Submitted: 12 December, 2022 Accepted: 22 February, 2023 Published: 30 July, 2023 DOI:10.22514/jomh.2023.052

JOMH
Journal of Men's Health

SYSTEMATIC REVIEW

Meta-analysis of the relevance between sperm parameters and serum vitamin D levels in infertile men

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Abstract

To systematically estimate the relevance between sperm parameters and serum vitamin D levels and the subsequent reproductive outcomes in men. PubMed, Web of Science and other databases were searched for studies that examined a possible correlation between serum vitamin D levels and sperm parameters and reproductive outcomes. The documents were screened according to the corresponding inclusion and exclusion criteria. Selection criteria included all published randomised and controlled trials and non-randomised studies that focus on vitamin D and the reproductive function of men The patients were classified into observation/intervention and control groups, the intervention group was given vitamin D supplementation and the control group was not. The meta-analysis was conducted using Stata 16.0 software. A meta-analysis of 11 clinical studies that enrolled a total of 1356 patients, revealed that the clinical pregnancy rate in the observation group was no statistically different in the control group. A meta-analysis of 8 studies demonstrated that there was no statistically difference in sperm concentration between the experimental group and the control group. A meta-analysis of 8 studies found that sperm progressive motility in the experimental group was greater than that in the control group by using a random-effects model. The mean concentration of vitamin D was significantly lower in the control group. Appropriate vitamin D supplement intervention in infertile men improves sperm progressive motility. Interpretation of these results should be done with caution due to the significant heterogeneity of the included studies. Furthermore, Well-conducted prospective cohort studies are needed to better explain the relationship between vitamin D and sperm parameters in infertile men.

Keywords

Male infertility; Semen parameters; Serum vitamin D; Reproductive outcome

1. Introduction

At present, 10–15% of couples of childbearing age suffer from infertility [1]. There is a trend of an increasing incidence of infertility in both men and women, with male factors accounting for 50% [1]. This trend has become a global concern. Semen parameters are declining globally [2]. Well-known causes include family history, history of adverse environmental exposures, trauma, micronutrient deficiencies and varicocele [2]. However, the etiology of male infertility is quite complicated, from medications, to lifestyle choices, to medical conditions, to genetic variations, and more which poses a huge challenge in treatment [2].

In the intervening years, studies have shown that vitamin D plays an increasingly vital role in the regulation of male testicular function [3–7]. The diverse location of the Vitamin D receptor (VDR) in human spermatozoa (including the sperm head, post-acrosomal region, neck and mid-sperm) provides evidence for the potential effects of Vitamin D on sperm function [8–11]. Furthermore, the fact that VDR was identified in spermatogonia, spermatids, spermatozoa, Leydig, Sertoli and mature germ cells, supports the idea that Vitamin D may be a potent player in male reproductive performance [10, 11]. Then, the fact that all Vitamin D metabolic enzymes are widely presented in the male reproductive track and found in spermatozoa also backing the idea that Vitamin D may modulate male reproductive functions [8–12].

However, some researchers have reached different conclusions on the correlation between sperm parameters and vitamin D in infertile men. On the one side, some studies have suggested there was no relationship between vitamin D levels and sperm parameter [13, 14]. On the other side, other studies found a negative association between vitamin D deficiency and semen quality [15, 16]. However, the association between vitamin D and semen quality or conception rates is partly based on *in vitro* studies, so it should be interpreted with caution.

The principal sources of vitamin D are sunlight, food and supplements. The main causes of vitamin D insufficiency

