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Original Research

Evaluation of the effect of vitamin D deficiency treatment on improving outcomes in patients with semen analysis disorders after varicocelectomy

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ABSTRACT

Introduction: Varicocelectomy is the most common surgery performed to treat infertility in men. Serum levels of vitamin D and its local metabolism play an important and effective role in the male reproductive system. In this study, we treat patients with vitamin D deficiency and evaluate its effect on semen analysis after varicocelectomy. **Methods:** A total of 29 patients with varicocele underwent surgery. Three months after surgery, patients' semen analysis was performed again. After vitamin D administration and treatment of patients, sperm testing was performed three months later and compared with before treatment. **Results:** No significant differences were observed in any of the four indicators of semen analysis before or after vitamin D treatment (P-value > 0.05). Varicocele surgery increased the number of sperm and the percentage of motile sperm (both with P value less than 0.05), sperm morphology Improved (P-value = 0.043), but The change in semen volume was not significant (P-value = 0.379). **Conclusion:** The results of the present study showed that there is no relationship between vitamin D treatment and semen analysis results in improving semen variables.

Key words: Infertility, Varicocele, Varicocelectomy, Serum vitamin D levels

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INTRODUCTION

Varicocelectomy is the most common surgery performed to treat infertility in men[1]. The prevalence of varicocele is 15% of the general population, 35% of men with primary infertility, and 75% to 81% of men with secondary infertility[1,2]. Animal and human studies have shown that varicocele is associated with a progressive, time-dependent decline in testicular function. This mechanism ultimately leads to male fertility defects, mainly due to DNA fragmentation and apoptosis, oxidative stress, susceptibility to aneuploidy, and intracellular metabolic and ionic changes[3,4]. Varicocele surgical repair stops further damage to testicular function and improves spermatogenesis in a high percentage of men, as well as increases the function of Leydig cells, thereby raising testosterone levels[5]. Vitamin D levels vary among different populations due to sun exposure, clothing style, skin pigment, geographical area, daily vitamin D supplementation, obesity, and air pollution. Vitamin D deficiency is considered one of the major health problems in advanced and developing societies. Vitamin D is important for bone health and calcium homeostasis, but in recent years the known range of effects due to vitamin D has increased[6].

Human and animal studies have shown that serum levels of vitamin D and its local metabolism play an important role in the male reproductive system[7]. Vitamin D levels are positively correlated with serum androgen levels in men. These observations led to the hypothesis about a possible association between vitamin D levels and sperm parameters[6]. The importance of vitamin D in male reproduction has been proven in numerous animal studies. VDR and vitamin D metabolizing enzymes are found in the ejaculatory ducts, the smooth muscle of the epididymis, spermatogonia, Sertoli cells, germ cells, and adult human spermatozoa[7,8]. The presence of VDR in spermatozoa indicates that vitamin D is important for sperm function, which is supported by the local metabolism of vitamin D in the testes, epididymis, seminal vesicles, and prostate, and this indicates the role of vitamin D in spermatogenesis and the maturity of sperm[9].

It should be noted that due to vitamin D-mediated responses that cause a transient and rapid increase in intracellular calcium concentration, sperm motility increases and the acrosome reaction is stimulated[7,9]. Vitamin D level is evaluated in humans by measuring 25 hydroxyvitamin D3. If its serum level is < 20 ng/ml, it is considered as Deficiency and at the level of 20 – 29 ng/ml as Insufficiency[10]. Considering the set

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of these findings, we decided to investigate the therapeutic effect of vitamin D and its effect on changes in semen analysis following varicocelectomy surgery in people with vitamin D disorders.

METHODS

Patients with varicocele whose semen analysis was impaired were included in the study over a 6-month period (beginning of July 2018 to end of December 2018). Entry factors for patients in this study include Varicocele grade 3, scrotal pain that does not respond to analgesia, impaired semen analysis, and sterility. Exclusion criteria include history of previous varicocelectomy, bilateral, testicular atrophy, inguinal surgeries, events affecting fertility (herniorrhaphy, previous testicular trauma, vasectomy, radiotherapy, chemotherapy, *etc.*), patient dissatisfaction, Smoking, and concomitant use of other drugs that are effective on fertility (cimetidine, methotrexate, corticosteroids, sports supplements, working conditions, *etc.*). Serum levels of vitamin D were assessed in all patients simultaneously as the request for sperm analysis. Vitamin D is measured in humans by measuring 25 hydroxyvitamin D3. If its serum level is < 20 ng/ml, it is considered as Deficiency and at the level of 20 – 29 ng/ml as Insufficiency [11]. Vitamin D levels in the subjects were measured by blood test and measurement of 25 hydroxyvitamin D. In patients with vitamin D deficiency, we treated with 50,000 units of vitamin D3 orally once a week for 8 weeks, and then 1000 units were prescribed daily. For patients with insufficient levels of vitamin D, 1000 units were prescribed daily. All these evaluations were performed in Razi Laboratory. Then all patients were operated on by one surgeon and all by inguinal varicocelectomy. Serum vitamin D levels and semen analysis were measured three months postoperatively. Patients with lower than normal vitamin D levels were divided into two groups: vitamin D deficiency and insufficiency.

