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Systematic Review

Vitamin D Supplementation in Infertile Men: Beyond Pooled Effects—A Critical Meta-Analysis of Heterogeneous Clinical Responses

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Abstract

Introduction: Male infertility is a complex global health challenge, with emerging evidence suggesting that vitamin D plays a pivotal role in testicular function and spermatogenesis. This systematic review and meta-analysis aimed to evaluate the impact of vitamin D supplementation on semen parameters and reproductive hormones in infertile men. Methods: A comprehensive search of electronic databases (PubMed, Cochrane Library, and Web of Science) was conducted to identify randomized controlled trials (RCTs) investigating vitamin D supplementation in infertile males. Primary outcomes included Follicle-Stimulating Hormone (FSH), total testosterone, and Sex Hormone-Binding Globulin (SHBG). Secondary outcomes focused on semen quality, specifically volume, concentration, and motility. Data were pooled using fixed-effects or random-effects models based on heterogeneity (I^2). Results: Analysis of six trials (n = 696) revealed that vitamin D supplementation significantly increased total testosterone levels compared to controls (SMD: 0.38; 95% CI: 0.13, 0.62; $p = 0.002$), with no statistical heterogeneity ($I^2 = 0\%$). In contrast, no significant differences were observed for FSH (SMD: 0.01; 95% CI: −0.28, 0.29; $p = 0.96$) or SHBG (SMD: 0.95; 95% CI: −0.12, 2.02; $p = 0.08$). For semen parameters, supplementation was associated with notable improvements in sperm concentration and progressive motility, whereas semen volume remained largely unchanged across the included studies. High heterogeneity in SHBG results ($I^2 = 91\%$) suggests that individual study characteristics, such as baseline vitamin D deficiency, may influence hormonal responses. Conclusions: Vitamin D supplementation selectively enhances endocrine function by increasing testosterone levels and improves functional semen parameters in infertile men. These findings support the use of vitamin D as a cost-effective adjuvant therapy, though its impact on definitive fertility outcomes, such as live birth rates, requires further large-scale clinical investigation.

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1. Introduction

Male infertility represents a significant global health issue with diverse etiologies and a substantial impact on couples' reproductive potential. According to Liang et al., the peak prevalence of male infertility is found in the 30–34 age group, with a notable increase in the 35–39 age range [1]. Regions such as Western Sub-Saharan Africa, Eastern Europe, and East Asia report the highest age-standardized prevalence rate for male infertility [2]. At the same time, the underlying causes are varied and can include genetic factors, hormonal imbalances, and lifestyle choices. Many cases are classified as idiopathic, underscoring the intricate nature of male reproductive physiology. In recent years, there has been a surge in interest in the potential role of micronutrients, particularly vitamin D, in influencing various aspects of human health, including reproductive function [3].

Initially, research on vitamin D primarily concentrated on its well-established role in maintaining calcium homeostasis and bone metabolism [4]. However, the scope of its biological actions has expanded considerably, with emerging evidence suggesting its involvement in numerous other physiological systems, including the reproductive system [3]. This broadening understanding has prompted investigations into the potential link between vitamin D status and male fertility. The observed geographic diversity in the prevalence of male factor infertility also raises questions about environmental influences, such as diet composition or sunlight exposure [5]. Vitamin D's potential effect on hormonal regulation further enriches its relevance. Meta-analytic data suggest it may positively affect testosterone synthesis by modulating Leydig cell function in response to luteinizing hormone stimulation [6]. Given that testosterone deficiency shares complications similar to those arising from low vitamin D, such as sarcopenia or decreased bone integrity, it is plausible that both deficiencies act synergistically to compromise reproductive potential.

The rationale for exploring the role of vitamin D in male infertility is strengthened by the identification of vitamin D receptors (VDRs) and vitamin D-metabolizing enzymes in the testes, the male reproductive tract, and human sperm [3]. These components suggest that vitamin D may directly affect the male reproductive system at the cellular level, influencing testicular function and sperm maturation [7]. This local expression hints at a potentially significant role for vitamin D that extends beyond its systemic hormonal effects. The current landscape depicts a nutrient with plausible pathways affecting both sperm quality, especially motility, and sexual hormone production but whose impact on broader fertility outcomes like pregnancy rates remains uncertain due to study design constraints [8].

Although several recent meta-analyses have examined the relationship between vitamin D supplementation and male reproductive parameters, their primary focus has been on pooled effect estimation, with comparatively limited attention to the biological and methodological sources of heterogeneity that may underlie inconsistent findings.

This report aims to critically evaluate the existing body of literature on vitamin D supplementation and male infertility, pinpoint key scientific gaps, and highlight areas where future research is most needed. Our primary objective was to systematically review and meta-analyze the effect of vitamin D supplementation compared to placebo or no treatment on semen parameters (sperm concentration, total motility, progressive motility, morphology) in infertile males. The secondary objectives were to assess the effect of vitamin D supplementation on relevant endocrine parameters (total testosterone, FSH,

LH, SHBG) if consistently reported, and to explore potential sources of heterogeneity through subgroup analyses (baseline vitamin D status, dose/duration of supplementation). In contrast to prior quantitative syntheses, the present study explicitly prioritizes the interpretation of inter-study variability and the dissociation between endocrine and spermatogenic responses, aiming to move beyond effect size aggregation toward a more mechanism-oriented understanding.

