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Commentary

The role of vitamin D in polycystic ovary syndrome

Vitamin D plays a physiologic role in reproduction including ovarian follicular development and luteinization via altering anti-müllerian hormone (AMH) signalling, follicle-stimulating hormone sensitivity and progesterone production in human granulosa cells[1]. It also affects glucose homeostasis through manifold roles. The potential influences of vitamin D on glucose homeostasis include the presence of specific vitamin D receptor (VDR) in pancreatic β-cells and skeletal muscle, the expression of 1-α-hydroxylase enzyme which can catalyze the conversion of 25-hydroxy vitamin D [25(OH)D] to 1,25-dihydroxyvitamin D, and the presence of a vitamin D response element in the human insulin gene promoter[2].

Polycystic ovary syndrome (PCOS) is a common cause of ovarian dysfunction in women with anovulation. The main symptoms are characterized by chronic anovulation, hyperandrogenism, and/or the presence of polycystic ovary morphology from ultrasound examination. The phenotypic manifestation of this disorder is associated with various degrees of gonadotropic and metabolic abnormalities determined by the interaction of multiple genetic and environmental factors. The prevalence of vitamin D deficiency in women with PCOS is about 67-85 per cent, with serum concentrations of 25(OH)D <20 ng/ml[3]. Although there is no significant difference in the 25(OH)D levels between PCOS and normal control women, high prevalence of vitamin D deficiency has been found to be associated with metabolic syndrome which may have great impact on public health[4]. Low 25(OH) D levels may exacerbate the symptoms of PCOS, including insulin resistance, ovulatory, menstrual irregularities, infertility, hyperandrogenism, obesity and elevate the risk of cardiovascular diseases. Many observational studies suggest a possible role of vitamin D in an inverse association between vitamin D status and metabolic disturbances in PCOS, but it is still hard to draw a definite conclusion in the causal relationship due to inconsistent findings from various individual studies and from a recent meta-analysis report of a systematic review[5].

Vitamin D supplementation can lower the abnormally elevated serum AMH levels and increase serum anti-inflammatory soluble receptor for advanced glycation end-products in vitamin D-deficient women with PCOS[1]. In particular, vitamin D and calcium supplementation in addition to metformin therapy in women with PCOS could result in the beneficial effects on menstrual regularity and ovulation[6]. However, Garg *et al*[7] recently demonstrated that there was no significant beneficial effect on insulin kinetics and cardiovascular risk factors after supplementation of vitamin D, at a dose of 4,000 IU/day for six months, among women with PCOS treated with metformin. Due to small sample size and the relatively short duration of follow up in previous observational study and clinical trial, the effects of vitamin D supplementation in relieving the symptoms in women with PCOS remain inconclusive[6,7]. Therefore, further research with high quality randomized controlled trials is warranted to establish the impact of vitamin D supplementation on the management of PCOS.

Low 25(OH)D levels are found to be significantly correlated with insulin resistance in women with PCOS[2]. Thus, genes involved in vitamin D metabolism have been suggested as candidate genes for the susceptibility to PCOS. A few polymorphisms in the *VDR* gene, such as Cdx2, Taq1, Bsm1, Apa1, and Fok1, were reported to play an influential role on insulin secretion and sensitivity in PCOS women[8].

The *VDR* Fok1 polymorphism was found to have a protective effect on the risk of type 2 diabetes mellitus, while the Bsm1 had a precipitating effect on the risk of type 2 diabetes. Besides, the Apa1 polymorphism was reported to confer a reduced risk of vitamin D deficiency[8].

In this issue Dasgupta *et al*[9] present findings of a study conducted in Hyderabad city, India, to investigate the association pattern of four *VDR* polymorphisms (Cdx2, Fok1, Apa1 and Taq1) with PCOS among Indian women. They found significant difference in the genotype and allele frequency distributions of the Cdx2 polymorphism between the PCOS and control women. A significantly higher frequency of the heterozygous GA genotype as well as the A allele of Cdx2 polymorphism was observed in controls when compared to cases (P<0.001), indicating a protective role of this single nucleotide polymorphism (SNP) against PCOS phenotype. After the adjustment of the covariates of age and body mass index the carriers of GA genotype and the A allele remain conferring protecting effect for PCOS. However, no other significant associations were observed between the other three *VDR* polymorphisms (Fok1, Apa1 and Taq1) and PCOS. They further examined the associations between *VDR* genotypes and some of the PCOS specific clinical/biochemical traits, and found that the Cdx2 genotypes were significantly associated with testosterone levels and the Fok1 polymorphism showed a significant association with the presence of infertility. Further, the two haplotypes composed of four polymorphisms, ACCA and ACTA, were also found to be significantly associated with PCOS.

In a cohort of Austrian women with PCOS, the *VDR* Cdx2 polymorphism was found to be associated with lower insulin resistance, and the Apa1 polymorphism was associated with lower testosterone levels[10]. However, others did not find significant differences in the *VDR* gene polymorphism frequencies between women with PCOS and normal controls[4]. We reported that the *VDR* 1a promoter polymorphisms were not associated with the risk of PCOS, but were associated with serum 25(OH)D levels in a cohort of Taiwanese Asians PCOS women[11]. Besides, our study also reported that significantly lower serum 25(OH)D levels were observed in subjects carrying the heterozygous 1521CG/1012GA haplotype of the *VDR* 1a promoter polymorphisms in both PCOS and control women. However, metformin treatment was only effective to increase serum 25(OH)D levels in women with PCOS carrying the homozygous 1521G/1012A haplotype[11].

Despite several polymorphisms in *VDR* gene have been implicated in PCOS, the results from both individual research and meta-analysis in PCOS patients were in considerable disagreement and, therefore, the role of these variants of the *VDR* gene in the pathogenesis of insulin resistance and PCOS remains debatable. The inconsistent findings may be due to different ethnic origin or evolutionary force, such as genetic drift or selection pressure, or even due to different techniques of genotyping assay. For example, significant associations of the variant of insulin receptor substrate *(IRS)-2* gene as well as the interaction of *IRS-1* and *IRS-2* genes with PCOS were observed in a Chinese population of Taiwan that was contradictory to the findings from the meta-analysis conducted in Caucasian and African American populations[12]. When we further examined the minor allele frequency of the *IRS-2* gene in different populations[11], we observed that the minor allele in our population was opposite to the allele in Caucasians and African Americans. This might partly explain the inconsistent results observed in different populations. Due to the wide heterogeneity of symptoms and signs of PCOS, which may be predisposed by different genetic and environmental factors, it may not be easy to evaluate putative functional correlations between *VDR* SNPs and PCOS. In addition, there are many interlinking factors which may affect the individual phenotypic expression of women with PCOS. So far, the role of vitamin D polymorphisms on metabolic disturbances in women with PCOS remains inconclusive. Further investigations with large independent cohorts as well as with diverse ethnic populations are necessary to clarify if the relationship between vitamin D and PCOS is ethnic-specific or with different thresholds under the interactions of other individual genotypes of women with PCOS.

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