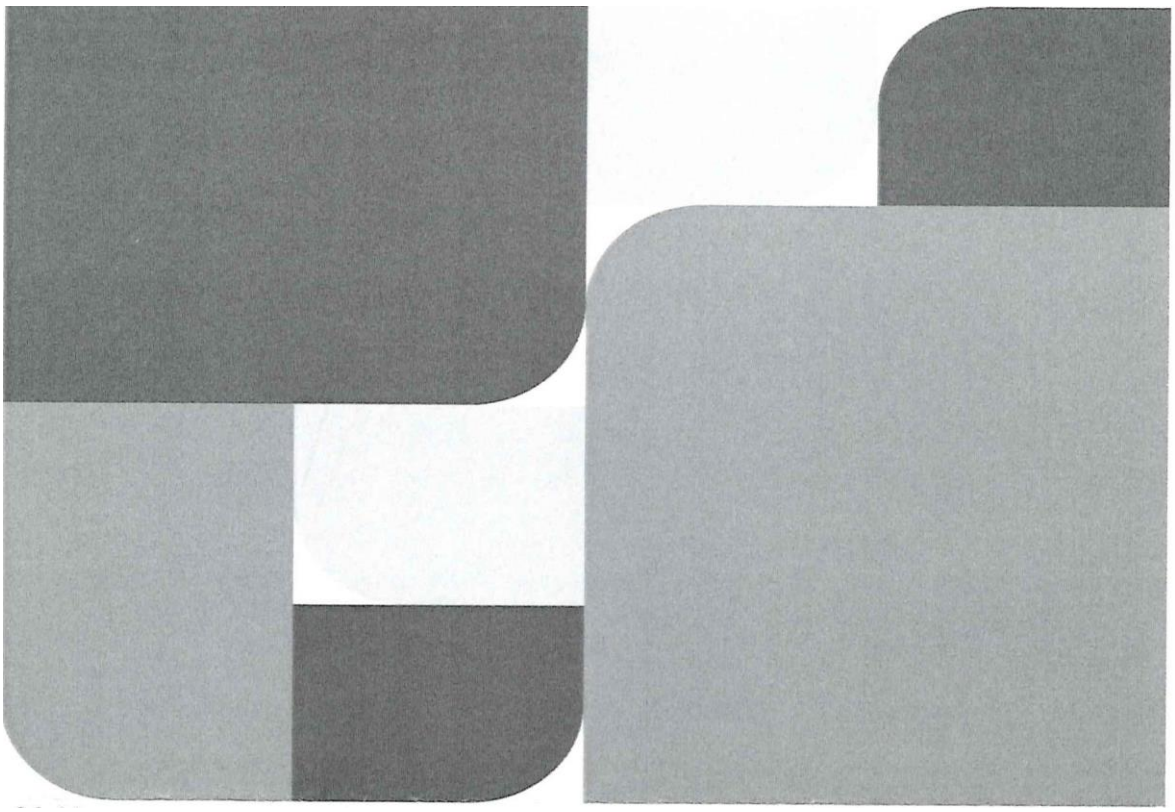

2024-06-09

Vitamin D : A natural boost for testosterone? A scoping Review.

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Rapport: **282798**
Literature study 2024

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Utförd under ST i allmänmedicin, Göteborg
inom kurs MFM340 Forskningsmetodik för hälso och sjukvårdsanställda, 10.5 hp

Kursort: Göteborg

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Abstract

Background : Vitamin D deficiency has been identified by the Global Health Organization as a widespread issue affecting various aspects of human health, including hormonal balance. Recent studies have suggested a potential link between vitamin D levels and testosterone production in adult men, which could have significant implications for men's health worldwide. Despite the growing body of research, there remains a need for comprehensive reviews of the literature to understand the implications of this association.

Objective : This scoping review aims to examine the existing research on the effect of vitamin D supplementation on testosterone levels in adult men.

Method : The review was conducted as a scoping study, mapping out existing research in the area of vitamin D supplementation and testosterone levels in adult men. Literature searches were conducted across 2 databases, with articles selected based on predetermined criteria to identify relevant studies for inclusion.

Results : A total of 12 studies were included, comprising both quantitative and qualitative research. The majority of the studies focused on the direct effects of vitamin D supplementation on serum testosterone levels. Findings suggest that vitamin D supplementation may have a positive effect on testosterone levels, particularly in populations with low baseline vitamin D status. However, the extent of the effect varies across studies, with some populations showing more pronounced benefits.

