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The Relationship between Vitamin D, Insulin Resistance and Infertility in PCOS Women

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Abstract

It has been speculated that the majority of individuals in the India are deficient in Vitamin D and that Vitamin D deficiency has become an epidemic in our country. There is widespread prevalence of varying degrees (50- 90%) of Vitamin D deficiency with low dietary calcium intake in Indian population according to various studies published earlier. A deficiency of Vitamin D not only causes poor bone mineralization but also has been implicated in numerous us chronic diseases. Vitamin D deficiency is common in women with polycystic ovary syndrome (PCOS), with the 67-85% of women with PCOS having serum concentrations of 25-hydroxy Vitamin D (25OHD) <20 ng/ml. Vitamin D deficiency may intensify symptoms of PCOS, with observational studies showing lower 25OHD levels were associated with insulin resistance, ovulatory and menstrual irregularities, lower pregnancy success rate, hirsutism, hyper-androgenism, obesity and elevated cardiovascular disease risk factors. There is some, but limited, evidence for beneficial effects of Vitamin D supplementation on menstrual dysfunction and insulin resistance in women with PCOS. Vitamin D deficiency may play a role in exacerbating PCOS, and there may be a place for Vitamin D supplementation in the management of this syndrome, but current evidence is limited and additional randomized controlled trials are required to confirm the potential benefits of Vitamin D supplementation in this population.

Keywords: Vitamin D; Insulin resistance; Infertility; PCOS women

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Vitamin D and insulin resistance

The growing incidence of pre-diabetes and clinical type 2 diabetes, in part characterized by insulin resistance, is a critical health problem with consequent devastating personal and health-care costs [1]. Vitamin D status, assessed by serum 25OHD levels, is inversely associated with diabetes in epidemiological studies. Several clinical intervention studies also support that Vitamin D, or its active metabolite 1,25(OH)2D3, improves insulin sensitivity, even in subjects with normal glucose tolerance. The mechanisms proposed which may underlie this effect include potential relationships with improvements in lean mass, regulation of insulin release, altered insulin receptor expression and specific effects on insulin action [2]. These actions may be mediated by systemic or local production of 1,25(OH)2D3 or by suppression of parathyroid hormone, which may function to negatively affect insulin sensitivity. Thus, substantial evidence supports a relationship between Vitamin D status and insulin sensitivity; however, the underlying mechanisms require further exploration [3] (Figure 1).

Vitamin D and polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is among the most common endocrine disorders in women of reproductive age and has a strong genetic component. It is characterized by ovarian dysfunction and its clinical manifestations may include obesity, increased insulin resistance and compensatory hyper-insulinemia, oligo-/anovulation and infertility [4]. Studies regarding Vitamin D status in patients with PCOS show an inverse correlation between Vitamin D levels and metabolic risk factors, e.g. insulin resistance, BMI, waist-to-hip-ratio, triglycerides, total testosterone and a positive correlation with insulin sensitivity [5-7]. Data on the role of gene variants involved in Vitamin D metabolism in PCOS are sparse but suggest an association of VDR and Vitamin D level-related variants with metabolic and endocrine parameters in women with PCOS [8]. Several studies although limited by modest sample sizes have suggested associations between VDR

polymorphisms and the development of PCOS as well as insulin resistance [8-12].

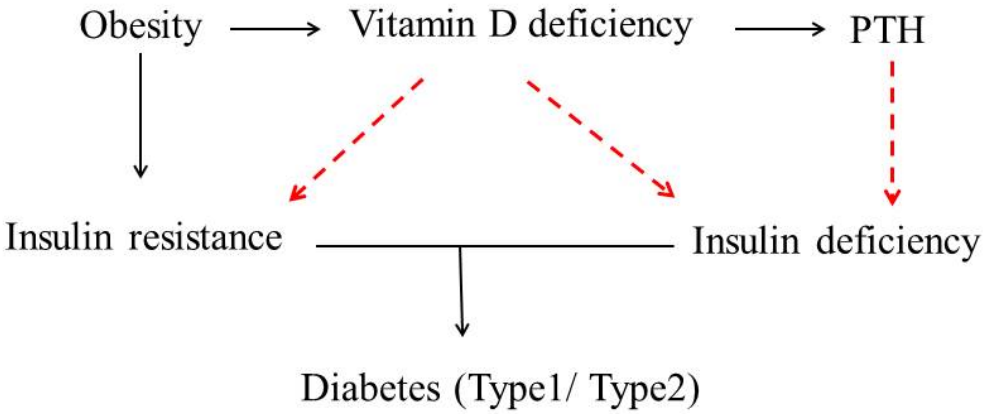

Figure 1: Obesity is an important criterion in the pathogenesis of type 2 diabetes (solid arrows). Vitamin D deficiency is an important feature of obesity mostly due to the storage of 25OHD vitamin in adipose tissue because of its lipophilic properties, causing, in turn, a compensatory increase in PTH (bold arrows). The decrease in 25OHD levels may occur through several mechanisms, resulting in worsening of insulin resistance and secretion and augmenting the risk of developing diabetes. Furthermore, hypo-vitaminosis D may increase insulin resistance indirectly, through the compensatory indirectly, through the compensatory increase in PTH levels. In addition, hypo-vitaminosis D-induced secondary hyperparathyroidism has been shown to inhibit insulin synthesis and secretion from β-cells and reduce insulin sensitivity (dotted arrows). Solid and bold arrows indicate cause and effect relationships; dotted ones indicate not firmly established evidence.