2. Materials and Methods

We conducted this meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines [9]. The Population, Intervention, Comparison, and Outcome (PICO) model informed the search keywords for this literature review. P (Population): Adult males ($\geq$18 years) who have been diagnosed with infertility (e.g., defined as failure to conceive after $\geq$12 months of regular unprotected intercourse, potentially with documented abnormalities in semen analysis according to WHO criteria relevant at the time of the study). Studies focusing solely on fertile men or on men with specific genetic causes of infertility (Klinefelter syndrome, Y-chromosome microdeletions) where vitamin D is not the primary focus were excluded. I (Intervention): This included vitamin D supplementation (any form, e.g., cholecalciferol, ergocalciferol; any dose, frequency, or duration). C (Comparator): This included placebo or no vitamin D supplementation. O (Outcomes): Studies must report at least one of the primary or secondary outcomes listed above. Data should be available for extraction (mean $\pm$ SD for continuous outcomes; number of events for dichotomous outcomes). Studies were primarily English-language publications, but efforts were made to include studies in other languages if resources allowed for translation.

Systematic literature searches were performed in MEDLINE, Scopus, and Embase using a predefined strategy. The search terms combined free-text and controlled vocabulary, as follows: Population: "male infertility", "subfertility", "oligospermia", "asthenospermia", "teratospermia", "semen analysis", etc.; Intervention: "vitamin D", "cholecalciferol", "ergocalciferol", "25-hydroxyvitamin D", "supplementation", etc. Inclusion criteria were: randomised controlled trials only; adults (>18 years); infertile men according to the WHO definition of infertility; vitamin D supplementation alone; placebo or untreated controls; reporting mean $\pm$ SD. Exclusion criteria were: observational studies, case reports, reviews, animal studies, mixed supplementation where the vitamin D effect cannot be isolated, duplicate cohorts, conference abstracts, and studies without extractable data.

Beyond conventional pooled effect estimation, particular emphasis was placed on interpreting patterns of heterogeneity, including the consistency of directionality across studies and the biological plausibility of observed divergences between outcomes. The search covered all available records up to 31 March 2026. Reference lists of relevant reviews and included articles were also screened manually to identify additional eligible studies. Duplicates were identified and removed using EndNote. When multiple publications reported on the same cohort, the most comprehensive report was selected. Two authors separately conducted the primary search and screened titles, abstracts, and full-text publications for eligibility. Any disagreements were settled by consensus, and if needed, a third reviewer participated in arbitration. We employed a standardized extraction technique, considering the study's design, demographic characteristics, results, and the risk-of-bias assessment. While participant age was documented in the included RCTs, it was not treated as a primary moderator in this meta-analysis because the individual study reports did not provide age-stratified data. Future studies should consider adjusting for age to better isolate the therapeutic effects of vitamin D. The PROSPERO registration ID for this meta-analysis is CRD420251035637.

The heterogeneity in sperm count improvement rates was assessed using the I^2 statistic, with $I^2 > 50\%$ indicating significant heterogeneity. To calculate the individual odds ratios and individual and pooled mean differences with a corresponding 95% confidence interval (CI), we used Review Manager (RevMan) (Computer program, Version 5.4, Copenhagen; The Cochrane Collaboration, 2020). The methodological quality of included randomised controlled trials was assessed using the RoB 2 tool developed by the Cochrane Collaboration, given its suitability for evaluating bias in randomised intervention studies and ROBINS-I for non-randomised studies. Its domain-based, outcome-level approach was considered appropriate given the heterogeneity of study designs, supplementation protocols, and outcomes in male infertility research. This methodology is consistent with PRISMA recommendations.

3. Results

The analysis revealed a marked contrast between the consistency of endocrine outcomes and the variability of semen-related parameters, a pattern that guided subsequent interpretation. Following the literature search, 456 potential articles were deemed suitable for inclusion in our study. Only 11 papers satisfied the inclusion criteria after removing duplicate entries and closely reviewing the titles, abstracts, and full texts; their characteristics are shown in Table 1. The PRISMA 2020 flow diagram showing the search procedure is shown in Figure 1.

Table 1. Characteristics of included studies.

Author	Publication Year	No. of Patients	Vitamin D Dose	Duration of Treatment	Control Group	Outcomes *
Amini et al. [10]	2020	62	50,000 IU	12 weeks	yes	1,2,3,4,5,6
Bartl et al. [11]	2021	34	2500 IU/day	6 months	self-comparison	1,2,4,5,6
Begum et al. [12]	2021	110	D 40,000 IU weekly for 6 weeks, and then 2000 IU daily for another 6 weeks	12 weeks	self-comparison	1,2,3
Gheflati et al. [13]	2021	40	50,000 IU	8 weeks	yes	1,2,3,4,5
Hayder et al. [14]	2022	112	5000 IU/day	4 weeks	yes	1,2,3
Holt et al. [15]	2023	307	Initial 300,000 IU cholecalciferol, after 1400 IU/day	150 days	yes	4,5
Jansen et al. [16]	2018	269	Initial 300,000 IU of cholecalciferol, after 1400 UI/day	150 days	yes	1,2,3,6
Maghsoumi-Norouzabad et al. [17]	2021	86	4000 IU	3 months	yes	1,2,3,4,5,6
Padmapriya et al. [18]	2022	80	4000 UI	72 days	yes	2,3
Wadhwa et al. [19]	2019	60	Cholecalciferol 60,000 IU weekly	6 months	self-comparison	6
Zarepoor et al. [20]	2024	136	50,000 IU every 2 weeks	3 months	yes	1,2,4,6

*: 1—sperm concentration, 2—progressive motility, 3—semen volume, 4—total testosterone, 5—SHBG, 6—FSH.

