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Association between Serum Vitamin D3 Levels and Sex Hormones in Infertile Men

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ABSTRACT

Background and Objective: The prevalence of male infertility is increasing worldwide and vitamin D deficiency can be one of the causes for this problem. The aim of this study was to investigate the relationship between serum vitamin D levels and reproductive hormones in infertile men with abnormal spermograms.

Methods: This cross-sectional study was performed on 220 infertile men with abnormal spermograms. Based on serum levels of vitamin D, they were divided into two groups of vitamin D less than 20 ng/ml (108 patients) and vitamin D greater than or equal to 20 ng/ml (112 patients). Then serum levels of FSH, LH, FT and TT were extracted and compared by referring to the medical records of the subjects.

Findings: The mean age and body mass index of participants were 34.46±5.60 years and 25.54±2.40 kg/m2, respectively. Hormone levels of FT, TT, and FSH did not show a statistically significant difference between the two groups. However, LH levels in the group with vitamin D deficiency (3.63±2.53) was significantly lower than the group with normal vitamin D (4.67±4.08) (p= 0.025).

Conclusion: The findings of this study showed a significant relationship only between LH levels in infertile men and their serum vitamin D levels.

Keywords: *Male Infertility, Vitamin D3, Sex Hormones, Sperm.*

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Introduction

Fertility is a highly important factor in the survival of a generation and its role in the health of the family and then the health of the community is very significant; therefore, it is referred to as one of the indicators of community health (1). The global prevalence of infertility varies between 2.5-15% and there are at least 30 million infertile men worldwide. The overall prevalence of primary infertility among Iranian couples is 17.3% (2, 3). The risk factors of infertility have attracted a lot of attention in recent years (4). In men, in particular, the risk factors include genetic disorders, varicocele, blockage of sperm ducts, genital infections, endocrine disorders and environmental factors (5). Oxidative stress is also one of the main causes of male infertility and underlies idiopathic infertility in men (6). Therefore, this issue should be considered in investigating the causes of male infertility and the treatment stages (7).

Today, special attention is paid to vitamins, particularly vitamin D, in the prevention and treatment of infertile men because these vitamins can protect the cells, membranes and nuclei of the body against the risk of free radicals with high energy levels. Studies have shown the effectiveness of vitamin D on metabolic and inflammatory condition and biomarkers of oxidative stress, and this vitamin has been effective in many clinical conditions. Vitamin D also reduces lipid peroxidase and increases the activity of antioxidant enzymes (8, 9). Vitamin D deficiency is the most widespread eating disorder in the world. In Iran, the prevalence of vitamin D deficiency in people aged 20 to 24 years is 59.9% and in people aged 30 to 44 years is 44.8% (10, 11). Vitamin D receptors are present throughout the male reproductive system. This suggests that vitamin D may play a role in regulating testicular function (12).

The results of studies are contradictory in showing the relationship between vitamin D and testosterone levels (13). The study of Zhao et al. supports this relationship (14); Abbasihormozi's study does not support this finding (15). Moreover, the results of a study by Rudnicka et al. showed that serum vitamin D levels were not associated with any of the fertility parameters, including sex hormones (16). However, researchers have suggested that in order to further investigate the association between vitamin D and sex hormones, it is better to conduct more detailed studies in order to obtain comprehensive information (14).

The increasing importance and prevalence of infertility along with the high prevalence of vitamin D deficiency requires further studies in this field. Therefore, this study was performed to determine the relationship between serum vitamin D levels and sex hormones in infertile men referred to the selected urology clinic in Tehran in 2020.

Methods

After obtaining permission from the ethics committee of Iran University of Medical Sciences with the ethics code IR.IUMS.REC.1399.286, this cross-sectional study was conducted among 220 infertile men aged 20-45 years with abnormal spermograms under infertility treatment. Their serum vitamin D levels, and hormonal parameters including Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH), Total Testosterone (TT), and Free Testosterone (FT) were measured at the beginning of diagnosis and before treatment in one of the specialized urology clinics in Tehran in 2020. In the present study, infertility was defined as lack of fertility after one year of unprotected intercourse (17). Infertile men with physical and mental health (according to the contents of the file), body mass index 18.5-30 (kg/m2), lack of azoospermia, with idiopathic spermogram and no smoking and hookah use in the past three months, no alcohol and drugs use, Iranian nationality and fertile wife and male infertility longer than one year were included in the study. In this study, no intervention was performed on patients and only the information collected from the patients' files was recorded in the checklists and if some of the patients' information was not available, the

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information was completed by phone contact. Hormone and spermogram tests were all performed in a laboratory center (Iran Pezeshk Laboratory). The sample size was determined based on 95% confidence level and 80% test power and assuming that the relationship between the studied variables was at least 0.2 to make this association statistically significant. After referring to the files, from the new to the old ones, the researcher included the cases that met the inclusion criteria. Depending on the levels of vitamin D3, men in this study were divided into two groups with normal vitamin D3 levels greater than or equal to 20 ng/ml (108 patients) and with vitamin D3 deficiency with vitamin D levels less than 20 ng/ml (112 patients). Measurement of Vitamin D3 was done by Biorexfars 25 (OH) D3 Diagnostic Kit based on ELISA method, FSH and LH by Pishtaz Teb Diagnostic Kit based on ELISA method, TT by IBL-America Laboratory Kit based on ELISA method and FT by Roch Diagnostic Kit based on ELISA method. Normal levels of vitamin D3 were considered to be 20 ng/ml or more (18). Data were analyzed using SPSS 21 software by independent t-test, Fisher and Spearman correlation tests and $p<0.05$ was considered significant.