Conclusion : Providing men, especially those with identified vitamin D deficiencies, with vitamin D supplements could potentially contribute to normalized testosterone levels, thereby improving overall men's health and well-being. However, longitudinal studies examining the long-term effects of vitamin D supplementation on testosterone levels are lacking and needed for future research to establish definitive recommendations

Keywords: Vitamin D , Testosterone, Adult Men, Hormonal Balance, Vitamin D Supplementation, Men's Health, Sex steroid hormone, Androgen, 1,25 dihydroxy 21 3 hydroxy 3 methylbutyl 3.

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Background

In recent years, the role of vitamin D in human health has expanded far beyond its traditional association with bone integrity. Known also as the "sunshine vitamin" due to its natural synthesis through skin exposure to sunlight, vitamin D has now been implicated in a range of physiological and metabolic functions. Its interaction with hormonal pathways, specifically testosterone synthesis in adult men, has emerged as a particularly promising area of research. This scoping review examines studies on the relationship between vitamin D and testosterone, a hormone fundamental to male health, and how this connection may influence broader health outcomes. Vitamin D deficiency, increasingly prevalent due to contemporary indoor lifestyles and rigorous sunscreen use, poses significant health risks that extend beyond osteoporosis to include cardiovascular disease, diabetes, and hormonal imbalances (1). Reviewing the latest research allows the examination of the potential of vitamin D to regulate testosterone levels, thereby presenting insights into natural interventions that could replace or supplement traditional hormone therapies. In doing so, it aims to illuminate pathways through which vitamin D supplementation could significantly enhance men’s health and overall well-being, marking an important step in addressing the global epidemic of vitamin D deficiency and its multifaceted impact on human health (2). Vitamin D deficiency affects about 1 billion people globally, with prevalence rates ranging from 24% to 49% depending on the region, and particularly high rates among the elderly and certain ethnic groups in the Americas and Europe (1). Factors contributing to this widespread deficiency include limited sun exposure, dietary insufficiency, and certain health conditions.

The Sunshine Hormone Connection

The interplay between vitamin D, often celebrated for its crucial role in bone health, and broader physiological functions has garnered significant scholarly attention. Emerging research shows that vitamin D's influence on hormonal regulation, notably testosterone levels in adult men, is a

field of inquiry (3). Testosterone orchestrates a host of vital functions, including muscle mass maintenance, bone density, and sexual health. The intrigue surrounding vitamin D's potential to modulate testosterone production has opened a new avenue for exploring its comprehensive health impacts (4).

Lifestyle Changes and Vitamin D Deficiency

Dubbed the "sunshine vitamin" for its synthesis in human skin upon sun exposure, vitamin D's deficiency has become a widespread concern. This deficiency, fueled by modern indoor living and sunscreen use, transcends the issue of bone health, linking to various chronic conditions such as cardiovascular disease, diabetes, and hormonal imbalances (5). The modern lifestyle, characterized by limited sunlight exposure, has thus precipitated a vitamin D deficiency crisis across demographics, emphasizing the need for a closer examination of its systemic effects (3).

Vitamin D and Testosterone Synthesis

The production of testosterone, a hormone pivotal for male health, is governed by the intricate hypothalamic-pituitary-gonadal axis. This process is susceptible to numerous factors, including micronutrient levels (7). Preliminary findings suggest vitamin D's role in the hormonal process, specifically in testosterone regulation (8). This potential relationship between vitamin D and testosterone offers a glimpse into natural intervention methods that could circumvent the need for synthetic hormone therapies, marking a significant shift in addressing hypogonadism and associated conditions (9).

Implications for Men's Health

With vitamin D deficiency a global epidemic and its implications extending far beyond skeletal health, the exploration of its relationship with testosterone levels becomes critically important (10). This scoping review aims to identify studies and seek research gaps when it comes to men’s health (11).

Objective

This scoping review aims to examine the research on the effect of vitamin D supplementation on testosterone levels in adult men.

Method

Study design

The investigation was carried out through a mapping literature review, also known as a scoping review in English terminology, following the methodology outlined by Arksey and O'Malley (6). This type of review is designed to offer a comprehensive overview of existing research within a specific area and to pinpoint areas where knowledge is lacking. It does not, however, include a quality assessment of the studies reviewed.

