

Vitamin D Level and Infertility

Vitamin D Düzeyi ve İnfertilite

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Abstract

Infertility is one of the major health problems of our time. In fact, infertility is caused by many factors. Among these factors the effect of vitamin D levels of infertility are overlooked. The prevalence of vitamin D deficiency varies between 20% and 66.8% in different countries. In fact, vitamin D deficiency can lead to infertility both women and man. Lack of vitamin D in women with polycystic ovary syndrome in the study, uterine fibroids, as well as has been demonstrated over a relationship with a decrease in reserves. In males it has been suggested to affect sperm count and morphology. At the same time vitamin D levels may play a role in facilitating implantation. Even in studies in vitro fertilization has been shown to increase the success rate with the support of vitamin D. In this article, vitamin D deficiency and infertility issues were revised in light of the current articles.

Öz

İnfertilite çağımızın önemli sağlık sorunlarından biridir. Aslında infertiliteye birçok faktör neden olmaktadır. Bu faktörler arasında D vitamini düzeyinin infertiliteye olan etkisi gözden kaçmaktadır. Vitamin D eksikliğinin görülme sıklığı değişik ülkelerde %20 ile %66,8 arasında değişmektedir. Aslında D vitamini eksikliği hem erkeklerde, hem de kadınlarda infertiliteye neden olabilmektedir. Çalışmalarda kadınlarda D vitamini eksikliğinin polikistik over sendromu, uterin miyom yanı sıra over rezervinin azalması ile ilişkisi ortaya konmuştur. Erkeklerde ise sperm sayısını ve morfolojisini etkilediği öne sürülmüştür. Bununla birlikte vitamin D düzeyi implantasyonu kolaylaştırıcı rol oynayabilmektedir. Hatta çalışmalarda in vitro fertilizasyon başarı oranlarının D vitamini desteği ile arttığı gösterilmiştir. Bu yazıda, D vitamini eksikliği ve infertilite konusu güncel makaleler eşliğinde gözden geçirilmiştir.

Keywords

Vitamin D, infertility, in vitro fertilization

Anahtar Kelimeler

D vitamini, infertilite, in vitro fertilizasyon

Received/Geliş Tarihi: 14.04.2015

Accepted/Kabul Tarihi: 15.07.2015

doi:10.4274/meandros.2399

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Introduction

It has been known for centuries that the human body needs many vitamins. Vitamin D is known as a steroid hormone produced mainly by ultraviolet B. Only about 10-20% of this vitamin can be taken by diet. Some genetic and environmental factors can cause this vitamin deficiency. These include high latitude living, traditional outdoor clothing, dark skin color, old age, inadequate vitamin D intake by diet, parenchymal diseases of kidney and liver, genetic defects preventing vitamin D synthesis and function, drugs and sunscreen use (1,2).

Epidemiology

Vitamin D deficiency first appeared in the 17th century by the German pathologist G. Pommer. The first scientific publication on vitamin D

deficiency was published in 1966 by Ramser et al. (3), who identified in six patient rib biopsies consistent with vitamin D deficiency. Studies conducted after these years have revealed the real effect of vitamin D on bone mineralization (2). Vitamin D deficiency of incidence ranges between 20% to 66.8% in different countries (4-6) has been reported, in a study conducted in Turkey 74.9% (7). Studies showing lack of vitamin D in different countries reported in the literature are shown in Table 1.

Vitamin D and Systemic Diseases

Recent epidemiological studies suggest that low levels of vitamin D are associated with several diseases such as certain cancers, hypertension, autoimmune and infectious diseases (8,9). It also has been reported that vitamin D protects DNA from oxidative stress through nuclear mechanisms and prevents telomeric shortening (9). A meta-analysis reported a 7% reduction in the risk of five-year mortality with an average intake of 528 IU/day vitamin D (10).

