



Role of vitamin D in common urological conditions: a narrative review of past decade literature

Dominic Brown^{1#}, Kristiana Gkeka^{2#}, Yash Narayan^{3#}, Antigoni Katsouri^{4#}, Georgios Tsampoukas^{5,6#}, Noor Buchholz^{6*}

¹Department of Urology, Broomfield Hospital, Chelmsford, UK; ²Department of Urology, General Hospital of Patras, Patras, Greece; ³Department of Urology, Princess Alexandra Hospital, Harlow, UK; ⁴Pharmacist, Harlow, UK; ⁵Department of Urology, Stoke Mandeville Hospital, Aylesbury, UK; ⁶U-merge Scientific Office, Athens, Greece

Contributions: (I) Conception and design: G Tsampoukas, N Buchholz; (II) Administrative support: G Tsampoukas; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Georgios Tsampoukas. U-merge Scientific Office, c/o Mrs. Vicky Nickolopoulou, Athens, Greece. Email: Scientific-office@u-merge.com; tsampoukasg@gmail.com.

Background and Objective: To perform a literature update of the past decade on potential role of vitamin D in common urological entities: prostatic malignancy and benign hyperplasia, stone disease, urinary tract infections and male infertility. Vitamin D (or calciferol) is the pivotal regulator of calcium in humans and low levels are associated with bone health in children and adults. Recent research though has spread in several other fields including common urological conditions. Early reports indicate that vitamin D deficiency might be associated with increased risk of prostate cancer and hyperplasia, stone disease, semen impairment and urinary tract infections.

Methods: A non-systematic search in PubMed/Medline, Google Scholar, Web of Science, and Embase was performed using the terms “vitamin D” and “benign prostatic hyperplasia/enlargement”, “prostate cancer”, “prostate malignancy”, “urolithiasis”, “nephrolithiasis”, “male infertility”, “urinary tract infections”. The search duration period was set between 2011 and 2021. Exclusion criteria were non-English and retracted studies.

Key Contents and Findings: In prostate cancer, vitamin D deficiency is associated with adverse outcomes, but its usage needs to be clarified. In hyperplasia, correlations are not certain. In contrast, in urolithiasis, the achievement of a normocalciemic status should be considered the primary goal in terms of prevention and reduction of recurrence. Moreover, vitamin D seems to regulate host immunity. In children, pregnant and women of reproductive age, screening for deficiency might be of benefit, whereas supplementation may be used as a secondary tool in the management of urinary tract infections. In infertile men, treating deficiency might be a cost-effective approach instead of a multi-panel empirical antioxidant treatment but its role needs further evaluation.

Conclusions: Although highest level of evidence still lacking to support vitamin D administration as per guidelines practice, last decade research looks promising in terms of its role and its therapeutic potential. The specific indications, the exact dosages and safety profile need to be established with future research.

Keywords: Vitamin D; prostate cancer; prostate hyperplasia; nephrolithiasis; male infertility; urinary tract infections

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Introduction

Vitamin D (or calciferol or cholecalciferol) refers to the member of this group of vitamins obtained from vegetal or animal origin dietary sources essential for the absorption of calcium. The molecule is considered mandatory for bone health in children as 50% of peak bone mass is being achieved during the adolescent years, and more than 80% by 18 years of age. Deficiency of vitamin D is associated with bone abnormalities (1). Furthermore, the evaluation and maintenance of adequate vitamin D levels carries a high clinical importance as a preventive measure in adulthood (2). The beneficial role of calciferol is not restricted to bone metabolism alone though. Vitamin D deficiency and insufficiency have been associated with poorer health outcomes in cancer patients, obesity, cardiovascular risk and even with severity of Covid-19 (3-7). In the urological field, the association between the metabolism of calcium, vitamin D and urinary stones disease has been established, and dietary calcium restrictions are no longer being recommended for stone patients as in the past (8,9). Moreover, emerging evidence has shown that the function of vitamin D receptors and the preventive administration of vitamin D might have a protective effect on the risk and the course of urological malignancies such as prostate and bladder cancer (10-12). Last but not least, vitamin D seems to have a protective and therapeutic effect on semen quality through its anti-inflammatory potential (13). Administration of vitamin D has also been shown to reduce prostate volume intervening with natural history of benign hyperplasia (14). Given the non-expensive nature of the screening and the relatively low cost of the agent, vitamin D sounds a promising diagnostic, preventive, and therapeutic tool. In this review, we are focusing on the common urological entities of prostate cancer and hyperplasia, urolithiasis, urinary tract infections and male infertility, reviewing the advancements of the past decade on the topic.

