INPLASY

The Impact of Vitamin D3 Supplementation on Androgens and Semen Parameters in Infertile Men: A Systematic Review and Meta-Analysis Based on Prospective Randomized Controlled Trials

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ADMINISTRATIVE INFORMATION

Support - None.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 9 January 2025 and was last updated on 9 January 2025.

INTRODUCTION

Review question / Objective To investigate the effects of Vitamin D3 supplementation on androgen levels and semen parameters in infertile men.

Condition being studied Male infertility is a growing global health issue, affecting 10-15% of couples, with male factors contributing to about half of these cases. The causes of male infertility are complex and include age, nutrition, lifestyle, environmental factors, and endocrine disorders. Oxidative stress, hormonal disruptions, and genetic issues also contribute significantly to idiopathic male infertility.
Vitamin D plays a vital role in male reproductive health, as it is found in various reproductive tissues and is essential for sperm production and function. Studies indicate that there is a positive correlation between serum vitamin D levels and sperm quality, particularly motility, and low vitamin D levels have been associated with increased male hypogonadism. While there is interest in the potential benefits of vitamin D supplementation for enhancing fertility, research findings regarding its effects on sperm motility, concentration, morphology, and testosterone levels are inconsistent and vary across studies.
Due to the prevalence of vitamin D deficiency and its implications for male reproductive health, it is crucial to establish strong evidence regarding its role in male fertility. To address this, the study aims to conduct a meta-analysis to combine data from randomized controlled trials and observational studies to better understand the impact of vitamin D on male reproductive health.

METHODS

Search strategy Literature Search
A comprehensive search was conducted across various databases, including PubMed, Web of Science, Cochrane Library, Scopus, and Embase. The search timeframe spanned from the inception of these databases up until December 2024. The search strategy incorporated a range of keywords and subject terms pertinent to vitamin D, male

infertility, semen parameters, and reproductive hormones. Additionally, the reference lists of the included studies were manually examined to ensure that no relevant studies were overlooked. For instance, the search strategy employed in the PubMed database was detailed as follows:
Vitamin D-related terms: "Vitamin D" OR "Cholecalciferol" OR "Ergocalciferols"[Mesh] OR "vitamin D" OR "vitamin D2" OR "vitamin D3" OR cholecalciferol OR ergocalciferol OR "25-hydroxyvitamin D" OR "25(OH)D" OR "1,25-dihydroxyvitamin D" OR "1,25(OH)2D"
AND
Male fertility-related terms: "Male Infertility" OR "Spermatozoa" OR "Semen" OR "Sperm Count" OR "Sperm Motility"[Mesh] OR "Testosterone" OR "Follicle Stimulating Hormone" OR "Luteinizing Hormone" OR "male fertility" OR "male infertility" OR spermatozoa OR sperm OR semen OR "sperm count"[tiab] OR "sperm concentration" OR "sperm motility" OR "sperm morphology" OR "semen quality" OR "semen parameters" OR testosterone OR "follicle stimulating hormone" OR "luteinizing hormone" OR "sex hormones"
AND
Study type filter: ("Randomized Controlled Trial" OR "Controlled Clinical Trial" OR "Random Allocation" OR "randomized" OR "randomised" OR "randomly"[tiab] OR “RCT").

Participant or population Inclusion criteria: (1) Study subjects are adult males; (2) Interventions involve vitamin D supplementation or assessment of vitamin D levels; (3) Outcome measures include semen parameters, reproductive hormone levels, or fertility rates; (4) Study design is a RCT.
Exclusion criteria: (1) Non-English literature; (2) Animal studies or in vitro experiments; (3) Reviews, commentaries, or case reports.

Intervention Administration of vitamin D.

Comparator No administration of vitamin D.

Study designs to be included Prospective Randomized Controlled Trials.

Eligibility criteria Literature Screening and Data Extraction
Two independent reviewers were tasked with using preset inclusion and exclusion criteria to find pertinent research throughout the literature screening phase. The process commenced with an evaluation of the titles and abstracts of identified articles. Once this initial screening was completed, a comprehensive full-text review of studies that appeared potentially eligible was conducted. To facilitate a systematic collection of data, the reviewers utilized a pre-designed data extraction form. This form was meticulously structured to gather crucial information, including the names of the authors, year of publication, type of study design, sample sizes, participant characteristics, details regarding interventions, vitamin D measurement techniques, outcome measures, and key findings from each study. In instances where discrepancies arose during the screening and data extraction processes, these were resolved through collaborative discussion, or, if necessary, by consulting a third reviewer to reach a consensus.

Information sources A comprehensive search was conducted in databases including PubMed, Web of Science, Cochrane Library, Scopus, and Embase for literature regarding the supplementation of Vitamin D3 and its effects on androgen levels and semen parameters in infertile males.