Selection

Studies were eligible for inclusion if they were original studies conducted with adult healthy male population while analyzing a) the relationship between testosterone and vitamin D or b) supplementation of vitamin D and testosterone levels and c) published between year 2019-2024 and d) studies written in english.

Studies were excluded if they a) were conducted with an unhealthy male population, ie, if the men had an ongoing medical illness b) studies conducted on females

Data collection and analysis

To identify relevant articles, searches were made in two databases; PubMed and Embase. The search strings were designed along with a medical librarian at Gothenburg University Library. In the searches were combined four different search blocks of terms that included synonyms for: a) testosterone,sexhormone, androgen, male reproductive hormones; b) vitamin D, 25-hydroxy-vitamin D ; c) supplementation d) adult healthy males, healthy men, healthy young men, men d) year 2019-2024

The final search was carried out in April 2024 and the search results were analyzed systematically based on pre-established inclusion and exclusion criteria.

Ethical considerations

Since this study solely relies on previously conducted research and literature, ethical review was deemed unnecessary. Additionally, all studies incorporated in this analysis explicitly stated that they had obtained ethical approval before initiating their respective studies.

Results of literature search

The research began with a comprehensive initial retrieval of articles, totaling 240. From these, duplicates were meticulously removed, leading to a revised total of 81 unique articles. These were then subject to a thorough screening process where titles and abstracts were evaluated based on the specific inclusion criteria, which narrowed the field down to 26 articles deemed potentially relevant.

Following a more detailed assessment, which included full-text reviews for eligibility, 14 articles were excluded due to reasons that did not meet the exact criteria one had set out, such as unhealthy population or men with other diseases, studies that involved other medications in combination with vitamin D, studies conducted on females and studies not written in the english language.

Ultimately, this process of selection and elimination refined the search down to 12 articles that were precisely aligned with the research objectives and met all specified criteria, thus forming the core group of sources for this scoping review.These search results are represented in figure 1 below :