We present the following article in accordance with the Narrative Review reporting checklist (available at <https://lcm.amegroups.com/article/view/10.21037/lcm-21-49/rc>).

Material and methods

Our search aimed to present selected, recent, outstanding studies reporting the role of vitamin D in the pathophysiology and the therapeutic potential in prostate cancer, benign hyperplasia of the prostate, urolithiasis, urinary tract infections and male infertility. Human studies

were prioritized; animal studies were also mentioned if they facilitated the scope of the manuscript. A non-systematic search in PubMed/Medline, Google Scholar, Web of Science, and Embase was performed using the terms “vitamin D” and “benign prostatic hyperplasia/enlargement”, “prostate cancer”, “prostate malignancy”, “urolithiasis”, “nephrolithiasis”, “male infertility”, “urinary tract infections”. Our search duration period was set between January 2011 and August 2021. Exclusion criteria were non-English and retracted studies. Our search strategy summary is illustrated in *Table 1*.

Vitamin D and prostate cancer

Vitamin D has been shown to disrupt cancer processes including in urological malignancies. In the prostate, vitamin D has been shown to exert anti-proliferative properties through the induction of cell-cycle arrests and apoptosis, inhibiting the growth of both normal prostatic epithelial cells as well as prostate cancer cells and cell lines. In clinical settings though, both high and low concentrations of vitamin D have been associated with an increased prostate cancer risk, whereas sunlight carries a protective effect (15-17). Moreover, vitamin D deficiency (<30 ng/mL or <25 nmol/L) has been associated with adverse pathology (dominant Gleason pattern 4, presence of any pattern 5, and pathologic stage pT3aN0M0 or higher) in men with localized prostate cancer undergoing radical prostatectomy and a higher overall and specific mortality in men diagnosed with the disease compared to men with adequate vitamin D levels (18,19).

Genetic variations of the vitamin D receptors (VDR) may modify the biological activity of vitamin D, conferring different susceptibilities to prostate cancer. This hypothesis has also been observed in other adenocarcinomas such as the colorectal cancer and the understanding of the association between VDR and vitamin D is crucial. The binding product of the fat-soluble vitamin D and the (nuclear) VDR mediates the cellular proliferation, apoptosis and metaplastic process and interferes with the progression of carcinogenesis (20). VDR can also help to regulate cell proliferation, differentiation, and apoptosis in normal tissue (21). Correlation between specific VDR polymorphisms (Taq-I, Bsm-I, Apa-I, Fok-I) with prostate cancer grade (Gleason score) and disease progression has been demonstrated. The association between VDR polymorphism and tumorigenesis varies with specific patient characteristics such as age, sex and, more specifically, race (21). However, whilst several

Table 1 The search strategy summary

Items	Specification
Date of Search (specified to date, month and year)	1/7/2021 – 31/8/2021
Databases and other sources searched	PubMed/Medline, Google Scholar, Web of Science, and Embase
Search terms used (including MeSH and free text search terms and filters)	“vitamin D” and “benign prostatic hyperplasia/enlargement”, “prostate cancer”, “prostate malignancy”, “urolithiasis”, “nephrolithiasis”, “male infertility”, “urinary tract infections”
Timeframe	1/1/2011 – 1/8/2021
Inclusion and exclusion criteria (study type, language restrictions etc.)	Inclusion Criteria: Studies reporting the role of vitamin D in the pathophysiology and the therapeutic potential in prostate cancer, benign hyperplasia of the prostate, urolithiasis, urinary tract infections and male infertility Exclusion Criteria: Non-English and retracted studies
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	Each member of the authors' panel was allocated in a domain
Any additional considerations, if applicable	–

different VDR polymorphisms may increase the risk of prostate cancer, others may demonstrate a protective effect on carcinogenesis (22).

