Association between Serum Testosterone and Vitamin D and Calcium Supplementation in Women with Polycystic Ovary Syndrome

Thesis

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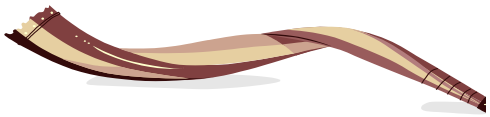

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List of Abbreviations

Abbr.	Full-term
ADA	: American Diabetes Association
AMH	: Anti Müllerian Hormone
ASRM	: American Society of Reproductive Medicine
BMI	: Body mass index
BV	: Bacterial Vaginosis
CAH	: Congenital adrenal hyperplasia
CI	: Confidence Interval
FAI	: Free androgen index
FAI	: Free androgen index
GI diet	: Glucose index diet
GTT	: Glucose Tolerance Test
HA	: Hyperandrogenic an ovulation
HOMA-IR	: HOMA of insulin resistance
HPO	: Hypothalamic-pituitary-ovarian
IGF-1	: Insulin-like growth factor 1
IU	: International unit

LH : Luteinizing hormone

mFG : Modified Ferriman–Gallwey score

NIH : National Institute of Health

PCO : Polycystic ovaries

PCOM : Polycystic ovarian morphology

PCOS : Polycystic ovary syndrome

QOL : Quality of life

SD : Standard deviation

SHBG : Sex hormone binding globulin

SPSS : Statistical package for social science

TV : Trans-vaginal ultrasonography

UL : Upper intake level

UL : Upper limit

UV : Ultraviolet

UVB : Ultraviolet band

VDD : Vitamin D deficiency

VDR : Vitamin D receptor

25OHD : 25-hydroxy vitamin D

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Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age, presenting in up to 18% of this population ***(March et al., 2010).***

PCOS is characterized by the presence of polycystic ovaries, menstrual dysfunction, infertility and biochemical (elevated androgens) and clinical (hirsutism and/or acne) hyperandrogenism ***(Dunaif et al., 1997; Azziz et al., 2009).***

Although the exact etiopathophysiology of this condition is unclear, PCOS can result from abnormal function of the hypothalamic-pituitary-ovarian (HPO) axis. A key characteristic of PCOS is inappropriate gonadotropin secretion, which is more likely a result of, rather than a cause of, ovarian dysfunction. In addition, one of the most consistent biochemical features of PCOS is a raised plasma total testosterone level ***(Barber et al., 2010).***

In October 2013, the Endocrine Society released practice guidelines for the diagnosis and treatment of PCOS they concluded that to diagnose PCOS Rotterdam criteria should be used, which are two of three criteria:

1. Oligoovulation and/or anovulation.

2. Excess androgen activity.

3. Polycystic ovaries (by gynecologic ultrasound) ***(Legro et al., 2013).***

Using newer ultrasound technology and a reliable grid system approach to count follicles it is concluded that a substantially higher threshold of mean follicle count per ovary is 26 versus 12 follicles – is required to distinguish among women with PCOS and healthy women from the general population. The threshold for of mean follicle count per ovary proposed by this study is more than double that proposed by the Rotterdam consensus ***(Lujan et al., 2013).***

Vitamin D is a group of fat-soluble steroids responsible for enhancing intestinal absorption of calcium and phosphate. In humans, the most important compounds in this group are vitamin D_3 (also known as cholecalciferol) and vitamin D_2 (ergocalciferol) ***(Holick et al., 2006).***

Vitamin D deficiency disrupts the function of all the systems of the body and increases the risk of chronic disease, including physical diseases such as cancer, cardiovascular, autoimmune and infectious diseases; and psychological disorders such as depression and chronic pain ***(Holick et al., 2007).***

It is found that serum 25-hydroxyvitamin D concentrations above 30 ng/mL (75 nmol/L) are "not consistently associated with increased benefit". Serum 25-hydroxyvitamin D levels

above 50 ng/mL (125 nmol/L) may be cause for *concern* ***(Ross et al., 2011).*** However, the desired range of serum 25-hydroxyvitamin D is between 20-50 ng/mL ***(Ross et al., 2011).***

Polycystic Ovary Syndrome and Vitamin D

A number of studies have demonstrated associations between vitamin D levels and various PCOS symptoms, including insulin resistance, infertility and hirsutism ***(Panidis et al., 2005).*** Vitamin D is thought to influence the development of PCOS through gene transcription and hormonal modulation influences insulin metabolism and fertility regulation ***(Mahmoudi et al., 2009)***.