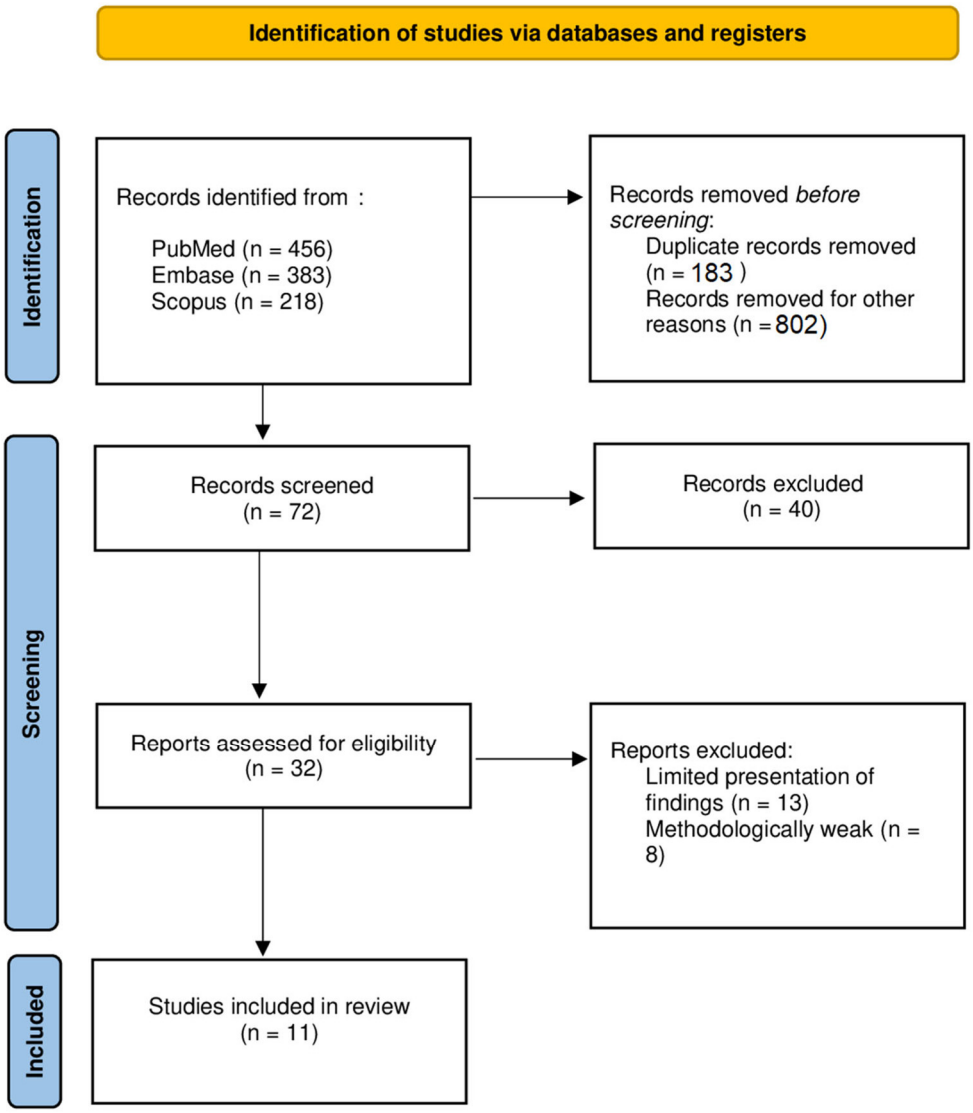


Figure 1. PRISMA flowchart of the included studies.

Sperm concentration was evaluated in 10 studies, including 1264 patients. Using a random-effects model, vitamin D treatment was positively associated with improved sperm concentration (SMD = 1.20; 95% CI: 0.48 to 1.92; $p < 0.001$).

The pooled analysis demonstrates a heterogeneous impact of vitamin D supplementation across different semen parameters. For sperm concentration, the combined estimate indicates a statistically significant improvement favoring the intervention group (SMD = 1.20; 95% CI: 0.48 to 1.92), although between-study heterogeneity was extremely high (I^2 = 99%), suggesting substantial variability in study populations, baseline deficiencies, and supplementation regimens. A similar pattern was observed for sperm motility, where vitamin D supplementation was associated with a significant increase (SMD = 3.51, 95% CI 2.81 to 4.21), again with considerable heterogeneity (I^2 = 99%), reinforcing concerns regarding consistency and external validity.

In contrast, semen volume did not differ significantly between groups (SMD = 0.05, 95% CI −0.03 to 0.12), with negligible heterogeneity (I^2 = 0%), indicating a consistent lack of effect across studies. This divergence suggests that vitamin D may selectively influence functional sperm parameters rather than seminal fluid production.

Overall, while the direction of effect for concentration and motility is favorable, the robustness of these findings is limited by substantial heterogeneity, whereas the null effect

on semen volume appears stable and reproducible across the included trials. Despite statistically significant pooled estimates for certain semen parameters, the extreme heterogeneity observed substantially limits the interpretability and generalizability of these findings. The magnitude of the pooled effects must therefore be considered in the context of underlying variability, which suggests that the observed improvements are not uniformly reproducible across clinical settings. The forest plot for sperm parameters is shown in Figure 2.