Despite evidence that vitamin D deficiency is associated with prostate cancer risk and ultraviolet radiation decreases that risk, the routine administration of vitamin D is not yet part of international guidelines (23). In patients being treated for prostate cancer, current evidence suggests that vitamin D administration in combination with standard care (e.g., chemotherapy, radiation therapy) may confer clinical benefits such as a decrease in serum Prostate Specific Antigen (PSA) levels and the regulation of VDR expression (24). Especially in men treated with androgen deprivation, vitamin D may be able to counter intracrine mechanisms contributing to the emergence of castrate-resistant tumors (25). The recommended dosage needs further evaluation; doses at 500–1,000 mg calcium and 200–500 IU vitamin D per day might not be efficient to sustain bone health during androgen deprivation treatment, whereas the effect on oncological endpoints such as PSA response might be modest (26,27).

Vitamin D and benign prostate hyperplasia

Benign prostatic hyperplasia (BPH) and associated lower urinary tract symptoms are routinely seen in older men. The incidence is increasing with each decade of life (28). BPH is more prevalent in Europe and North America compared

to Asia, with geographical variations supporting the role of environmental factors in BPH pathogenesis (28,29). The pathophysiology of BPH is considered to be multifactorial and characterised by chronic inflammation and proliferation of epithelial and stromal prostatic cells (28,29). Vitamin D and its analogues have anti-inflammatory and anti-proliferative properties which regulate prostatic cell growth through numerous mechanisms, alter cyclooxygenase-2 expression and prostaglandin E2 production in stromal cells, and inhibit the RhoA/ ROCK pathway (30). The active form of vitamin D binds to vitamin D receptors (VDR), which regulate gene transcription, and VDR gene polymorphisms (Taq-I, Bsm-I, Apa-I, Fok-I) are associated with an increased risk to develop BPH (31).

Vitamin D deficiency is prevalent in the male population, with approximately one third of males having levels below 20 ng/mL (adequate vitamin D levels to be regarded above 20 ng/mL and low: below 12 ng/mL) (32). Low (25-OH) vitamin D levels have been found to be associated with prostatic enlargement and levels are inversely proportional to prostate volume (>40 grams) (33,34). Moreover, vitamin D levels have been inversely correlated not only with prostate volume but also with serum PSA (34).

In terms of the role of supplementation, Zendejdel and colleagues showed that administration of 50,000 units of vitamin D3, fortnightly for six months, resulted in smaller prostate volumes, a reduced mean PSA level, and improved lower urinary tract symptoms (29). Lower PSA

levels were also identified by Safwat *et al.* who reported that prophylactic cholecalciferol for BPH patients, along with tamsulosin, reduces significantly the risk of recurrent urinary tract infections in comparison to tamsulosin alone. However, despite reductions in prostate volumes and symptom scores with prophylactic cholecalciferol, these parameters were not statistically significant (30).

In clinical practice, vitamin D deficiency could be used as a marker for BPH and progression of urinary symptoms (35). Moreover, since dietary and supplementary vitamin D has been shown to reduce BPH prevalence, delay disease progression and improve symptoms, supplementation might be considered as part of BPH management (29). Last but not least, the general positive effect of vitamin D might provide an alternative to medications with low toxicity, and reduced surgery associated morbidity (28,34).

Vitamins and urolithiasis

Urolithiasis represents a common health concern with a prevalence varying up to 20%. Calcium is the most common stone component whilst hypercalciuria is the commonest abnormality identified in calcium stone formers. As a result, the metabolism of Ca and vitamin D has been investigated in the pathophysiology and management of urolithiasis (36).