Main outcome(s) The systematic review and meta-analysis evaluated the effects of Vitamin D3 supplementation on androgen levels and semen parameters in infertile men, including six studies with a total of 959 participants. Among these studies, two focused on individuals with 25-hydroxyvitamin D [25(OH)D] levels ≤ 50 nmol/L and another two included those with levels below 30 nmol/L.
Regarding androgen levels, Vitamin D3 supplementation showed a slight increase in testosterone and sex hormone-binding globulin (SHBG), but these changes did not reach statistical significance. Specifically, the standardized mean difference (SMD) for testosterone was 0.07 (95% CI: -0.11, 0.26), and for SHBG it was 0.44 (95% CI: -0.40, 1.28), with notable heterogeneity observed among studies for SHBG levels.
In terms of semen parameters, significant increases in total sperm count and the percentage of progressively motile sperm were found following Vitamin D3 supplementation. The SMD for total sperm count was 1.07 (95% CI: 0.18, 1.95), while the SMD for the percentage of motile sperm was 0.82 (95% CI: -0.00, 1.64). These findings suggest a potential positive impact of Vitamin D3 on male fertility.
Overall, while the effects on androgen levels were not statistically significant, the notable improvements in semen parameters highlight the possible importance of Vitamin D3 in male reproductive health. The authors call for further research to explore the underlying mechanisms and validate these findings.

Quality assessment / Risk of bias analysis For the assessment of the quality of the randomized

controlled trials included in the review, the two independent reviewers employed the Cochrane Risk of Bias Assessment Tool (ROB2). This all-inclusive instrument assesses the risk of bias in five different areas: (1) bias resulting from the randomization procedure; (2) bias resulting from departures from planned interventions; (3) bias resulting from the lack of outcome data; (4) bias in outcome measurement; and (5) bias associated with the selection of reported results. The risk level of each domain was classified as "low risk," "some concerns," or "high risk." The overall risk of bias for each study was determined by aggregating the evaluations across these five domains, allowing for a nuanced understanding of the quality of the evidence presented.

Strategy of data synthesis In terms of statistical analysis, the study computed the weighted mean difference (WMD) for continuous outcome variables, along with corresponding 95% confidence intervals (CIs) to assess the effect size. For dichotomous outcomes, the risk ratio (RR) and its 95% CI were calculated. Anticipating clinical and methodological heterogeneity among the studies, a random-effects model was selected for data synthesis. To evaluate the extent of heterogeneity, Cochran's Q test and I^2 statistics were employed. The interpretation of I^2 values followed established guidelines: values between 0-40% indicated negligible heterogeneity, 30-60% suggested moderate heterogeneity, 50-90% signified substantial heterogeneity, and values from 75-100% indicated considerable heterogeneity. In cases where I^2 exceeded 50%, subgroup analyses and meta-regression analyses were carried out to identify potential sources of variability. Additionally, funnel plots were utilized for a visual examination of publication bias, supplemented by Egger's test to provide a statistical evaluation. If any signs of publication bias were detected, the trim-and-fill method was applied to assess its potential impact on the overall findings. All statistical analyses and graphical representations were executed using R software, ensuring a robust and comprehensive approach to data analysis.

Subgroup analysis The intervention methods were classified based on the administration of vitamin D, resulting in an experimental group consisting of 473 participants and a control group comprising 486 participants.

Sensitivity analysis 1. Quality of Studies
Objective: To assess the impact of study quality on the overall effect size.
Method: Studies will be classified according to their quality using the Cochrane Risk of Bias Tool. A sensitivity analysis will be performed by excluding studies deemed low quality to observe changes in the pooled effect size.
2. Inclusion Criteria
Objective: To evaluate how different inclusion criteria affect the results.
Method: Sensitivity analysis will exclude studies that include participants with severely low baseline vitamin D levels (e.g., below 30 nmol/L) to assess its impact on overall results.
3. Data Handling and Statistical Models
Objective: To evaluate the influence of statistical model choice on the findings.
Method: A comparison will be made between results obtained from a random-effects model and a fixed-effects model to examine if model selection significantly alters the effect size.
4. Duration of Intervention
Objective: To investigate the effect of the duration of vitamin D3 supplementation.
Method: Studies will be categorized as short-term (less than 3 months) and long-term (3 months or more). Separate meta-analyses will be conducted for each category, with results compared for consistencies in outcomes.
5. Publication Bias
Objective: To ensure that the overall results are not influenced by publication bias.
Method: Funnel plots and Egger's test will be employed to assess publication bias. We will selectively exclude studies with a potential for bias to observe any changes to the pooled effect size.
6. Subgroup Analysis
Objective: To understand the effect of different subgroups on overall outcomes.
Method: Studies will be divided based on geographic regions or demographics (e.g., age groups), and separate analyses will be performed to assess variability and its impact on overall findings.

Country(ies) involved China.

Keywords Infertility; Vitamin D3; Androgens; Semen Parameters.

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