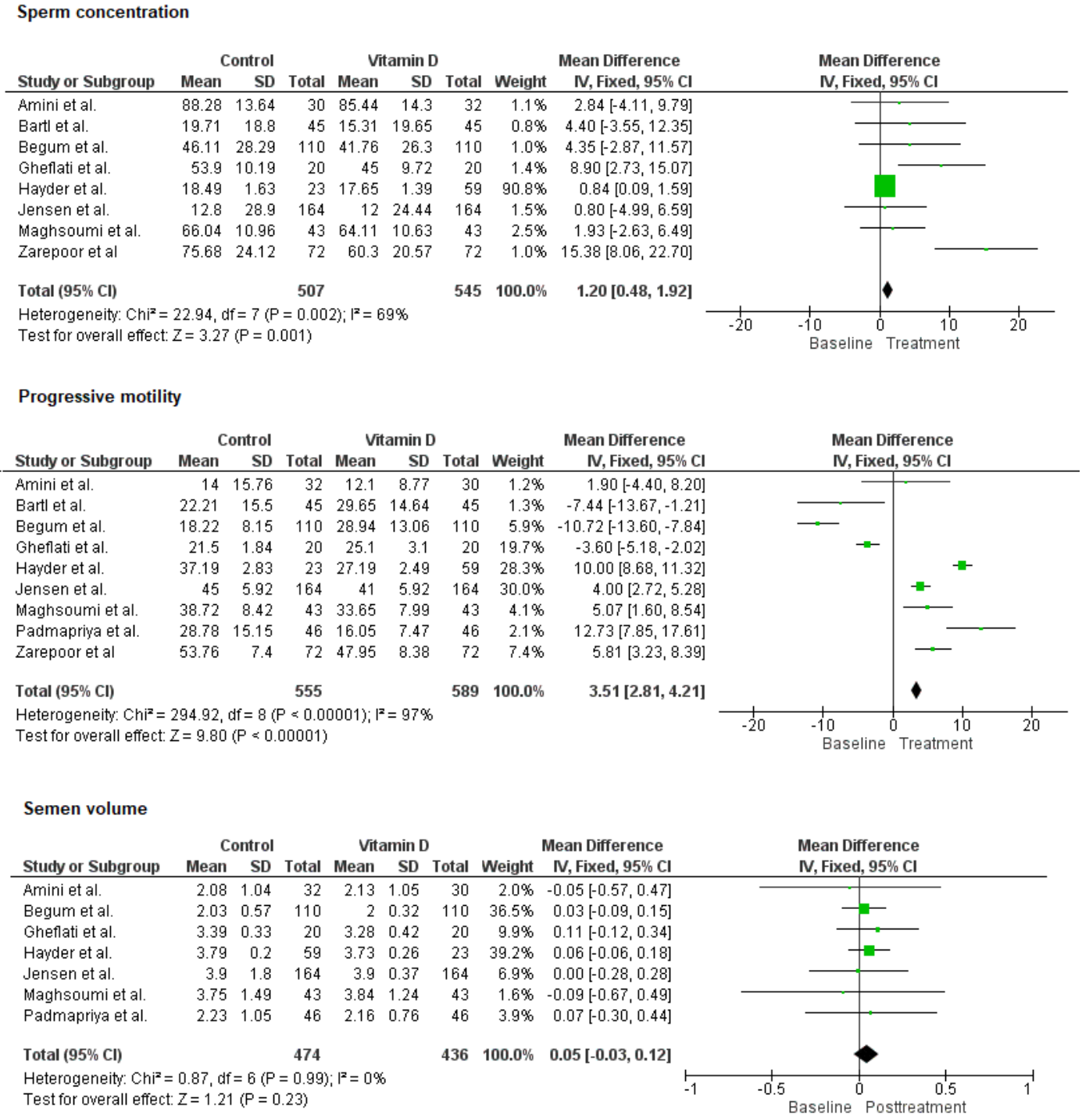


Figure 2. The forest plot for sperm parameters [10–14,16–18,20].

The analysis of FSH levels across six studies (n = 793) revealed no statistically significant difference between Vitamin D and control groups. The overall mean difference was a

negligible 0.01 units (95% CI: −0.28 to −0.29; $p = 0.96$), with remarkably low heterogeneity ($I^2 = 0\%$). Similarly, SHBG levels showed no significant overall change ($p = 0.08$). While the mean difference was 0.95 (95% CI: −0.12, 2.02), this result was influenced by high heterogeneity ($I^2 = 91\%$), largely driven by the Gheflati et al. study, which favored the control group significantly more than other included trials. In contrast, Vitamin D supplementation demonstrated a statistically significant increase in testosterone levels. Across six trials (n = 696), the pooled mean difference was 0.38 (95% CI: 0.13, 0.62; $p = 0.002$). This finding was robust, characterized by a complete absence of statistical heterogeneity ($I^2 = 0\%$), suggesting a consistent positive effect of Vitamin D on testosterone production across the varied study populations. Forest plots for hormonal parameters are shown in Figure 3.