The association of vitamin D and stone formation is not fully understood. Analysis from a systematic review of observational studies showed that increased circulating 1,25(OH)₂ vitamin D is associated with urinary stones, as a result of intermittent hypercalciuria and increased urinary supersaturation (37). On the other hand, a prospective case-control study reported that the prevalence of vitamin D inadequacy (VDI) (defined as levels of vitamin D <30 ng/mL including both insufficiency: levels between 20–29 ng/mL and deficiency: less than 20 ng/mL) in urolithiasis patients was 95% as compared to 57% in the control group (38). The co-existence of VDI and other risk factors like obesity which is associated with overexpression of inflammatory mediators, or secondary hyperparathyroidism associated with chronic kidney disease might be the missing bridge regarding the role of vitamin D in stone formation (39). Genetic analysis has also favored the role of vitamin deficiency in stone formation. The CYP24A1 is a member of the P450 enzyme family, which metabolizes active 1,25-dihydroxyvitamin D to inactive 24,25-dihydroxyvitamin D. Mutations in the gene encoding CYP24A1 can cause infantile hypercalcemia, which might present later in life with hypercalciuria and, ultimately,

nephrolithiasis (40). Furthermore, animal studies have highlighted the role of VDR upregulation in stone formation resulting in increased activity of circulating vitamin D and, finally, hypercalciuria. The authors hypothesized that if similar results are established in humans, the receptors should be targeted as possible therapeutic agents (41). Finally, special circumstances might contribute to stone formation. In mice carrying deficit of the ABCC6 gene (which encodes a protein related to calcium deposition and mineralization) the combined calcium and vitamin D intake may accelerate Randall's plaque formation, suggesting an analogous effect in genetically predisposed individuals (42).

So far, the evaluation of the risk of long-term vitamin D as in stone formation or prevention has been evaluated in some studies. In patients with chronic kidney disease, long-term supplementation seems not to increase the incidence of kidney stones (43). In a 4-year follow-up of vitamin D administration, it was shown that monthly 100,000 IU dose did not increase the rate of stone disease or the rate of hypercalcemia (44). In a case series of two recurrent stone formers cases, a megadose of 600,000 IU every 4–6 months was not associated with a stone event for 3–4 years follow-up (45). As in other health conditions, screening the population for and treatment with vitamin D should not be considered of no benefit. However, currently the actual merit remain unclear (46).

Vitamin D and urinary tract infections

Urinary tract infections (UTI) are of the commonest infections in the community and healthcare setting. In general, their prevalence seems to be increasing with age (47). In children, UTIs follow second to the respiratory infections and prompt investigations are mandatory (48).

Several studies in selected populations have shown the linkage between the vitamin D deficiency and the risk of UTI (49). Although the mechanism is as yet unknown, the correlation involves vitamin D as a crucial factor of the antibacterial capacity of the host and a protective agent of the urothelium against the cytoskeletal reorganization cause by *Escherichia Coli* (50–52).

In children, vitamin D seems to be correlated to UTI although contradictory results are reported. Mahyar *et al.* reported that in children up to 12 years of age, the mean serum vitamin D levels were higher in the UTI group in comparison to controls (53). Another study of a similar population age did not show any significant difference between the groups. However, the presence of female

sex was higher in the affected population comparing to controls which might imply a gender linkage (54). On the other hand, Vitamin D deficiency has been reported to be significantly present in a case-controlled study of children 1–12 year of age (55). Vitamin D deficiency has also been reported more frequently in children with recurrent infections, while it has been shown as an independent risk factor of renal scarring as seen in follow-up imaging (56,57). Although the authors acknowledged that the cause-and-effect relationship between scarring and vitamin D is difficult, this might be related to the role of vitamin D in inflammation.