Vitamin D has been shown to prevent hypertension by suppressing the renin gene. Observational studies have shown that low vitamin D levels correlate with blood pressure, coronary artery calcification, and the presence of cardiovascular disease. Research suggests that suboptimal vitamin D levels are associated with an increased risk of cardiovascular disease (9). The recent studies on animal models and humans have shown that vitamin D regulates glucose metabolism, and may play an important role in the development of type 1 and type 2 diabetes mellitus (DM). In particular, it is known that there is a link between infantile vitamin D deficiency and type 1 DM development (11). Breast, colon, prostate cancer cells and leukemic cells also have vitamin D receptors (VDR). Calcitriol is known to be an inhibitory effect on these cells. Although its mechanism is not fully understood, vitamin D is thought to be involved in cellular regulation, induction of differentiation, impaired growth stimulation,

inhibition of angiogenesis and increased apoptosis of malignant cells (12). It is known that the phagocytic activity of macrophages is increased in the presence of vitamin D (13). In addition, VDR activation increases gene expression of cathelicidin, a bacteriocidal protein known to be lethal for tuberculosis and other infective agents (14).

Several studies have shown that vitamin D affects the growth and differentiation of immune system-regulating cells such as macrophages, dendritic cells, T and B lymphocytes. Vitamin D may be used in the treatment of autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, type 1 DM, inflammatory bowel diseases and multiple sclerosis (MS) (15). Studies support that lower levels of vitamin D are associated with greater severity in patients with MS (16). Vitamin D deficiency is associated with depression and decreased cognitive function (17). In short, vitamin D affects many systems and deficiencies cause disorders in these systems. Table 2 shows the effects of D vitamins.

Vitamin D and Infertility

Vitamin D deficiency can actually cause many gynecological problems. These are mentioned below.

Vitamin D Deficiency and Polycystic Over Syndrome

Although many gynecological diseases are associated with vitamin D deficiency, polycystic ovarian syndrome (PCOS) is the most commonly studied and described. This syndrome is known as the most common endocrine disorder in the reproductive ages. The prevalence of the syndrome has been reported to be approximately 6-8%. Infertility can be seen in this syndrome, which is diagnosed by oligo-anovulation, clinical and/or biochemical hyperandrogenism findings and ultrasonographic polycystic ovaries.

It has been suggested that sex hormone-binding globulin decreases with vitamin D deficiency. Thus, androgen levels are increasing and providing the basis for PCOS (18).

Table 1. Studies on the D vitamin deficiency in different countries

	Country	Time	Season	Number	Vitamin D deficiency rate
Maghbooli et al. (4)	Iran	2002	Winter	552	66.8%
Weiler et al. (5)	Canada	2002-2004	All year	183/146	32%/30.4%
Nanri et al. (6)	Japan	2010-2011	Summer-winter	529	9.3%-46.7%
Hekimsoy et al. (7)	Turkey	2007	Winter	209	74.9%

Table 2. Effects of vitamin D

Cell differentiation
Calcium and phosphorus balance in skeletal system
Antiproliferative effect
Anti-inflammatory effect

In a prospective cohort study of 91 patients with PCOS, less follicular development was observed after 50 mg of clomiphene citrate treatment in the group with vitamin D deficiency (19). In another study, it was reported that 60 PCOS-diagnosed infertile patients were divided into 3 groups, metformin in the first group, vitamin D in the second group, and vitamin D and metformin in the last group, resulting in higher number of dominant follicles in the combination therapy group (20).

In a recent study, vitamin D levels were associated with decreased insulin resistance. Patients with PCOS have been reported to have improved insulin resistance, androgen levels, folliculogenesis, and menstrual irregularities with the addition of vitamin D to treatments (21). In Reyman et al.'s (22) study, it was noted that supplementation of vitamin D, a disease with PCOS deficiency of vitamin D, improves menses and follicular developmental abnormalities, thus increasing pregnancy rates.

In other studies, it has been shown that fat patients with PCOS is treated with vitamin D deficiency, resulting in increased weight loss and improved menstrual cycle rhythms. Similarly, adolescent obese persons were observed to be thinner when vitamin D deficiency was eliminated (23,24).

In another study of 127 patients with PCOS but not treated and 117 normal subjects, 25-hydroxy-D [25(OH)D] vitamin levels below 50 nM/mL were defined as vitamin D deficiency and those above 75 nm/mL were normal. In this study, there was no significant difference between the vitamin D levels of the two groups when there was a negative correlation between metabolic syndrome and vitamin D level (25). In a 24-week study of 57 polycystic over patients with vitamin D deficiency, the patient was given 20.000 IU of vitamin D per week and reported a 50% improvement in oligomenorrhea and anovulation, as well as a marked decrease in fasting blood glucose (26).