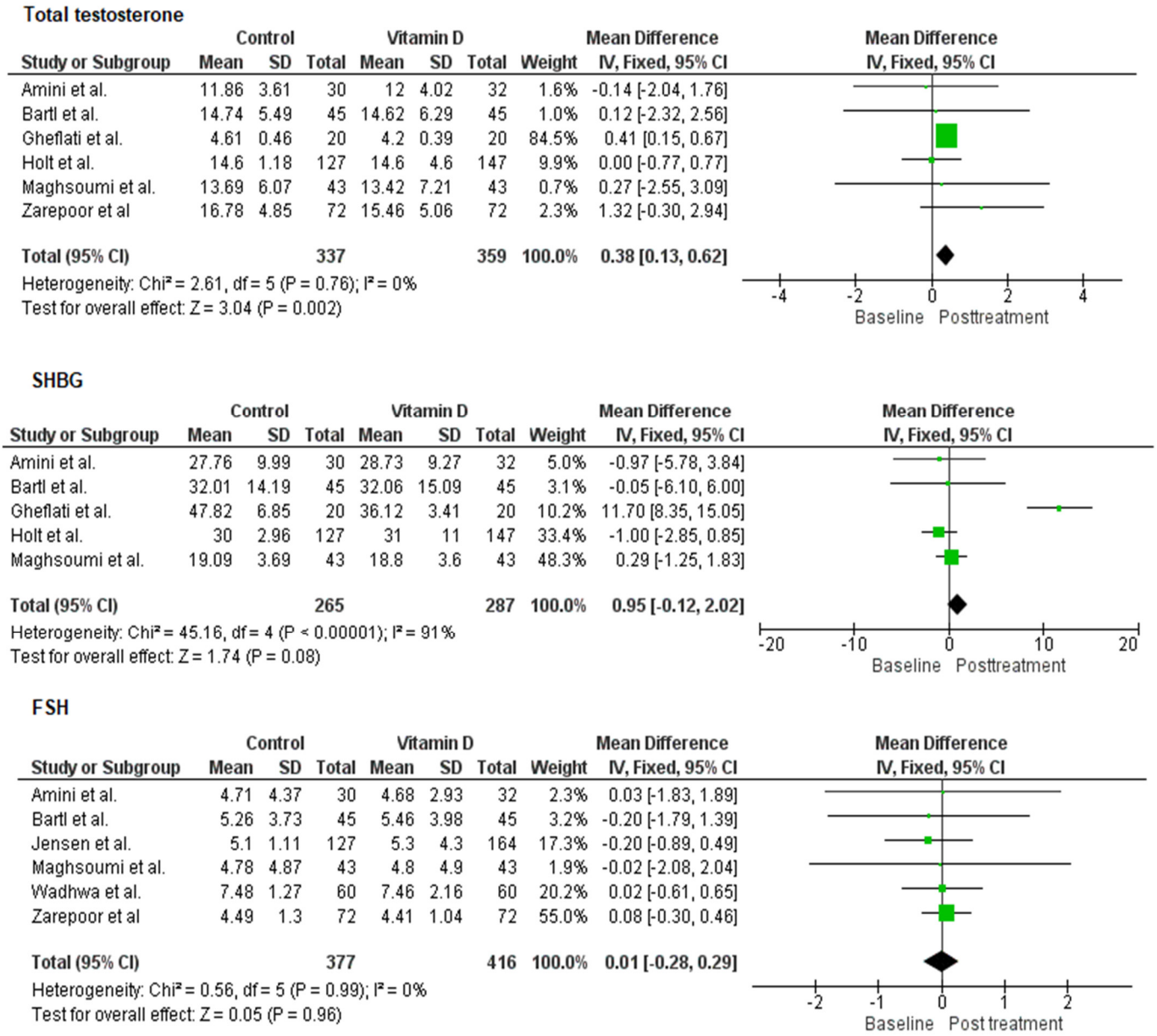


Figure 3. The forest plot for hormone parameters [10,11,13,15–17,19,20].

Figure 4 shows the ROB v2 risk-of-bias evaluation. Due to their minimal risk of bias across the five methodological evaluation areas, all RCTs were deemed suitable for inclusion in the meta-analysis. The studies by Padmapriya et al. [18] and Zarepoor et al. [20] are not randomized trials; for this reason, the risk of bias was assessed using ROBINS-I

instead of RoB 2. Detailed assessments of potential sources of bias for each included study are presented in Supplementary Table S1.