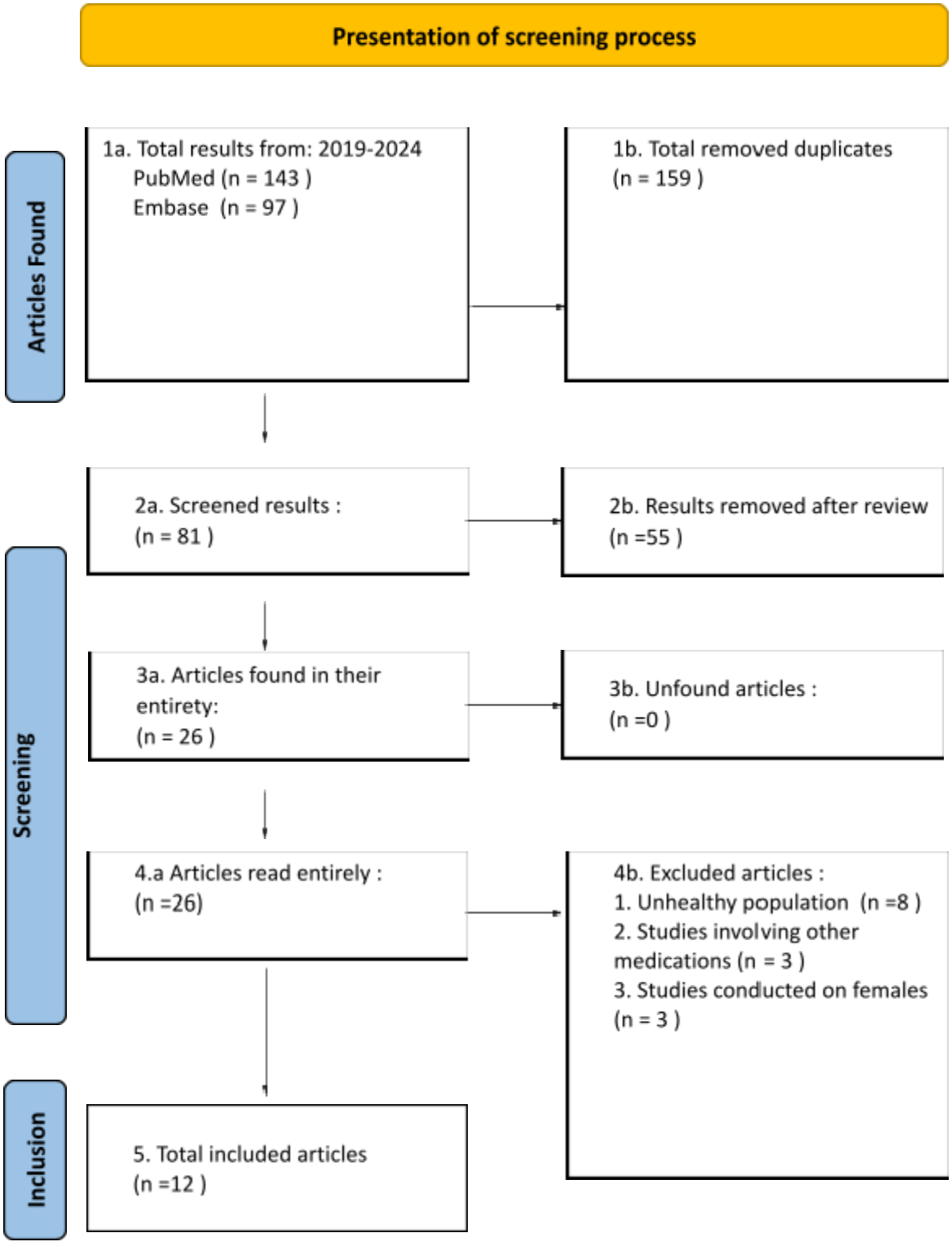

Figure 1 : Presentation of screening process

Table 1 : Summary of included articles

Authors	Study Design	Purpose	Population	Results
Yeo JK, Park SG, Park MG. Effects of Vitamin D Supplementation on Testosterone Prostate and Lower Urinary Tract Symptoms: A Prospective Comparative Study (4)	Prospective, Comparative Study	Investigate the effect of vitamin D supplementation on testosterone, prostate, and lower urinary tract symptoms in men.	57 men over 40 with vitamin D deficiency	Significant increase in vitamin D levels, decrease in postvoid residual urine volume, no significant change in prostate volume, improved hypogonadal symptoms.
Buenaluz-Sedurante M, Bruno R, Dagang DJ, Co MI, Tee M. Association Between 25-hydroxyvitamin D Levels and Testosterone in Healthy Non-Obese Young Adult Filipino Men (5)	Cross-sectional Study	Determine the association between vitamin D and testosterone in healthy adult males.	110 healthy, non-obese, young adult Filipino men	No significant differences in testosterone or SHBG levels across different vitamin D statuses.
Książek A, Mędraś M, Zagrodna A, Słowińska-Lisowska M, Lwow F. Correlative studies on vitamin D and total free bioavailable testosterone levels in young healthy men (3)	Observational Study	Explore the correlation between serum vitamin D levels and testosterone.	176 middle-aged men	Significant correlation found between higher vitamin D levels and increased testosterone levels.
D'Andrea S, Martorella A, Coccia F, Castellini C, Minaldi E, Totaro M, Parisi A, Francavilla F, Francavilla	Systematic Review and Meta-analysis	Summarize existing research on the relationship between vitamin D and	Studies involving 982 adult men	Mixed results; more robust association in studies with longer duration of vitamin D supplementation.

S, Barbonetti A. Relationship of Vitamin D status with testosterone levels: a systematic review and meta-analysis (7)		testosterone levels in men.		
Ciccone IM, Costa EMF, Pariz JR, Teixeira TA, Drevet JR, Gharagozloo P, Aitken RJ, Hallak J. Serum vitamin D content is associated with semen parameters and serum testosterone levels in men (8)	Cross-sectional Study	Investigate the impact of vitamin D on semen quality and testosterone levels in men.	508 men undergoing fertility evaluation	Positive association between vitamin D levels and improved semen quality and testosterone levels.
Santos HO, Howell RS, Nichols K, Teixeira FJ. Reviewing the Evidence on Vitamin D Supplementation in the Management of Testosterone Status and Its Effects on Male Reproductive System (Testis and Prostate): Mechanistically Dazzling but Clinically Disappointing (9)	Observational Study	Assess the effectiveness of vitamin D supplementation on testosterone levels and male reproductive health.	Various studies on 79 men and reproductive health	Findings highlight mechanistic potentials but clinical outcomes are inconsistent and often disappointing.
Lerchbaum E, Trummer C, Theiler-Schwetz V, Kollmann M, Wölfler M, Heijboer AC, Pilz S,	Randomized Controlled Trial	Evaluate the effect of vitamin D supplementation on androgen levels in	200 men with low testosterone levels	Significant improvement in testosterone levels following vitamin D supplementation.