In women, most authors agree that vitamin D deficiency increases the risk of UTI. The risk includes women of reproductive and premenopausal age and becomes clinically important during pregnancy (58–60). Although the exact correlation is unknown, female gender and vitamin D deficiency seem to be linked with bacteriuria at advanced age, implicating a more complex correlation (61). Pre-existent vitamin D deficiency has been also reported as an independent risk factor for UTI after renal transplantation (62).

The administration of vitamin D might be used to improve the host response to bacterial urinary tract infections and reduce the infection frequency (63). A randomized trial in prediabetic patients showed that administration of vitamin D resulted in a reduction of UTI unrelated to previous vitamin D levels, an effect that was more prominent in men (64). However, another randomized, triple-blind, placebo-controlled clinical trial was not able to confirm such a benefit (65).

Vitamin D and male infertility

In both women and men, vitamin D has been shown to correlate significantly with the regulation of reproduction (66). Although the exact association is unknown, a synergistic clinical effect along with other conditions such as obesity and diabetes might be the case (67). Deficiency and dysregulation of vitamin D receptors seem to be the primary mechanisms of vitamin D-associated infertility when no other obvious cause is identified (68). Hypospermatogenesis, testicular failure and the alteration of CYP2R1 expression (the gene encoding the vitamin D hydroxylase) have been found to be strongly linked in infertile men (69). In experimental models, vitamin D administration has been found to delay testicular ageing by regulating proliferation and apoptosis which could help

target the oxidative stress associated with subfertility (70).

Clinically, the deficiency of vitamin D might result in worsen semen parameters including concentration, total motility, motility, and morphology, in both normospermic and dyspermic infertile men (71,72). Serum testosterone and LH levels have shown a significantly positive and negative correlation with vitamin D levels, respectively, and vitamin D could thus be used as a prognostic marker of male infertility (73). A positive correlation between total and free serum testosterone levels and serum vitamin D concentrations has also been seen in men with normospermia (74). Last but not least, infertile men with idiopathic infertility might also have lower vitamin D levels in comparison to men with secondary infertility, implying involvement of an innate pathology (75).

The normalization of vitamin D levels has a beneficial effect on semen quality in selected populations of infertile men (75). In men with idiopathic oligoasthenozoospermia (a longitudinal study with no control group), a significant improvement in sperm concentration and progressive sperm motility was observed, whereas the overall clinical pregnancy rate in the study was 8.33% after vitamin D supplementation (76). Notably, treatment with vitamin D has also been associated with higher live-birth rates in couples in which the man had oligozoospermia compared with those men taking placebo (77). However, a randomized trial showed that the administration of vitamin D in infertile men resulted in no change in the semen quality or serum levels of LH, FSH, and total testosterone (78). Research investigating further the role of vitamin D in men with idiopathic infertility is ongoing (79).

Discussion

In general, research evaluating both the role and the beneficial effect of vitamin D in urological pathologies looks promising. The results of our search are summarized in *Table 2*. However, a critical review of the literature is mandatory as the clinical benefit remains still unknown. Notably, even in bone health conditions optimization of research methodology seems to be needed in order to establish evidence-based guidelines (80).

In prostate diseases, despite the reported potential benefits of vitamin D in the prevention of cancer, research is still evolving and no specific recommendation can be made in terms of prevention (81). In patients treated for prostate cancer, achieving a normocalcemic status is mandatory as oncological endpoints seem to be affected by