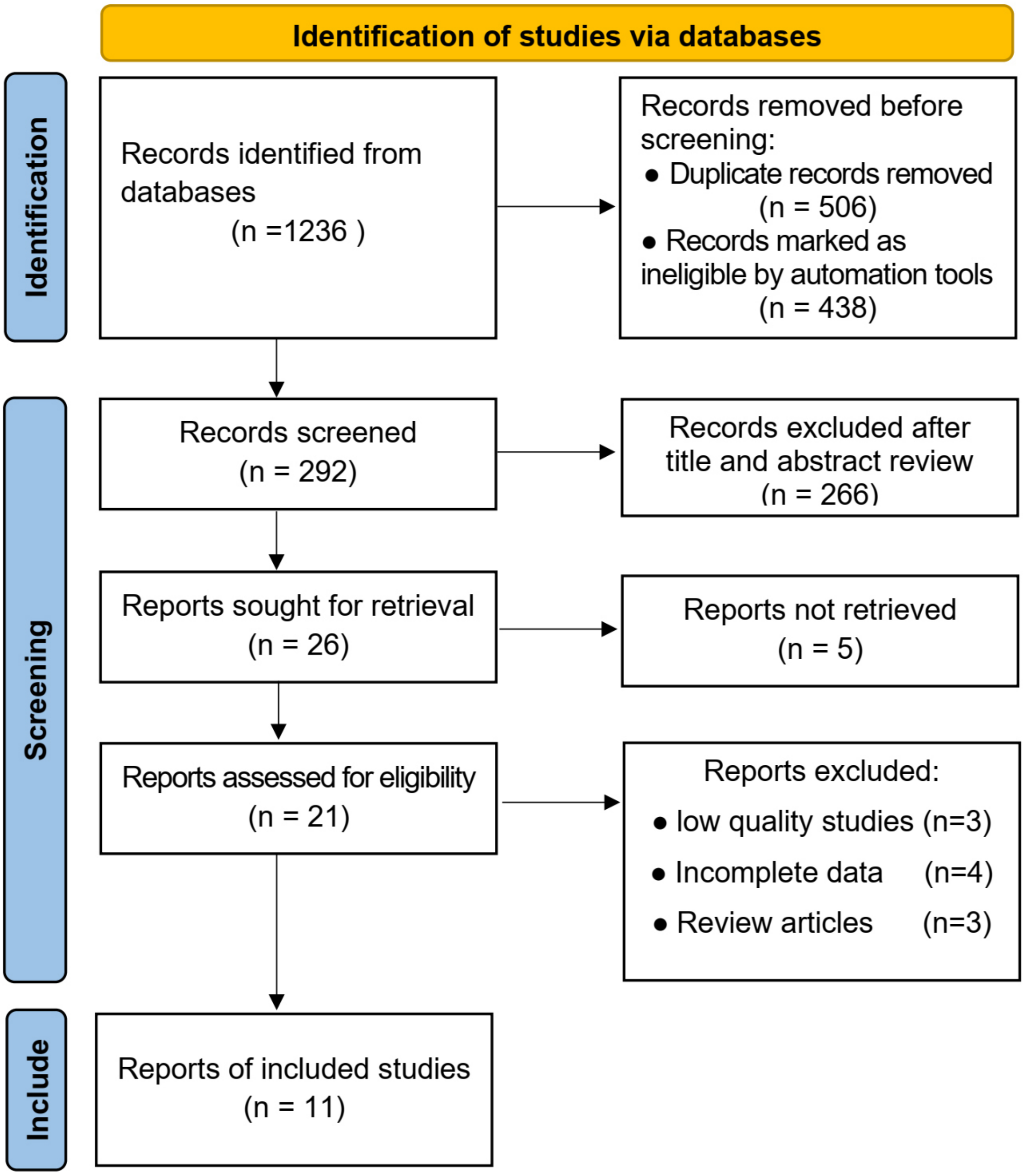

FIGURE 1. Flowchart of preferred reporting items for systematic reviews and meta-analysis (PRISMA).

include poor sun exposure, dark colored skin, and food habits [17]. For this reason, vitamin D supplementation continues to be a cornerstone in the treatment of vitamin D deficiency. The objective of this study was to explore the possible association between serum vitamin D levels and its impact on vitamin D supplementation in vitamin D-insufficient/deficient infertile males with sperm parameters by systematic evaluation and meta-analysis to support evidence-based medical evidence for this clinical problem.

2. Materials and methods

2.1 Inclusion criteria for literature selection

① The patients included in the study met the definition of infertility (which means that a couple fails to conceive for 1 year [18]). ② The study included patients ≤40 years old; Patient's body mass index is less than 25 kg/m^2. ③ The studies were published in the last 7 years. ④ The full text of the article is available, and the necessary data can be obtained from the published article. Articles were selected for inclusion if they were analyzed the association between vitamin D and semen quality or infertility. Also reported means, medians or odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) for the following outcomes: sperm motility, progressive motility, concentration and clinical pregnancy rate. Articles were disqualified if they were non-human experimental studies, review articles, poster abstracts, case reports, editorials, or if they lacked initial data or relevant outcome data.