Vitamin D Level and Over Reserve

Reduced over-reserves is one of the important causes of infertility. Anti-Müllerian hormone (AMH) is accepted as the laboratory test that shows the best over reserve. As is known, AMH reduces oocyte loss rate. There was a positive correlation between serum vitamin D level and serum AMH level. When vitamin D deficiency was eliminated, estradiol (9%), estrone (21%) and progesterone (9%) production from over, in addition the amount of insulin-like growth factor binding protein was increased. It has been shown that there is a positive correlation between levels of serum AMH and vitamin D in women in the premenopausal period (27). Serum AMH levels are 18% lower in the winter months than those in the summer months, but there is no such seasonal fluctuation seen in AMH when vitamin D deficiency is eliminated (28).

All this information with low AMH levels should be considered vitamin D deficiency. However, there are few studies in the literature regarding low AMH and vitamin D deficiency. For this reason, randomized controlled trials are needed for vitamin D replacement therapy.

Vitamin D Level and Uterine Myom

Vitamin D has a regulatory role in the development of uterine fibroids. Patients with myomas with low levels of vitamin D were observed to have a higher risk of myoma formation and more myomas, they were larger than the control group (29). Another study reported a decrease in the rate of myomas in patients with D-vitamin supplementation. Vitamin D3 has been shown to reduce myoma cell proliferation *in vitro*, and *in vivo* animal models to decrease tumoral myoma growth. These results support that vitamin D3 is effective and safe in the medical treatment of myoma (29,30).

Vitamin D Level and In Vitro Fertilization

In vitro fertilization (IVF) rates are influenced by many factors in our time, and as days go by, we become aware of the majority of these factors. Some of them look like vitamin D. Patients with serum vitamin D level <30 ng/mL were found to have a low pregnancy rates (31). In a study conducted, the serum and follicular fluid also had a positive correlation with the measurement of 25(OH)D levels and IVF ratios.

However, follicular fluid 25(OH)D levels were recorded inversely proportional to body mass index. As a result, follicular fluid 25(OH)D vitamin levels were predicted to be an independent predictor of IVF success. In study conducted by Ozkan et al. (32), it was observed that with 1 ng/mL vitamin D increase in follicular fluid, 6% increase in live pregnancy was observed.

Contrary to these views, the follicular fluid with high levels of vitamin D is found in studies showing that the number of enucleated oocytes and embryo quality are reduced. One of them has found that the high D vitamin levels have been impaired the developmental properties of the embryo and the IVF success has been adversely affected (33).

In addition to studies showing increased vitamin D and IVF ratios, there are studies suggesting that there is no relationship. Among them, 517 patients were studied by Franasiak et al. (34), and vitamin D was reported to be unrelated to pregnancy outcomes after embryo transfer. As a result, it was emphasized that serum 25OH vitamin level failed to predict the implanted blastocyst.

Vitamin D levels may play a role in facilitating implantation. Calcitriol reduces T cell function. Calcitriol reduces cytokines released from endometrial cells. During the calcitriol treatment, in natural killer cells the secretion rates of cytokines such as colony-stimulating factor 2, interleukin (IL)-1, IL-6 and tumor necrosis factor decreased. For this reason, vitamin D deficiency may play a role in the habitual abortus (31).

Vitamin D Level and Male Infertility

Low levels of vitamin D may cause infertility in males as well as infertility in females. There was a positive correlation between the number of motile sperm and progressive motile sperm and the serum level of 25(OH)D vitamin. *In vitro* studies have shown that vitamin D increases sperm motility and induces acrosome reaction (35). Contrary to this view, it has been found to correlate with high vitamin D content and sperm count and normal morphological deterioration (36).

Two recent large-scale studies have shown a positive correlation between serum D-vitamin levels and serum testosterone levels (37,38). The enzyme that metabolizes vitamin D is CYP24A1. This enzyme has been found in the human testis, the ejaculatory duct, the mature spermatozoa and the Leydig cells

(39). In a study of 77 infertile men and 50 healthy men, CYP24A1 expression was measured and there was a significant decrease in CYP24A1 expression in infertile men (40). As a result, it has been shown that changes in vitamin D levels affect infertility through several mechanisms. For this reason, it is also necessary to consider examining the level of vitamin D when following a routine infertility patient.

Ethics

Peer-review: Externally and internally peer-reviewed.

Financial Disclosure: The authors declared that this study received no financial support.

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