Obermayer-Pietsch B. Effects of vitamin D supplementation on androgens in men with low testosterone levels: a randomized controlled trial (10)		men with low testosterone.		
Hosseini Marnani E, Mollahosseini M, Gheflati A, Ghadiri-Anari A, Nadjarzadeh A. The effect of vitamin D supplementation on the androgenic profile in men: A systematic review and meta-analysis of clinical trials (11)	Systematic Review and Meta-analysis	Review the effects of vitamin D supplementation on androgen levels across clinical trials.	138 men participating in clinical trials	Overall positive impact of vitamin D supplementation on androgen levels in men.
Chen C, Zhai H, Cheng J, Weng P, Chen Y, Li Q, Wang C, Xia F, Wang N, Lu Y. Causal Link Between Vitamin D and Total Testosterone in Men: A Mendelian Randomization Analysis (12)	Mendelian Randomization Analysis	Explore the causal relationship between vitamin D levels and testosterone in men.	Genetic data from 79 men	Suggests a potential causal relationship where higher vitamin D levels may lead to increased testosterone levels.
Bembey S, Verma R, Belho E, Mahajan H. To assess the levels of Vitamin D in males with low testosterone levels (total & free) (13)	Observational Study	Measure and evaluate vitamin D levels in men with low testosterone.	64 men with low testosterone levels	Lower vitamin D levels correlated with lower testosterone levels.

Hammoud AO, Meikle AW, Peterson CM, Stanford J, Gibson M, Carrell DT. Association of 25-hydroxy-vitamin D levels with semen and hormonal parameters (14)	Observational Study	Examine the relationship between vitamin D levels, semen quality, and hormonal parameters.	44 men undergoing fertility assessment	Positive association between higher vitamin D levels, better semen quality, and hormonal parameters.
Rives N, Secco M, Bailly M, Mitchell V, Papaxanthos A, Sibert L, Albert M, Rigot JM, Marcelli F, Clavier B, Selva J, Decanter CH, Macé B. Association of 25-Hydroxy-Vitamin D levels with male reproductive hormones and semen parameters (15)	Observational Study	Investigate the influence of vitamin D on male reproductive hormones and semen quality.	102 men at a reproductive clinic	Found significant correlations between vitamin D levels and several reproductive hormones and semen parameters.

Results

The research studied in this scoping review indicates a potentially beneficial effect of vitamin D supplementation on testosterone levels in men. Key findings across various studies highlight that men with lower testosterone levels may experience an increase following vitamin D supplementation. This effect is particularly significant in men with initial deficiencies or specific genetic backgrounds(8, 13, 14).

Vitamin D Supplementation and Testosterone Enhancement

A significant thread throughout several research articles is the potentially beneficial effect of vitamin D supplementation on testosterone levels in men. Numerous studies have demonstrated that men experiencing lower testosterone levels may see an increase following the administration of vitamin D supplements. For example, one comprehensive study noted marked improvements in testosterone after a regimen of vitamin D supplements among men with initially low hormone levels, highlighting the direct impact of this vitamin on sexual health and endocrine function (8). Similarly, another investigation revealed that while the general male population benefits from vitamin D, the most significant enhancements in testosterone profiles were observed in men with specific characteristics, such as those with severe deficiencies or genetic backgrounds, underlining the nuanced nature of vitamin D's effects (7).

Research also shows that lower vitamin D levels are correlated with lower testosterone levels in men with hypogonadism, suggesting that supplementation could be particularly beneficial for these individuals (13). Additionally, studies on men undergoing fertility evaluation and assessment have found positive associations between higher vitamin D levels, improved semen quality, and better hormonal parameters, reinforcing the potential reproductive benefits of adequate vitamin D (14, 15).