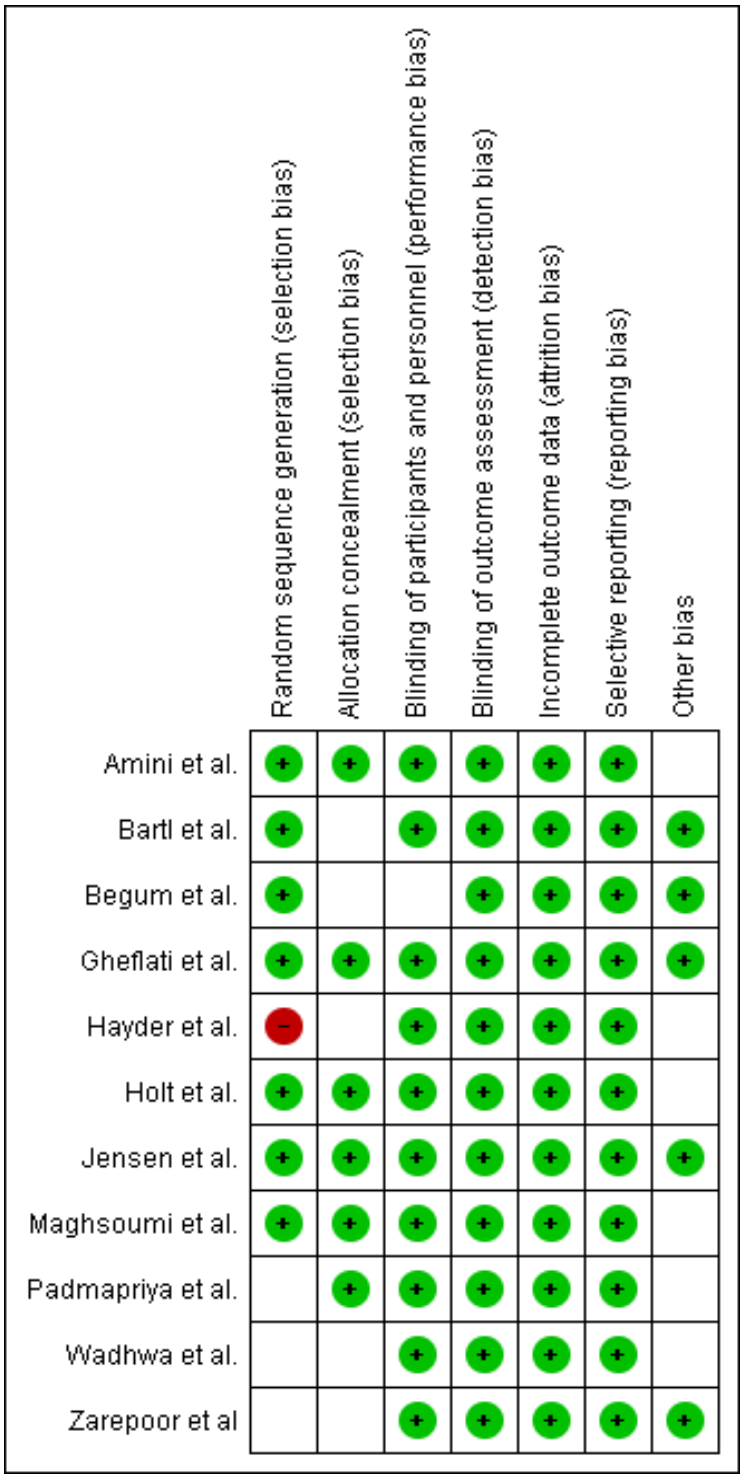


Figure 4. Risk of Bias for assessment of clinical trial studies [10–20].

4. Discussion

While previous meta-analyses have largely focused on determining whether vitamin D supplementation exerts a measurable effect on semen quality, the present findings suggest that the more relevant question may be under what biological conditions such effects emerge, if at all [21]. Evaluating nutritional strategies for improving reproductive health in men with idiopathic infertility inevitably brings attention to micronutrients and bioac-

tive compounds capable of modulating oxidative stress, hormonal balance, and gamete functionality. Among these, vitamin D has emerged as an intriguing candidate due to the presence of its receptor in multiple reproductive tissues, including Leydig cells, Sertoli cells, epididymis, the seminal vesicles, and even the spermatozoa head region itself [17]. Nutritional interventions carry the advantage of being non-invasive and relatively inexpensive compared to medical or surgical treatments. In contexts where oxidative damage has been proposed as a primary driver of functional sperm decline, dietary antioxidants, whether as isolated supplements or as part of multinutrient formulas, have demonstrated improvements in motility and DNA integrity [22,23].

The presence of vitamin D receptors and activating/inactivating enzymes in Sertoli cells, Leydig cells, and germ cells positions vitamin D as a candidate modulator at multiple checkpoints [24]. In Sertoli cells, which are pivotal for providing physical support and metabolic substrates to maturing germ cells, vitamin D receptor activation may regulate transcriptional networks necessary for sustenance of the seminiferous epithelium. Vitamin D has been implicated in fine-tuning this steroidogenic output. According to Cito et al., calcitriol's modulation of intracellular Ca^{2+} within Leydig cells might alter the activity of key enzymes such as 17β-hydroxysteroid dehydrogenase or aromatase [24]. Alterations here could shift local androgen-to-estrogen ratios, a balance that is important for optimal germ cell development. In rodent studies, hypovitaminosis D co-occurred with lower circulating testosterone levels alongside diminished spermatogenic efficiency; correcting calcium levels partially rescued testicular morphology and sperm counts even when systemic vitamin D remained low [25].

Clinical interventions provide mixed but suggestive evidence linking vitamin D supplementation with improvements in parameters related to spermatogenic output. Some trials have observed an increase in sperm concentration after repletion from deficiency states, whereas others report negligible effects on sperm count despite gains in motility [26,27]. This divergence could reflect differences in whether supplementation restored only systemic calcium–phosphate balance or also engaged sufficient local receptor-mediated actions within seminiferous tissue. Reports also suggest a U-shaped association, in which excessively high serum levels ($\geq$50 ng/mL) confer no additional benefit and may disrupt intracellular ionic equilibria necessary for orderly spermatogenesis [11].

Vitamin D's relationship with sperm motility appears to be one of its most reproducible associations across studies, even though some variability in findings remains. In observational human data, serum vitamin D concentration has been positively correlated with total and progressive motility across multiple cohorts [28]. This correlation tends to be most marked in men with lower baseline levels; supplementation from deficiency states often produces detectable improvements in motility percentages. Randomised controlled trials focusing on idiopathic infertility have confirmed this trend: pooled analyses show that vitamin D repletion yields gains in progressive motility even when total sperm count or semen volume remain unchanged [8]. Morphological outcomes are less consistent across the literature. Some datasets report notable increases in the proportion of morphologically normal sperm following supplementation, while others report negligible change [28,29]. In interventional designs in which morphological improvement is observed, mechanisms may include vitamin D's role in regulating cellular lipid composition, thereby affecting membrane architecture and mitigating oxidative damage during spermiogenesis. Oxidative stress can alter head shape through impaired chromatin condensation and damage tail structure integrity; antioxidant benefits attributed to vitamin D could thus protect against such defects indirectly by maintaining ROS at physiological levels conducive to maturation [8].