2.2 Search strategy

PubMed, GeenMedical, Cochrane Library, Web of Science, Medline and Scopus were databases for literature retrieval. A single query was used by two different investigators to identify all relevant studies describing a possible association between male fertility and vitamin D. The authors chose all articles indexed by the above databases using the following queries: vitamin D, sperm quality, and male infertility. Titles and abstracts were screened, and articles were classified according to the predetermined inclusion and exclusion criteria. After reading the abstract, we conducted a more in-depth evaluation by analyzing the full text.

2.3 Literature screening strategy

A total of 1236 published articles were obtained from the above mentioned databases, and 21 remained after removing irrelevant and duplicate literature. After careful reading of the full text, duplicate studies were excluded and titles and abstracts were analysed using the included criteria listed above. The full texts of the other included studies were checked for inclusion using the pre-specified criteria. The review was reported following the Preferred Reporting Item for Systematic Reviews and Meta-Analyses (PRISMA) statement [19]. The literature screening process is shown in Fig. 1.

2.4 Basic information of the included literature

A total of 1356 male infertility patients were enrolled in the 11 studies. Ten were written in English and 1 in Chinese. Literature including 707 cases in the observation/intervention group (given vitamin D supplementation) and 649 cases in the control group. The randomization method was described in detail in 4 studies, and a blinding method was used in 1 study, covering 4 randomized controlled trial (RCT) and 1 cross-sectional study (Table 1).

2.5 Methodological quality assessment of the included studies

Quality evaluation of the randomized controlled studies was carried out according to the Cochrane Handbook's 5.1 system, and for the other studies, the risk of bias in nonrandomized controlled studies tool was adopted [33]. The results of the bias risk assessment of the included non-RCTs are shown in **Supplementary material** (**Supplementary Table 1**) and those for the RCTs are shown in Table 2 [33]. Selection criteria included all published RCTs and non-randomized studies (such as observational, prospective, retrospective cohort studies, case-control studies), focusing on vitamin D and male reproductive function. Two independent reviewers conducted the review steps (the electronic search, study eligibility, inclusion criteria, risk of bias, data extraction and analysis) [34].

2.6 Statistical processing and results

Meta-analysis was performed on the data using Stata 16.0 (StataCorp LLC, TX, USA). The counting data are shown as the relative risk odds ratio (OR value), the measurement data are shown as the weighted mean difference (MD), and the 95% confidence interval (95% CI) was calculated. A Z-test was used to analyze the heterogeneity of the results of each study. The I^2 index was used to assess inhomogeneity, low, moderate and high inhomogeneity were defined as an I^2 index of 25, 50 and 75% respectively [35]. A fixed-effects model was used for analysis. If statistical heterogeneity existed, a random-effects model was used for analysis [36].

3. Results

3.1 Correlation between vitamin D and reproductive outcomes

Four articles mentioned pregnancy outcomes, including a total of 485 patients, with 255 patients in the observation group and 230 patients in the control group. The results of the heterogeneity analysis showed that $I^2 = 0\%$ and $p < 0.001$, indicating that there was no obvious inhomogeneity. A fixed-effects model analysis should have been carried out, but there were very few studies. To increase the reliability of the meta-analysis, a random-effects model was selected instead. Meta-analysis revealed that the pregnancy rate in the observation group was no substantial association than that in the control group (OR = 1.04, 95% CI (0.35, 1.74), $p < 0.001$) (Fig. 2).

3.2 Relationship between sperm concentration and vitamin D

Eight articles mentioned sperm concentration, including a total of 921 patients, with 502 in the observation group and 419 in the control group. The results of inhomogeneity analysis showed that $I^2 > 75\%$, indicating apparent inhomogeneity, and a random-effects model was adopted. The meta-analysis results revealed that there was no obvious difference in sperm concentration between the observation group and the control group (MD = 1.38, 95% CI (−0.35, 3.12), $p > 0.05$) (Fig. 3).

3.3 Relationship between vitamin D and sperm progressive motility

Eight studies mentioned sperm progressive motility, involving a total of 699 patients, including 385 in the observation group and 314 in the control group. The results of heterogeneity analysis revealed that $I^2 > 75\%$, indicating apparent inhomogeneity, and a random-effects model was applied. The meta-analysis revealed that sperm progressive motility in the observation group was higher than that in the control group (MD = 1.83, 95% CI (0.13, 3.53), $p < 0.05$) (Fig. 4).