Results

The mean age of male participants was 34.46±5.60 years and the mean body mass index (BMI) was 25.54±2.40 kg/m2 (Table 1). There was no statistically significant difference between the two groups in terms of demographic characteristics. In addition, the mean levels of vitamin D in the two groups with normal vitamin D and vitamin D deficiency were 30.43±9.80 and 14.21±4.24 ng/ml, respectively. There was no significant association between vitamin D and sex hormones (Table 2). Serum levels of free and total testosterone in the two groups were not statistically significant. However, infertile men with normal vitamin D had higher LH levels compared to infertile men with vitamin D deficiency (Table 3) (p=0.02).

Table 1. Demographic characteristics of infertile men in the two groups

Group Variable	Normal Vitamin D3 Mean±SD or Number(%)	Vitamin D3 deficiency Mean±SD or Number(%)	p-value
Age (years)	34.16±4.84	34.60±5.15	0.93
Body mass index (kg/m2)	25.47±2.51	25.63±2.28	0.61
Duration of marriage (years)	5.20±2.72	5.29±3.04	0.82
Duration of infertility (years)	3.01±2.08	762±1.98	0.35
Level of Education			
Primary	1(0.9)	0(0)	0.58
Middle and high school	42(38.9)	43(38.4)	
University	65(60.2)	69(61.6)	
Employment status			
Employee	56(51.9)	54(48.2)	0.64
Worker	48(44.4)	51(45.5)	
Self-employed	4(3.7)	7(6.3)	
The economic situation			
Undesirable	9(8.3)	9(8.0)	0.88
Relatively desirable	77(71.3)	83(74.1)	
Desirable	22(20.4)	20(17.9)	
History of infertility treatment			
Yes	16(14.8)	12(10.7)	0.36
No	92(85.2)	100(89.3)	

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Table 2. Relationship between total levels of vitamin D3 and sex hormones

Vitamin D3 / Hormones	Correlation test results	
	r	p-value
FSH (Iu/L)	-0.03	0.74
LH (Iu/L)	0.04	0.63
TT (ng/dl)	0.07	0.42
FT (pg/ml)	-0.07	0.41

Table 3. Comparison of sex hormone levels in the two groups

Group / Hormones	Natural Vitamin D3 (values greater than 20 ng/ml) Mean±SD	Vitamin D3 deficiency (values less than 20 ng/ml) Mean±SD	p-value
FSH (Iu/L)	5.46±4.64	4.30±4.36	0.058
LH (Iu/L)	4.67±4.08	3.63±2.53	0.025
TT (ng/dl)	3.43±1.42	3.28±1.13	0.38
FT (pg/ml)	9.19±4.04	8.99±3.92	0.71

Discussion

In the present study, serum testosterone levels did not show a statistically significant association with serum vitamin D levels. The hypothalamic-pituitary-gonadal axis plays an important role in regulating reproductive activities with hormone control. Understanding the role of factors such as vitamin D in the activity of the hypothalamic-pituitary-gonadal axis (19) and especially the secretion of hormones that are very important in male fertility, such as testosterone, seems necessary (20). The exact mechanism of the molecule that binds vitamin D to testosterone production is still unknown. However, it may be indirectly effective through calcium homeostasis. This vitamin is effective for calcium transfer in the epididymis and therefore, the concentration of calcium in the epididymis and prostate is 2 to 3 times higher than its level in serum (21). Since vitamin D regulates calcium levels through calcium receptors, and vitamin receptors are expressed throughout the male reproductive system, this suggests that vitamin D plays a role in regulating testicular function (12, 15).

Other results of the present study indicated a significant difference in serum LH levels between the two groups with normal values and vitamin D deficiency. The unique role of vitamin D in the production of LH hormone by the pituitary gland can justify this finding. Since impaired function due to vitamin D deficiency is adjustable for the body, this finding can be helpful in finding ways to correct reproductive function through vitamin D and calcium supplements (22). In a study by Abbasihormozi, no association was found between serum vitamin D levels and FSH, LH, FT and TT hormones and sperm parameters in infertile men. This is probably an indication that the effect of low levels of vitamin D on sperm parameters is not controlled by the hypothalamic-pituitary-gonadal axis alone (15). However, in the study by Wang et al., it appears that vitamin D deficiency is able to regulate parathyroid hormone and can increase free intracellular calcium in adipocytes, reduce the lipolytic response to catecholamines and enhance lipogenesis. Therefore, part of this relationship can be justified by obesity (22).

According to studies, sperm quality and sperm count depend on many parameters, including the desired levels of enzymes, hormones and antioxidants (23). Vitamin D levels may not directly affect sperm production but can be an important factor in fertility (24). In a study in Iran, no significant relationship was

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reported between vitamin D and spermogram parameters and sex hormones in men with normal sperm (15). Some studies have confirmed the association between serum vitamin D levels and total and free testosterone, while others have rejected it. However, there is no consensus on the optimal concentration of vitamin D in the reproductive system and the role of vitamin D as an indicator of reproductive health is not clear (25). However, the use of antioxidants to reduce oxidative stress has been considered in a wide range of risk factors for male infertility (26, 27) and the process of prescribing antioxidants to all men with infertility is growing, even without a thorough evaluation or related guideline (28).

This study was performed on infertile men with spermograms, so generalization of the results of this study should be done with caution. In addition, since male infertility is affected by a number of factors, performing interventional studies prescribing vitamin D3 to infertile men with vitamin D deficiency may be helpful.

Finally, the results of this study showed that in infertile men with normal serum levels of vitamin D compared to infertile men with low levels of vitamin D, only the serum level of LH is significantly higher. There is definitely a need for studies that can determine the role of vitamin D in the hormone regulation and sperm parameters of infertile men and determine the effective level of vitamin D in improving healthy fertility parameters.

Conflict of interest: The authors have not reported any conflict of interest.

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