Vitamin D may influence male reproductive hormones through direct activation of vitamin D receptors in Leydig and Sertoli cells and indirect modulation of the hypothalamic–pituitary–gonadal axis [30]. Although observational studies report inconsistent associations between vitamin D status and testosterone levels, our findings support a modest but consistent increase in testosterone following supplementation. Vitamin D may also influence androgen bioavailability by reducing SHBG levels, thereby increasing free testosterone [31]. In contrast, FSH appears largely unaffected by vitamin D supplementation, despite experimental evidence suggesting indirect effects on Sertoli cell function [29,30]. The dissociation between the consistent hormonal response and the highly variable effects on semen parameters suggests that vitamin D may act more reliably on steroidogenesis than on spermatogenesis, and that improvements in endocrine function do not necessarily translate into clinically meaningful gains in sperm production.

Controversy persists regarding LH modulation. Some reports note an inverse relationship between serum LH and vitamin D levels, possibly reflecting heightened Leydig cell efficiency, thereby reducing the required LH drive; others find no significant link or even suggest positive correlations, depending on whether baseline deficiency is present [29,31,32]. Supra-physiological vitamin D levels might disrupt homeostatic feedback loops by altering ionic equilibrium in pituitary or hypothalamic cells that express VDR and CYP27B1, leading to unpredictable shifts in gonadotropin output. Estradiol's role further complicates androgen-focused interpretations. In men, intratesticular estradiol is produced primarily by aromatization of testosterone in Leydig cells; under certain conditions, Sertoli and germ cells also contribute [30]. According to de Angelis et al., Vitamin D exerts non-genomic effects through VDR-dependent modulation of numerous intracellular signaling pathways, likely mediated by a putative membrane-associated VDR. These rapid actions are thought to ultimately activate the MAPK–ERK 1/2 cascade, which involves several intermediary molecules that respond when vitamin D binds to VDR [33]. Upon activation, VDR promotes calcium influx, which then triggers calcium-dependent signaling routes such as protein kinase C (PKC). In addition, vitamin D may stimulate G-protein-coupled receptors (GPCRs), leading to activation of downstream pathways including PI3K, adenylate cyclase, Ras, and PLCγ. These signaling networks can converge to activate ERK–MAPK 1/2, which may interact with the classical genomic VDR pathway to influence gene expression, as shown in Figure 5.

Follicle-stimulating hormone (FSH) levels remained largely unchanged following vitamin D supplementation, with consistently negligible effect sizes and minimal heterogeneity across studies. This stability suggests that vitamin D does not exert a meaningful influence on the hypothalamic–pituitary–gonadal axis at the level of pituitary gonadotropin secretion [33,34]. This could influence the management of males with azoospermia [35]. Given that FSH primarily reflects Sertoli cell stimulation and spermatogenic drive, the absence of change further supports the notion that vitamin D's effects are more prominent in steroidogenesis than in upstream regulatory pathways. These findings also reinforce the dissociation between endocrine modulation and spermatogenic outcomes observed in this analysis. Consequently, FSH does not appear to be a sensitive biomarker for monitoring the reproductive effects of vitamin D supplementation in infertile men.

RCTs investigating the effect of vitamin D supplementation on male infertility provide a structured approach to determining causal relationships between intervention and reproductive outcomes. Designs often vary in inclusion criteria, dosing strategies, and measured endpoints, which can influence comparability. In several studies, male subjects with idiopathic infertility and documented vitamin D insufficiency or deficiency were recruited, sometimes accompanied by matching fertile controls for baseline comparisons [31]. Pooled analyses from this and other RCTs have shown more consistent gains in motility measures

compared to other sperm metrics. A systematic review and meta-analysis of five RCTs reported improvements in total and progressive sperm motility following supplementation, along with increased rates of normal morphology [8]. However, there was no statistically robust evidence for changes in total sperm count, concentration, or semen volume. Such a dissociation between functional enhancement and quantitative output suggests that vitamin D may act predominantly through mechanisms that influence mitochondrial efficiency, calcium homeostasis, and membrane fluidity rather than directly boosting spermatogenic throughput [12].

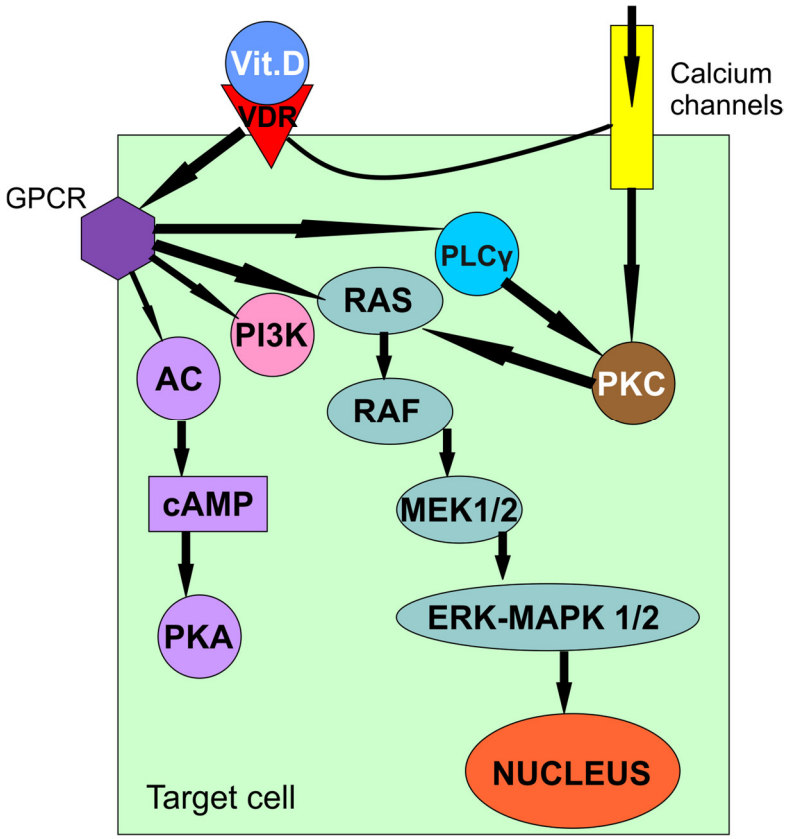


Figure 5. Non-genomic actions at the cellular level of vitamin D.