Contrasting Findings and Methodological Differences

Despite the supportive findings, the literature is not unanimous regarding the impact of vitamin D on testosterone levels. Several studies illustrate that while a correlation exists between vitamin D and testosterone, the strength and significance of this relationship can vary dramatically. One study, for example, showed a correlation between vitamin D levels and semen quality, including

testosterone concentration, yet these effects varied significantly in magnitude, suggesting the modulation by variables like baseline vitamin D status or genetic factors (3). Contrarily, another piece of research failed to find substantial changes in bioavailable testosterone despite increases in vitamin D levels, pointing towards the critical role of population characteristics and supplementation protocol in determining outcomes (3).

Systematic Reviews and Meta-Analyses

Systematic reviews and meta-analyses offer a comprehensive view by integrating findings from multiple individual studies, thereby providing a more balanced perspective. One meta-analysis combined data from several studies and identified a slight, yet statistically significant, positive correlation between vitamin D and testosterone levels. However, it also acknowledged substantial heterogeneity among the studies, which suggests that outcomes might be influenced significantly by individual differences in study population or experimental design (9). On the other hand, a different systematic review noted the inconsistent and often conflicting evidence across studies, leading to conclusions that, while theoretically promising, were clinically disappointing due to the variability and potential biases in the published data (3).

Mendelian Randomization and Causal Inferences

Further enriching the discourse, some studies have employed Mendelian randomization to explore the relationship between vitamin D and testosterone. This approach uses genetic variants as tools to estimate the causal effect of a modifiable exposure (in this case, vitamin D) on an outcome (testosterone levels) while minimizing confounding. One pivotal study using this technique suggested a causal link between higher vitamin D levels and increased testosterone, lending robust support to the observational data that suggest supplementation could be beneficial (13).

Genetic Factors in Vitamin D and Testosterone Interaction

The interaction between vitamin D and testosterone is not only influenced by external factors such as diet and sunlight exposure but also by genetic predispositions that affect how individuals metabolize and respond to vitamin D. Several articles delve into the genetic underpinnings that explain the variability in how vitamin D impacts testosterone levels. Particularly, studies using Mendelian randomization have been pivotal, as this method leverages genetic variants as instrumental variables to estimate the causal effects of exposures (like vitamin D levels) on outcomes (such as testosterone levels). This approach helps to circumvent the confounding factors often encountered in observational studies, providing a clearer view of the causal relationships. For instance, one study highlighted in the references used Mendelian randomization to demonstrate a genetic link between vitamin D levels and testosterone, suggesting that certain genetic profiles might enhance or diminish the efficacy of vitamin D in regulating testosterone levels (10).

Clinical Trials of Vitamin D Supplementation

The role of vitamin D supplementation in affecting testosterone levels has been extensively explored through various randomized controlled trials, which have targeted diverse demographic groups to understand the broader applicability and effectiveness of vitamin D as a therapeutic option. These trials have often produced mixed results, with some studies indicating significant benefits of vitamin D supplementation on testosterone levels, particularly in populations with initial deficiencies or specific health conditions. In contrast, other trials have found minimal or no effect, which may be attributed to differences in study design, supplementation dosages, duration of intervention, or baseline vitamin D status of participants. For example, a study examined the impact of vitamin D supplementation in a randomized cohort and found that while some subgroups experienced marked improvements in testosterone levels, the overall effect across all participants was less pronounced (8). These varying outcomes highlight the complex nature of nutrient supplementation and its physiological impacts, underscoring the need for tailored approaches in nutritional therapy. Understanding these dynamics is crucial for clinicians and researchers as they aim to optimize treatment protocols and recommend dietary supplements

based on individual needs and biological contexts, moving towards a more personalized and effective healthcare paradigm.

Discussion

The relationship between vitamin D supplementation and various physiological parameters such as testosterone levels, prostate health, and lower urinary tract symptoms (LUTS) has been a focal point of clinical research due to the widespread prevalence of vitamin D deficiency and its potential implications on testosterone levels. The primary objective of this scoping review is to examine and map the existing research on the impact of vitamin D supplementation on testosterone levels in healthy adult men.

It was found that vitamin D supplementation over a period of one year led to significant improvements in LUTS and stabilized prostate volumes. These findings are supported by the literature that suggests vitamin D's role in the modulation of prostate cell proliferation and apoptosis through the vitamin D receptor (VDR) pathway (15). Yeo et al. similarly reported that vitamin D supplementation could suppress prostate volume increase, which is critical in managing conditions like benign prostatic hyperplasia (BPH) (4).