4. Discussion

The vital role of vitamin D in male fertility mainly depends on the interlinked roles of vitamin D metabolic enzymes and vitamin D receptors [37]. Studies have proven that vitamin D metabolic enzymes are widely present in various human systems, especially in testicular tissue in the reproductive system [37]. Testicular germ cells and somatic cells can locally synthesize and degrade vitamin D and are isolated from vitamin D metabolism in the circulatory system [37]. In addition, the expression of vitamin D receptors in the testis demonstrates that vitamin D may have an autocrine and paracrine role, which may play an important part in adjusting testicular function, thus affecting male sterility [38].

Our study estimated the effect of serum vitamin D levels

TABLE 1. Basic information of the included literature.

Study	Country	Cases	Intervention measures		Intervention time	Experimental Design	Diagnostic criteria	Observation index
			Test group	Control group				
Yu [20]	China	50	D_2 + daylight	Daylight	12 wk	RCT	Unclear	1, 2, 3
Leena [21]	India	60	D_2 + Ca	None	12 wk	Observation	Unclear	1, 2, 3
Akhavizad [22]	Iran	103	None	None	no	Review	Hollis [24]	1, 2
Tirabassi [23]	Italy	52	None	None	no	Review	Unclear	1, 2
Zhu [25]	China	91	None	None	no	Review	Unclear	2
Abb [26]	Iran	157	None	None	no	Review	IOM [27]	1, 2
Tartagni [28]	Italy	100	None	None	no	RCT	IOM [27]	3
Blo jense [15]	Denmark	235	D_2 + Ca	Placebo	12 wk	RCT	Unclear	3
Rehman [29]	Saudi-Arabia	313	None	None	no	Cross	Unclear	1
E.Azizi [30]	Iran	36	None	None	no	Review	Rahnavard [31]	1, 2
Alzoubi [32]	Jordan	90	D_2	None	8 wk	RCT	FNB [1]	1, 2

Note: 1. Male sperm concentration 2. Sperm progressive motility 3. Pregnancy outcome.
Test group, which group was given vitamin D supplementation and the control group was not. IOM: Institute of Medicine; FNB: Food and Nutrition Board; RCT: randomized controlled trial. Ca: Calcium.

TABLE 2. Bias risk assessment results of the included RCT literature.

Included study	Random	Distribution of hidden	Blinded	Results evaluated blind	Data integrity	Report findings selectively	Other sources of bias
Yu [20]	yes	undefined	undefined	undefined	safe	Safe	safe
Tartagni [28]	yes	undefined	undefined	undefined	safe	Safe	safe
Blo jense [15]	yes	yes	yes	yes	safe	Safe	safe
Alzoubi [32]	yes	undefined	undefined	undefined	safe	Safe	safe