Statistical analysis

Data were analyzed using SPSS software version 23. The results were reported as frequency and percentage or determination of mean and standard deviation. Comparison of qualitative variables was assessed using the McNemar's test. KS test was used for the normality test. A paired t-test (or Wilcoxon test) was used to compare quantitative parameters before and after treatment. An independent t-test (or Mann–Whitney U test) was used to compare the two groups before and after according to the two groups of vitamin D deficiency and Insufficiency. Intention-To-Treat analysis (ITT) was used to maintain the results of all samples in the analysis.

RESULTS

The total number of patients participating in the present study was 29. The mean age of patients was 28.75 + 3.57 years (**Table 1**). The minimum age of patients was 19, and the maximum was 48 years. 9 patients (31.03%) were single, and 20 cases (68.96%) were married. Out of 20 married patients, 2 had secondary infertility (10%), and 18 had primary infertility (90%).

All patients had left side varicocele. In addition, thirteen cases (44.82%) had grade 2 varicocele, and 16 cases (55.17%) had grade 3 varicocele. Abstinence time in all cases was 72 hours, and the method of semen collection was through masturbation in the laboratory.

No significant differences were observed between the two groups in terms of varicocele grade and serum vitamin D level (P-value = 0.778). There is no significant difference in any of the four indicators of semen analysis before or after treatment with vitamin D after surgery in people with low vitamin D levels (**Table 2**). The rate of change in the four semen parameters (results after treatment with vitamin D minus results before treatment with vitamin D) did not significantly differ with treatment with vitamin D (**Table 3**).

The overall rate of change of the four indices without considering the serum level of vitamin D before and after treatment with vitamin D showed that varicocele surgery increased the number of sperm and the percentage of motile sperm (both with P value less than 0.05), sperm morphology Improved (P-value = 0.043) but has no effect on semen volume (P-value = 0.379) (**Table 4**).

DISCUSSION

The present study was a cross-sectional analytical study that was performed with the participation of 29 patients who were in two equal groups. In the current study, the sampling method is non-probability, easy or accessible. According to previous studies [12] where the average percentage of motile sperm is mentioned from 18.41 $\pm$ 9.82% to 28.4 $\pm$ 27.47% and with 95% confidence and 90% test power, at least 13 people in each group are required.

$N = (Z1\text{-}\alpha/2 + Z1\text{-}\beta)^2 . (\sigma 12+\sigma 22)/(\mu 1 - \mu 2)^2 = (1.96+1.28)^2 * (9.822+ 4.472) / (28.27\text{-}18.41)^2 = (3.24)^2 * (116.4133) / (9.86)^2 = 12.56 = 13$

Considering the 10% drop, 15 patients were considered inadequate for vitamin D group deficiency, and 15 patients were considered insufficiency vitamin D group (30 $\pm$ 1 patients in total).

Table 1: Mean age of patients in the two study groups

Variables	Groups	Average	Standard Deviation	P value
Vitamin D level	Insufficiency	28.50	4.223	0.3821
	Deficiency	29.00	3.018	

Table 2: Results of the main variables of semen analysis before and after treatment with vitamin D

Variable	Groups	Average	Standard Deviation	P value
Semen volume before Vitamin D therapy (ml)	Insufficiency	2.767	0.9037	0.1520
	Deficiency	2.429	0.8287	
Semen volume after Vitamin D therapy (ml)	Insufficiency	2.433	0.5936	0.1275
	Deficiency	2.700	0.5936	
Sperm count before Vitamin D therapy (million/ml)	Insufficiency	19.37	5.307	0.2489
	Deficiency	18.07	4.807	
Sperm count after Vitamin D therapy (million/ml)	Insufficiency	29.73	25.64	0.1550
	Deficiency	22.36	7.497	
Progressive sperm before Vitamin D therapy (%)	Insufficiency	15.53	4.627	0.4925
	Deficiency	15.57	6.173	
Progressive sperm after Vitamin D therapy (%)	Insufficiency	26.10	19.15	0.1806
	Deficiency	33.07	21.26	
Normal morphology sperms before Vitamin D therapy (%)	Insufficiency	18.47	9.403	0.2074
	Deficiency	15.57	9.411	
ormal morphology sperms after Vitamin D therapy (%)	Insufficiency	20.03	5.789	0.1401
	Deficiency	17.43	6.925	

Table 3: The rate of changes in the four semen indicators inthe two groups of patients and its relationship with vitamin D treatment

Variable	Groups	Average	Standard Deviation	P value
Semen volume Difference (ml)	Insufficiency	0.334	0.99	0.418
	Deficiency	0.271	0.92	
Sperm count Difference (million/ml)	Insufficiency	10.36	22.96	0.583
	Deficiency	4.29	15.43	
Progressive sperm Difference (%)	Insufficiency	10.57	16.43	0.436
	Deficiency	17.5	21.58	
Normal morphology Difference (%)	Insufficiency	1.56	9.11	0.685
	Deficiency	1.86	9.38	