Several studies have reported low levels of vitamin D in women with PCOS, with average 25-hydroxy vitamin D (25OHD) levels between 11 and 31 ng/ml ***(Panidis et al., 2005)*** with the majority having values less than 20 ng/ml (67–85%) ***(Selimoglu et al., 2010).***

Recently, lower levels was reported in women with PCOS (n = 545) compared to the control women (n = 145; 25·7 *vs* 32·0 ng/ml, respectively), and the PCOS women were significantly younger (27 *vs* 29 years, respectively) ***(Wehr et al., 2011a).***

Three out of four women with PCOS may have vitamin D deficiencies in randomized controlled study at the Medical University of Graz in Austria ***(Wehr et al., 2009).***

Studies have shown that women with PCOS have mostly insufficient vitamin D levels, and vitamin D replacement therapy may have a beneficial effect on insulin resistance in women with PCOS ***(Selimoqlu et al., 2010).***

People with higher levels of this vitamin are 40% less likely to develop diabetes. The vitamin helps the pancreas secrete insulin. It also reduces systemic inflammation, which influences insulin resistance ***(Oxfirat and Chowdhury, 2010).***

In a randomized clinical trial investigating the effects of calcium– vitamin D and metformin in regulating the menstrual cycle, 60 infertile women with PCOS were randomized to one of the three treatments consisting of 1000 mg calcium + 400 IU vitamin D per day; 1000 mg calcium + 400 IU vitamin D + 1500 mg/day metformin, or 1500 mg/day metformin ***(Rashidi et al., 2009).*** The patients were treated for 3 months and followed up for a further3 months. The number of dominant follicles (14 mm) during the 2 –3 months of follow-up was higher in the calcium –vitamin D–metformin group than in either of the other two groups (P = 0· 03). However, no significant differences were seen in the rates of pregnancy, although improvements in menstrual irregularities were more noticeable in the vitamin D–calcium –metformin group. The authors concluded that metformin and calcium –vitamin D could be effective for the treatment of anovulation and oligomenorrhoea in women with

PCOS. However, they did not measure serum 25OHD levels before or after the intervention, so the levels of deficiency and the magnitude of change are unknown. A recent uncontrolled pilot study in 46 women with PCOS also observed improvements in reproductive function, with 50% (23/46) of oligo- or amen-orrhoeaic women at baseline reporting improvements in menstrual frequency after 24 weeks of weekly cholecalciferol (20 000 IU), which significantly increased 25OHD levels (28.0 –52.4 ng/ml) ***(Wehr et al., 2011b).***

Another randomized controlled study aimed to provide daily vitamin D3 (2000IU) and monthly vitamin D2 (50,000IU); D2 regimen was modified to 50,000IU weekly after observation of a suboptimal rise in serum 25OHD in the first 5 participants. All received 530mg of elemental Ca/day. Compliance was verified by pill count and tolerance was assessed, significant reduction in total testosterone and lowering in serum androstenedione were observed compared to baseline values ***(Pal et al., 2012).***

Association between vitamin (D) and calcium and total testosterone level (as biomarker of hyperandrogenism in polycystic ovary syndrome):

The effects of Vitamin (D) are mediated via both genetic and cellular pathways. Vitamin d regulates gene transcription through nuclear vitamin d receptors that are

distributed across various tissues, including skeleton, parathyroid glands and the ovaries ***(Baynes et al., 1997).***

The pathogenesis of PCOS has been linked to the effects of vitamin (D) receptors on LH and SHBG levels, testosterone levels. Insulin resistance and serum insulin level ***(Wehr et al., 2011b).***

Vitamin (D) deficiency increase parathormone production**,** which is regulated through levels of serum calcium and vitamin (D), and increased parathormone, is independently associated with increased testosterone level, polycystic ovary syndrome and anovulatory infertility ***(Bourlon et al., 1999).***

A recent study found that in women with PCOS,a lower calcium intake was independently associated with higher serum testosterone level ***(Lerchbaum et al 2012)*** suggesting that a low calcium intake might also contribute to the hormonal dysregulation that occurs in PCOS ***(Kinuta et al., 2000).***