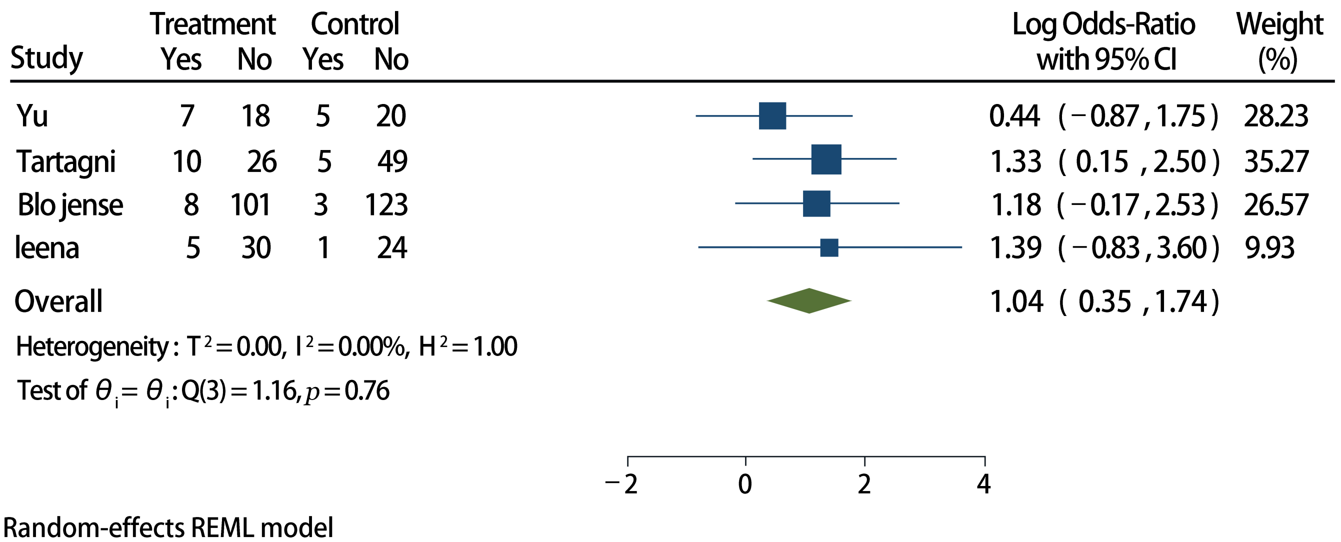

FIGURE 2. Meta-analysis of the clinical pregnancy rate. CI: confidence intervals.

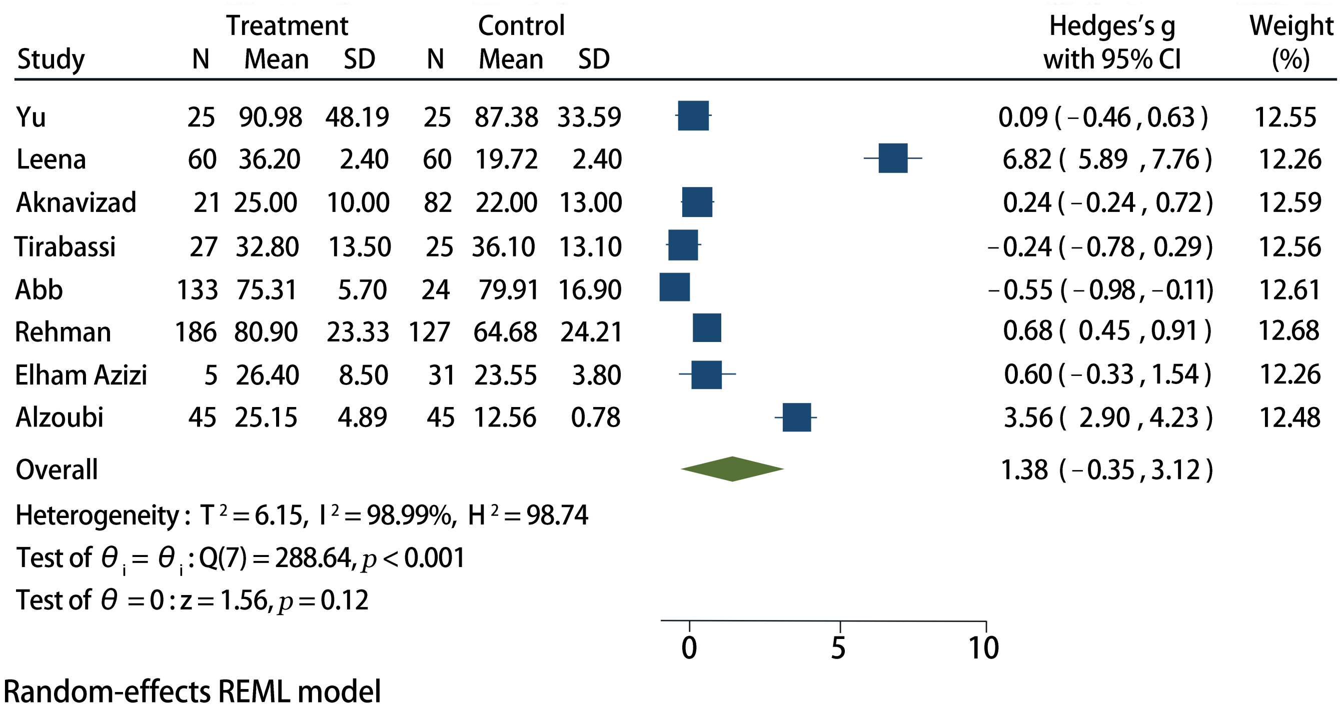

FIGURE 3. Meta-analysis of sperm concentration. CI: confidence intervals; SD: Standard deviation.