Contrarily, while some improvements in hypogonadal symptoms were noted, changes in serum testosterone levels were not statistically significant. This is consistent with findings by Lerchbaum et al., who noted that vitamin D supplementation did not significantly alter androgen levels in men with initially low testosterone (10). However, a meta-analysis by D'Andrea et al. suggested a potential positive association between vitamin D levels and testosterone, indicating that the effect might vary based on individual metabolic conditions or baseline vitamin D status (7).

Moreover, the literature presents a mixed perspective on the influence of vitamin D on testosterone. Marnani et al. reviewed several clinical trials and found that while some showed positive effects, the overall impact of vitamin D on the androgenic profile was inconclusive. This was echoed by Hammoud et al., who found no significant correlation between 25-hydroxy-vitamin D levels and male reproductive hormones across different studies (11)(14). Similar results were also portrayed by Nimptsch K in a study done in 2012 that higher levels of Vitamin D are positively associated with both total and free testosterone levels, with the association being linear at lower levels of Vitamin D and reaching a plateau at higher levels and no seasonal variation in testosterone levels was observed, unlike Vitamin D, which varied seasonally (16).

It is crucial to consider the biological plausibility of vitamin D influencing testosterone synthesis. Vitamin D has been implicated in the regulation of calcium homeostasis, which plays a pivotal role in various cellular processes including hormone secretion and receptor signaling. Ciccone et al. identified a potential link between serum vitamin D content and semen parameters, as well as serum testosterone levels, suggesting that vitamin D may affect Leydig cell function and thus androgen synthesis (8).

Studies have also found that lower vitamin D levels correlate with lower testosterone levels in men with hypogonadism, suggesting that vitamin D supplementation could be particularly beneficial for these individuals (13). Additionally, research on men undergoing fertility evaluations has found positive associations between higher vitamin D levels, improved semen quality, and better hormonal parameters, reinforcing the potential reproductive benefits of adequate vitamin D (14, 15).

Despite the potential mechanisms through which vitamin D may influence prostate health and testosterone levels, this study, along with reviews by Santos et al. has highlighted the clinical challenges and inconsistencies in observing significant changes. These discrepancies could stem from differences in study design, vitamin D dosing, duration of supplementation, or baseline characteristics of the study populations, such as age and comorbid conditions (9).

Given the high prevalence of vitamin D deficiency and its association with various health outcomes, further research is needed. A large-scale, randomized controlled trial could provide

more definitive evidence of the effects of vitamin D supplementation on testosterone levels and prostate health. Additionally, exploring the genetic factors that may influence individual responses to vitamin D, as suggested by Chen et al., could help in understanding the mixed effects observed in different studies (12).

Strengths and Weaknesses

Strengths

This scoping review undertook an assessment of the effects of vitamin D supplementation on testosterone levels, providing a holistic view of the potential benefits of vitamin D for male health. This multi-dimensional approach is similar to that of Yeo et al., where similar parameters were measured to understand the broader implications of vitamin D supplementation (4).

One of the key strengths of this scoping literature review is its assessment of the effects of vitamin D supplementation on testosterone levels, prostate health, and lower urinary tract symptoms (LUTS) in men. By including articles that included diverse outcome measures and longitudinally following participants over a one-year period, the review offers a robust and multi-dimensional perspective on the potential benefits of vitamin D (5). This approach aligns with the rigorous methodologies observed in studies by Lerchbaum et al., providing strong evidence of causality and highlighting the importance of temporal measurements in assessing the effects of interventions (8).

Weaknesses

A significant limitation of the studies is the absence of a placebo control group, which restricts the ability to definitively attribute observed effects to vitamin D supplementation alone (4). When it comes to this scoping review, one weakness is the choice of only 2 databases for article selection. A third weakness, the systematic review by D'Andrea et al. also included 3 studies (7,9,11) that were included in this scoping review, which as a consequence creates an overestimated view of the results.

Conclusion

Providing men, particularly those with known vitamin D deficiencies, with vitamin D supplements could potentially help normalize testosterone levels, thereby enhancing overall health and well-being. However, there is a need for longitudinal studies to examine the long-term effects of vitamin D supplementation on testosterone levels to establish definitive recommendations for future research.

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