention, and smooth muscle cell proliferation[23-25]. Also, IR may impair the endothelial cell production of nitric oxide (N0), a substance that can stimulate some factors to cause vasodilatation[26]. It can be seen that IR and its secondary metabolic abnormalities are the risk factors of cardiovascular disease (CVD).

There have been reports that insulin excess is associated with CVD in non-diabetic individuals[27], and increases cardiovascular risk in patients with type 2 DM[28].Certainly, it is well-recognized that type 2 DM is the most important risk factor for CVD[29]. Interestingly, impaired glucose metabolism (IGT) is reported as a risk factor for CVD[29]. In addition, obesity, hypertension, and dyslipidemia, the components of MS are also the risk factors for CVD[30-33].

The diagnosis of MS

There are two criteria for the diagnosis of MS which are used worldwide. One is the World Health Organization (WHO) criteria which was adopted in 1999[21]. The other is proposed by Expert Panel on Detection, Evaluation, and Treatment of High blood Cholesterol in Adults (ATP III)[22]. In the WHO criteria [21], the diagnosis of MS was made if there are any type of abnormal glucose metabolism (AGM) such as impaired fasting glucose (IFG) or IGT or DM or IR plus 2 or more of the following abnormalities: i) dyslipidemia: triglyceride $\geq$ 150 mg/dL and /or HDL-C < 39 mg/dL; ii) obesity: BMI >30kg/m^2 and /or WHR >0.85; iii) hypertension: BP $\geq$ 140/ $\geq$ 90 mmHg; iv) microalbuminuria. The definition of IFG, IGT and DM are as follows (14): i) IFG: fasting glucose (FG) $\geq$ 110 and < 126 mg/dL; ii) IGT: 2-hour glucose (2-hG) $\geq$ 140 and < 200 mg/dL; iii) type 2 DM: FG $\geq$ 126 mg/dL and/ or 2-hG $\geq$ 200 mg/dL. Microalbuminuria is diagnosed when at least 2 out of 3 urine specimens revealed the albumin to creatinine ratio (A/C) > 30 mg/g.

In the ATP III criteria[22], the diagnosis of MS was made when there are $\geq$ 3 of the following abnormalities: i) fasting glucose $\geq$ 110 mg/dL; ii) serum triglycerides $\geq$ 150 mg/dL; iii) serum HDL-C < 50 mg/dL; iv) waist circumference > 88 cm; v) blood pressure $\geq$ 130/ $\geq$ 85 Hg.

PCOS and the metabolic syndrome

With regard to the same pathophysiology, the PCOS women are at risk of several metabolic disorders as well as MS. The studies of abnormal glucose metabolism[34-36], dyslipidemia[37-41], hypertension and other risk factors which are the components of MS have been reported[42-46]. Recently, the study of MS in PCOS has been reported [47,48].

PCOS women are at risk for glucose intolerance, and type 2 DM. The prevalence of IGT of 31.1-35% and type DM of 7.5-10 % have been reported [34,35] which much higher than that of the age and BMI matched controls[34]. Likewise, Weerakiet, et al[36] also reported the comparable prevalence of IGT (22.8 %) and type 2 DM (15.2 %) in the Thai women with PCOS.

Dyslipidemia in PCOS women has been reported since mid 1980's. Wild, et al[49] showed that women with PCOS had lower HDL-C, higher triglyceride levels, and higher LDL-C/HDL-C ratio when compared with the aged-matched, regular menstrual women. The following studies confirmed the finding of dyslipidemia in the PCOS women[37,38,40]. Importantly, Talbott E, et al[40] reported that the higher LDL-C and total cholesterol levels have persisted since younger age and were significantly higher than those of aged-matched controls.

More recently, hemostatic factor and inflammation marker abnormalities, which are associated with IR and CVD have been studied in PCOS. Plasminogen activator-inhibitor-1 (PAI-1), hemostatic factor, and C-reactive protein (CRP), inflammation marker, were

higher in the PCOS women than the controls after adjustment for age and BMI[44-46].

The study of MS in PCOS was first reported by Glueck, et al[47]. With the ATPIII criteria, the prevalence of MS was 46% of 138 PCOS women which was higher than that of the general population of US (22.8%, $p < 0.001$)[47]. In that study, the prevalence of obesity (waist > 88 cm) was most prevalent (85.5%), followed by dyslipidemia (32.6%, for high triglyceride and 64.5% for low HDL-C). Abnormal glucose (FG $\geq$ 110 mg/dL) was found in 5.1%.

Weerakiet, et al[48] reported that the prevalence of MS in 105 Thai PCOS women was 37.2 and 26.5% by the ATPIII and the WHO criteria, respectively, which was not statistically significantly different. Interestingly, the prevalence of AGM was found in 9.5% by the ATPIII, whereas it was 47.6% by the WHO criteria. This evidence confirms the previous studies that the fasting glucose levels could identify only 5% and 30% of women with AGM and DM, respectively[36].

In conclusion, PCOS is a more common endocrinological disorder in reproductive age. IR and compensatory hyperinsulinemia are the main pathophysiologies of this syndrome. With regard to IR, PCOS women are at risk for several metabolic abnormalities including, carbohydrate, lipid, obesity, hemostasis, and inflammation. Therefore, PCOS women are at risk for MS, and accordingly have the potential risk of CVD.

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