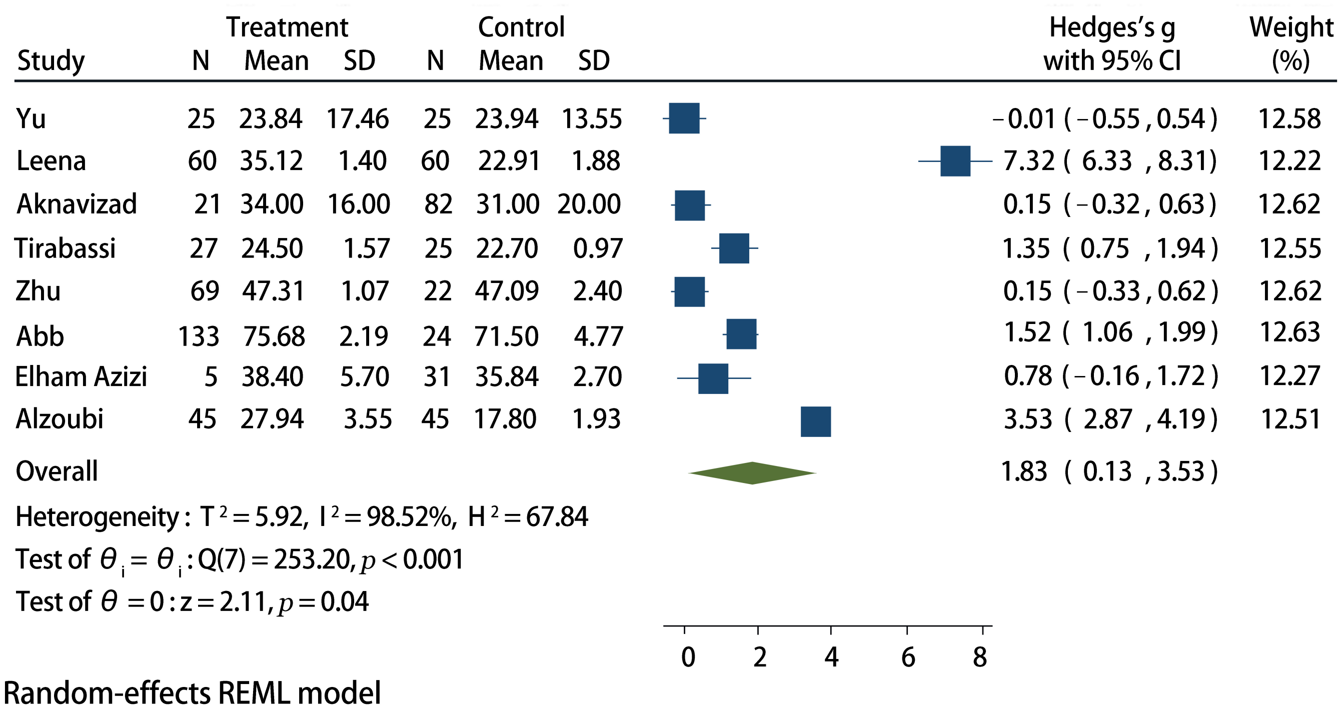

FIGURE 4. Meta-analysis of sperm progressive motility. CI: confidence intervals. SD: Standard deviation.

on sperm parameters and pregnancy outcomes after treatment. We comprehensively searched the literature. In strict accordance with the inclusion criteria of our study, the data from 11 studies were found to meet the criteria for meta-analysis after multiple screenings. Certainly, the main object of our search was the correlation between serum vitamin D levels in infertile men and sperm parameters. Although the correlation between Vitamin D, semen count and morphology rate are still equivocal, the results on association with sperm motility appear more informative. Most of the specifically related articles included in the review reported a positive association of Vitamin D serum level with semen motility, in infertile males; moreover, in many cases, this positive association of Vitamin D level and semen total motility had statistical significance [13, 29, 39–42]. All these data suggested the potential benefits of vitamin D on male reproductive and sexual health, especially by improving sperm progressive motility [22, 23, 25].

The relevance between sperm concentration and vitamin D levels is much debated. Vitamin D is not associated with sperm concentration as reported in several studies [14, 25, 26, 28, 42–44]. Few studies have analyzed reproductive outcomes in sterile men with vitamin D insufficiency. In addition, only four studies included in our systematic review reported reproductive outcomes, and the analysis suggested that normal levels of vitamin D appeared to be associated with a higher pregnancy rate but were not associated with risk factors [15, 20, 21, 28]. Other studies have pointed out that in cases of vitamin D insufficiency, the abortion rate has an increasing trend, but it has no statistical significance [45].