Vitamin D dosing regimen may influence treatment response through differences in pharmacokinetics and serum 25(OH)D stability. Daily supplementation maintains more consistent vitamin D concentrations and may provide sustained activation of reproductive tissues, whereas intermittent high-dose regimens can produce transient serum peaks with uncertain physiological effects [16,36]. Some evidence suggests that excessively high vitamin D levels may adversely affect sperm motility, supporting a possible U-shaped relationship between vitamin D status and reproductive outcomes [11,28]. Clinical studies further indicate that improvements in progressive motility are more likely after daily supplementation maintained for at least one spermatogenic cycle, although evidence remains limited and inconsistent [12,17].

From a clinical perspective, these findings support a more individualized approach to vitamin D supplementation in male infertility. Rather than applying a uniform treatment strategy, assessment of baseline vitamin D status and endocrine profile may help identify patients more likely to benefit. Furthermore, the variability in dosing regimens across studies underscores the need for standardized protocols that consider both pharmacokinetics and tissue-specific activation of vitamin D metabolites. Recent meta-analyses have reported

modest improvements in semen parameters; however, these analyses did not fully address the biological heterogeneity underlying these findings [21].

Despite growing evidence linking vitamin D to male reproductive function, important knowledge gaps remain. Most randomized controlled trials are underpowered and rely on surrogate laboratory outcomes rather than clinically meaningful endpoints such as pregnancy or live birth rates, limiting the translation of observed improvements in semen parameters into fertility outcomes [30,37]. Furthermore, substantial heterogeneity arises from inadequate participant stratification, as most studies include men with idiopathic infertility without considering baseline vitamin D status, oxidative stress, or specific semen abnormalities. Future studies should prioritize well-defined subgroups, particularly men with severe vitamin D deficiency, to better identify those most likely to benefit from supplementation. Another limitation is the frequent use of multinutrient formulations containing vitamin D alongside zinc, selenium, carnitines, antioxidants, and omega-3 fatty acids, making it difficult to isolate the independent effect of vitamin D supplementation [35,38].

Although several pooled estimates reached statistical significance, the magnitude of these changes should be interpreted cautiously. Most included trials were not powered to detect clinically meaningful reproductive outcomes such as spontaneous pregnancy, live birth, or assisted reproductive technology success. Consequently, improvements in surrogate semen parameters cannot currently be assumed to translate into enhanced fertility, emphasizing the need for larger adequately powered randomized trials.

This study has several limitations that warrant consideration. As with all meta-analyses, aggregating data from heterogeneous populations introduces the risk of masking subgroup-specific effects. Variability in study design, inclusion criteria, and outcome reporting further complicates direct comparisons. Additionally, the relatively small number of high-quality randomized controlled trials limits the precision of pooled estimates for certain outcomes. Despite these constraints, the consistency observed in hormonal responses and the systematic evaluation of heterogeneity strengthen the interpretability of the findings.

5. Conclusions

The present analysis indicates that vitamin D supplementation does not have uniform effects across reproductive domains in infertile men. While increases in circulating testosterone appear consistent and biologically plausible, improvements in semen parameters are highly variable and lack robustness because of substantial between-study heterogeneity. This dissociation suggests that vitamin D may preferentially modulate endocrine function rather than directly enhance spermatogenesis.

Importantly, the magnitude of observed changes in semen quality—when present—must be interpreted cautiously, as statistical significance does not necessarily translate into clinically meaningful improvements in fertility outcomes. The absence of consistent effects on parameters such as semen volume and follicle-stimulating hormone further supports a selective, context-dependent mechanism of action.

Taken together, the current evidence does not justify routine vitamin D supplementation as a generalized therapeutic strategy for male infertility. Instead, potential benefits are more likely confined to specific subgroups, particularly individuals with underlying deficiencies or altered hormonal profiles. Future research should prioritize stratified trial designs, standardized outcome reporting, and mechanistic endpoints to clarify which patients, if any, derive meaningful reproductive benefit from supplementation.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/endocrines7030051/s1. Table S1: Detailed Risk of Bias Assessment (Cochrane RoB 2). Each study was evaluated using the Cochrane ROB v2, rating each domain as low risk, high risk, or some concerns/unclear risk.

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Abbreviations

The following abbreviations are used in this manuscript:

FSH	Follicle-Stimulating Hormone
LH	Luteinizing Hormone
SHBG	Sex Hormone-Binding Globulin
VDR	Vitamin D Receptor
RCT	Randomized Controlled Trial
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PICO	Population, Intervention, Comparison, Outcome
WHO	World Health Organization
SMD	Standardized Mean Difference
CI	Confidence Interval
I^2	I-squared statistic (measure of heterogeneity)
RoB 2	Risk of Bias 2 Tool
RevMan	Review Manager
PROSPERO	International Prospective Register of Systematic Reviews
GnRH	Gonadotropin-Releasing Hormone
ROS	Reactive Oxygen Species
ATP	Adenosine Triphosphate
Ca^{2+}	Calcium Ion
25(OH)D	25-Hydroxyvitamin D
CYP27B1	25-Hydroxyvitamin D-1α-hydroxylase

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