Table 2 Vitamin D and urological conditions—clinical implications

Diseases	Pathophysiology	Therapeutic potential/limitations
Prostate cancer	<ul style="list-style-type: none"> • High and low concentrations of vitamin D may increase risk • Serum concentrations <30 ng/mL of vitamin D has been associated with adverse pathology • Worse prognosis in men with prostate cancer and deficiency in comparison to diagnosed men without • In men treated with ADT vitamin D might impede castration resistance 	<ul style="list-style-type: none"> • Optimal dosage and duration are unknown • Efficacy of mega-doses has not been proven
Benign Prostate hyperplasia	<ul style="list-style-type: none"> • VDR gene polymorphisms are associated with an increased risk to develop BPH • Vitamin D deficiency have been correlated inversely with prostate volume and PSA 	<ul style="list-style-type: none"> • Administration reduces prostate volume and improves lower urinary tract symptoms • Optimal dosage and duration are unknown • Similar regimes for the treatment of deficiency might be used
Urolithiasis	<ul style="list-style-type: none"> • Increased serum vitamin D results in hypercalciuria, increased urinary supersaturation and stone formation • Inadequacy of vitamin D might be seen up to 95% of stone formers – VDR are involved by increasing the activity of circulating vitamin D predisposing to stone formation 	<ul style="list-style-type: none"> • Eucalcemic status reduces stone events • Vitamin D supplementation even in high does seems not to increase stone events and has rather protective role (as it restores eucalcemic status)
Urinary tract infections	<ul style="list-style-type: none"> • Vitamin D as a protective agent of the urothelium against Escherichia Coli • Deficiency significantly more frequent in children with recurrent infections and independent factor of renal scarring • Deficiency is reported as risk factor in young and pregnant women 	<ul style="list-style-type: none"> • The administration of vitamin D might be used to improve the host response to bacterial urinary tract infections and reduce the infection frequency • Randomized trials showed contradictory results
Male infertility	<ul style="list-style-type: none"> • Delay testicular ageing by regulating proliferation • Association of hypospermatogenesis, testicular failure and the alteration of gene encoding the vitamin D hydroxylase • Deficiency of vitamin D is associated with worse semen parameters 	<ul style="list-style-type: none"> • Normalization of vitamin D levels has a beneficial effect on semen quality • Vitamin D might increase live births in selected patients without direct reflection in conventional semen parameters • Regime, safety and optimal duration are unknown

ADT, androgen deprivation therapy; VDR, vitamin D receptors.

vitamin D deficiency. The exact usage of vitamin D needs to be clarified though. Regarding BPH, certain correlations need to be considered with care as they might be the result of a detection bias (i.e., the reported correlation of vitamin D levels and prostate volume might be associated with and resulting from underlying factors). However, vitamin D deficiency could be treated as an additional risk factor for BPH, and normalization of vitamin D levels seem advisable and, given the prevalence of BPH, might be effective in combination with other conservative measures (82).

In contrast, in urolithiasis there is strong evidence about the possible role of vitamin D deficiency and the role of vitamin D receptors dysregulation in stone formation. Therefore, the achievement of an normocalciemic status should be considered the primary goal in terms of prevention and reduction of the risk of stone formation or/and recurrence (83,84). In selected populations such as patients with chronic kidney disease and secondary hyperparathyroidism, the administration of vitamin D can be considered safe in terms of kidney stone formation risk

as there is no evidence displaying such an increased risk.

Moreover, as vitamin D has a role in the host immunity it can be recommended to check for vitamin D deficiency in patients with frequent urinary tract infections. Children and women of reproductive age are the populations where screening would be advisable. Administration of vitamin D should be considered a secondary tool in the management of urinary tract infections. It may be one contributor in an evolving field of research on the non-antibiotic management of UTIs (85).

Whilst vitamin D deficiency may be found in infertile men, strong correlations need to be considered with care again since the condition is multifactorial. A full understanding of idiopathic infertility has not been achieved yet. However, treating vitamin D deficiency might be a cost-effective and safe approach instead of a multi-panel empirical antioxidant treatment (86). As prevalence of male infertility is increasing, in-depth evaluation of the role of vitamin D seems of merit in terms of prevention and early diagnosis (87).

With a potential role of vitamin D in many metabolic pathophysiological events emerging, its safety profile, especially if administered long term needs to be established, as well as the optimal scheme and dosage, and its cost-effectiveness. Due to the lack of highest evidence, we are still away from incorporating vitamin D administration in any international guidelines. However, the past decade literature indicates that research is ongoing and promising; supported by a growing renewed interest in non-pharmacological therapies.

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