Four of the articles included in this systematic review were interventional studies. One of these four articles used an intervention of vitamin D_2 injection + calcium D_3 tablets oral + sun exposure and it showed no statistically significant difference in sperm motility or pregnancy rate compared to the control group [20]. However, the control group also received sun exposure and is not clear whether the sun exposure increased their vitamin D levels, thereby improving their semen parameters.

In the study of Alzoubi [32], which was the first of its kind to show the effect of vitamin D supplementation on seminal parameters in males who suffer from idiopathic infertility. vitamin D levels in patients with primary male sterility were significantly lower than those in the control group and patients with secondary infertility. After vitamin D treatment, the progressive motility and total motility of sperm were significantly improved. Serum vitamin D levels were significantly associated with sperm parameters in the research population. This study also mentioned that human spermatogenesis takes up to 74 days [46]. This length of time should be taken into account when taking vitamin D supplements.

In the study by Elham Azizi *et al*. [15]. it was found that Vitamin D may affect sperm motility and morphology, Low serum vitamin D levels may affect male fertility and should be considered when evaluating men with an abnormal seminogram. there is still a paucity of data on the mechanism of action of Vitamin D in the male genital system, but the evidence that the human testis and ejaculatory tract are sites of Vitamin D metabolism has led to the idea that local activation of Vitamin D plays an important role in spermatogenesis and sperm maturation [8]. In addition, the vitamin D inactivating enzyme 24-hydroxylase (CYP24A1) regulates the response of cells to vitamin D and is transcriptionally regulated by vitamin D [34].

CYP24A1 expression at the ring of human spermatozoa was strongly correlated with sperm concentration, sperm motility and morphology and is a novel marker of semen quality [47].

Despite the few of data, one aspect that can be agreed upon is the positive association between seminal plasma Vitamin D and sperm kinetic parameters: activated Vitamin D may improve sperm motility by promoting the activation of the sperm mitochondrial respiratory chain to produce adenosine triphosphate (ATP) and by increasing the intracellular calcium ion concentration [40, 43, 44]. In this regard, seminal plasma Vitamin D better represents the status of male reproduction when compared to serum Vitamin D.

Although the overall results on this topic suggested that Vitamin D supplementation had no significant association with changes in all semen parameters, the data on spontaneous pregnancy rates in couples with infertile men were surprising [5]; in particular, results from two interventional studies in infertile men with Vitamin D deficiency showed the increased chances of spontaneous pregnancy in the population treated with Vitamin D and Vitamin D plus calcium supplementation [5, 13]. Of course, these are preliminary data, but they are an important contribution to further research in this field.

All of the studies included in this systemic review had wide variations in design, especially in the study population, methods and number of participants, the ways used to determine vitamin D levels, and the adjustments to the models. Such as in Leena's research [21], only patients with oligospermia were included. the mean sperm concentration at baseline was 19.72×10^6/mL, which is above the lower reference limit [21]. In addition, the existence of confounding factors may cause deviations in the data in this research. In this respect, the main confounding factors may be explained by different study populations and ethnicities and different treatment methods, which affect sperm quality.

In summary, the existing observational and interventional studies have yielded controversial results. Additional research is required to explain the effects of vitamin D on sex hormones and semen in fertile and sterile men. More clinical studies are required to establish whether vitamin D supplementation improves semen viability and reproduction. If so, an appropriate vitamin D threshold must be identified to establish a correlation between reproductive parameters and positive reproductive outcomes in men and women.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

JZ—conceived the idea, the draft-revision. WDZ and ZWL—designed the study. JZ and WDZ—collected data. WDZ—Data analysis, the first draft-writing. All authors read and agreed with the ultimate version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The Ethics Committee of Zhuzhou Hospital Affiliated to Xiangya School of Medicine, Central South University (ZZCHEC2022042-01), approved the study.

ACKNOWLEDGMENT

We thank the nurses and scientific staff of the reproductive center for the teamwork that generated this manuscript.

FUNDING

Grant support was provided by the Natural Science Foundation of Hunan Province (No. 2022JJ50102, 2021JJ50070) and the Health and Family Planning Commission of Hunan Province (N0. 202205034020).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.jomh.org/files/article/1685851393194115072/attachment/Supplementary%20material.docx.

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How to cite this article: Wenda Zou, Ziwei Liu, Juan Zhang. Meta-analysis of the relevance between sperm parameters and serum vitamin D levels in infertile men. Journal of Men's Health. 2023; 19(7): 8-15. doi: 10.22514/jomh.2023.052.