Table 4: The rate of change in the four semen indicators inall patients

Variable	Average	Standard Deviation	P value
Semen volume Difference (ml)	-0.25	0.63	0.379
Sperm count Difference (million/ml)	8.34	24.70	0.003
Progressive sperm Difference (%)	12.65	15.82	0.001
Normal morphology Difference (%)	1.78	8.64	0.043

As far as we know, and despite extensive research, there is no similar study evaluating the therapeutic effect of vitamin D on the results of semen analysis after varicocelectomy in people with vitamin D disorder. In the present study, the overall mean age of patients was 28.75 + 3.57 years. Studies have shown that the incidence of varicocele increases by almost 10% per decade, so that at the age of 30 – 39, 18%, 40 – 49, 24%, 50 – 59, 33%, 60 – 69, 42%, 70 – 79, 53%, 80 – 89, 75% of people have varicocele[13].

All patients in the present study had unilateral left side varicocele. Most cases of varicocele also involve the left testicle[1,3,5,14–17]. Inguinal varicocelectomy surgery is currently the most accepted method of varicocelectomy surgery[1] Various studies have shown the effect of this surgery on improving semen parameters in infertile men so that a meta-analysis performed by Agrawal *et al.* Showed that microsurgical varicocelectomy could increase 9.71 million sperm per milliliter and 9.92% in sperm motility and 3.16% normal morphology[10]. The findings of the present study showed almost the same results. varicocelectomy surgery increased sperm count and percentage of motile sperm (with P-value equal to (0.003) and (0.001), respectively) and improved sperm morphology (P-value = 0.043) but had no effect on semen volume (P-value = 0.379). It is also worth noting that a recent study found that while all varicocele surgery techniques improve semen parameters, especially sperm count, sclerotherapy has both a lower recurrence rate and a higher fertility rate compared to With surgical techniques[18]. In the present study, there was no significant relationship between vitamin D treatment and any of the four indicators of semen volume, sperm count, percentage of motile sperm, and sperm with normal morphology (P-value > 0.05). In various studies, contradictory results have been reported in this field: Rubahi *et al.* reported there was no significant relationship between serum vitamin D levels and semen parameters, but by dividing patients into two groups with normal vitamin D levels (above 30 ng/ml) and below 30 ng/dl, he showed Significantly, the number of sperms was higher in patients with normal levels of vitamin D, but in the group of patients with abnormal levels of vitamin D, the number of sperms with normal morphology was higher[19]. On the other hand, in a review study conducted by De Angelis et al., The highest association between serum vitamin D levels and sperm motility was reported[20]. The essential role of vitamin D on male reproductive function in previous studies by showing the effect of active vitamin D on germ cells, spermatozoa, epididymis, and prostate and improvement of reproductive dysfunction in cases of vitamin D deficiency by giving vitamin D and calcium supplements has been proven[6,21,22]. On the other hand, Jueraitetibaike *et al.* Showed that the level of vitamin D in the seminal vesicle was associated with sperm motility. In contrast, the level of vitamin D in the seminal vesicle was not related to the serum level of vitamin D[23].

Considering all the results of previous studies and the results of the present study, the effectiveness of varicocelectomy surgery on improving semen parameters was re-emphasized, but to prove the presence or absence of effect of vitamin D treatment on these indicators, the results are still ambiguous. In this regard, a randomized, double-blinded clinical trial with a significant population of patients should be performed.

One of the limitations of the present study is the lack of measurement of testicular volume with the help of ultrasound and its measurement based solely on clinical judgment.

CONCLUSIONS

The present study results showed no relationship between the therapeutic effects of vitamin D after varicocelectomy surgery in patients with impaired vitamin D levels in improving semen variables.

ABBREVIATIONS

DNA: Deoxyribonucleic acid
ITT: Intention-To-Treat analysis
VDR: Vitamin D receptor

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AUTHOR'S CONTRIBUTIONS

Hossein Abdi: Conceptualization and design of the study, data acquisition, interpreted the results, reviewed the literature and manuscript; Mahmoudreza Moradi: Project development, interpreted the results, manuscript editing and writing; Zohreh Bartani: Project development, statistical analysis and interpretation, data acquisition, preparation and editing of manuscript; Kaveh Fatahi: Investigation, methodology, formal analysis and prepared first draft of manuscript. All authors read and approved the final manuscript.

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AVAILABILITY OF DATA AND MATERIALS

Data and materials used and/or analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This research was conducted according to the principles expressed in the Declaration of Helsinki and was approved by the Deputy of Research and Ethics Committeeof Kermanshah University of Medical SciencesIR.KUMS.REC.1399.1033.

CONSENT FOR PUBLICATION

Not applicable.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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