Different distributions e.g. of VDR Apa-I and Fok-I gene polymorphisms were found in a cohort of 162 women with PCOS and their controls [10]. It seems possible that variants in the VDR through their effect on luteinizing hormone, sex hormone binding globulin levels and testosterone are involved in the pathogenesis of PCOS [8, 11]. Further genes involved in Vitamin D synthesis, hydroxylation and transport and their role in PCOS are currently under investigation [8]. Clinical trials with either Vitamin D supplementation or administration of Vitamin D3 analogues showed positive effects on insulin secretion, lipid profile, menstrual cycle and follicular development and a decrease of fasting and stimulated glucose and C-peptide levels [13-17]. However, most of the studies had rather small sample sizes and experimental set-up was quite hetero-genous. One of the great confounders in all studies was the presence of obesity. In some studies an association of Vitamin D and insulin resistance was only seen in obese patients or 25OHD3 levels were only associated with obesity and insulin resistance but not with PCOS per se [7,18,19]. Lower serum levels of 25OHD3 were shown in obese PCOS patients (e.g. 31.9 ± 9.4 nmol/l) than in non-obese (73.1 ± 20.2 nmol/l) [7,20]. Consequently, the association of hypo-vitaminosis D with features of PCOS may be associated with obesity but not with the presence of PCOS. Recently it was hypothesized that vitamin D deficiency is not only in association with obesity but a potentially reason [21]. As Vitamin D supplementation evidently has positive effects on the outcome of PCOS the question whether to substitute patients with PCOS to ameliorate insulin resistance and prevent other health complications, such as diabetes mellitus type 2, has to be addressed in large intervention trials.

Vitamin D and reproductive function in women with PCOS

There is much evidence, that in addition to sex steroid hormones, the classic regulators of reproduction, Vitamin D also modulates

reproductive processes in women; its nuclear receptor has been identified in the uterus, oviduct, ovary, placenta, and fetal membranes [22]. It has been reported that Vitamin D deficiency reduces mating success and fertility in female rats. Female rats fed a Vitamin D deficient diet are capable of reproduction, but overall fertility is decreased by 75%, and litter size is reduced by 10% [23]. Both VDR (Vitamin D Receptor) and 1α-hydroxylase knockout female mice are infertile and present with uterine hypoplasia, impaired folliculo-genesis, and anovulation [22,24,25]. However, there might be various mechanisms explaining the role of Vitamin D in human reproduction. First, a possible mechanism may be the direct stimulatory effect of 1,25(OH)2D3 on the aromatase gene expression in reproductive tissues, which has been demonstrated in female mice. Supplementation with estradiol corrected the reproductive phenotype of VDR null mice, whereas partial correction of calcium homeostasis by a high calcium diet was only partially effective, which indicates a direct effect of Vitamin D on the reproductive system [26]. Second, it has been shown that HOXA10 expression is up-regulated by 1,25(OH)2D3 in human endometrial stroma cells indicating that altered Vitamin D signaling might impact HOXA10 expression and fertility [22]. Hox genes were first recognized as an evolutionary conserved family of transcription factors critical to the control of early embryonic development. However, HOXA10 expression is important for the development of the uterus and essential for endometrial development, allowing uterine receptivity to implantation [27]. Aberrant HOXA10 expression in patients with infertility confirms its function in human implantation [28]. Vitamin D is the key regulating hormone in calcium homeostasis. It has been shown that calcium plays a role in oocyte activation and maturation resulting in the progression of follicular development [29]. In this context, Vitamin D and calcium repletion might lead to normalization of menstrual cycles and restoration of ovulation in PCOS women [16]. More recently, it has been shown that women with a sufficient Vitamin D level undergoing in vitro fertilization (IVF) are more likely to achieve clinical pregnancy than women with low Vitamin D levels [30]. On the contrary no significant differences in pregnancy rates and embryo quality were found between patients with low (< 50 nmol/l) and moderate (50-75 nmol/) 25OHD3 follicular fluid levels, at high Vitamin D levels in follicular fluid (> 75 nmol/l) even a decrease in pregnancy rate and embryo quality was seen [31]. While the results of human studies are contradictory the role of Vitamin D on human fertility and reproductive physiology merits further assessment by appropriate longitudinal studies. However, the effects of Vitamin D deficiency on human reproduction and fetal development are poorly studied.

Human and animal data suggest that low Vitamin D status is associated with insulin resistance, impaired fertility and polycystic ovary syndrome. The determination of optimal 25OHD levels in the reproductive period and the amount of Vitamin D supplementation required to achieve those levels for the numerous actions of Vitamin D throughout a PCOS woman's life would have important public health implications.

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