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The Association between Long-Term Vitamin D Supplementation and Increased Risk of Nephrolithiasis in Adults: A Problem-Based Critical Review

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ABSTRACT

Background: Nephrolithiasis has high recurrence and causes a decrease in the patients' quality of life. One of the hallmarks of the disease is hypercalciuria. Vitamin D is known to have a role in calcium homeostasis and can increase risk of hypercalciuria. To date, not many studies have looked at the association between long-term (≥ 1 year) vitamin D supplementation in adult patients with the increased risk of nephrolithiasis and many of the available study results are still inconsistent and thus, inconclusive, due to a great variability in treatments duration and daily dose of vitamin D supplementation.
Objective: To investigate the association between long-term (≥ 1 year) vitamin D supplementation of 2000 IU/day with the increased risk of nephrolithiasis in adult patients.
Method: This study used literature search on Pubmed, Cochrane Library, and EMBASE through suitability with the clinical question and eligibility criteria determined by the authors.
Results: Based on the critical review of 6 literatures comprising 2 SR/MA, 2 RCTs and 2 prospective cohorts, the study concluded that there is no increased risk of nephrolithiasis in adults taking long-term (≥ 1 year) vitamin D supplementation of 2000 IU/day.
Conclusion: Long-term (≥ 1 year) vitamin D supplementation of 2000 IU/day in adult patients does not increase the risk of nephrolithiasis.

Keywords: Vitamin D, ergocalciferol, cholecalciferol, supplementation, supplementation, nephrolithiasis, kidney stones, renal calculi.

CLINICAL PROBLEM

A 55-year-old female patient came to the clinical nutrition physician clinic in radiotherapy department for consultation related to decreased appetite and weight loss. The patient's nutritional status was grade I obesity and there had been a weight loss of 1.6 kg or 2.8% within 1 month. The patient was scheduled to start radiation therapy for endometrial carcinoma stage 1B and was advised not to lose more weight by the radiation oncologist. At the time of visit, the patient had also complained of low back pain with visual analogue scale (VAS) of 1-2 and urinary hesitancy for the last week despite drinking a lot. The pain did not interfere with daily activities. The patient was concerned about her condition hence looked for information online and found that low back pain and urinary hesitancy

could be caused by nephrolithiasis. The patient's mother died from complications of nephrolithiasis so the patient was worried about having the same disease. The patient had never experienced symptoms like this prior to the visitation. The patient's kidney function laboratory results came out normal (blood urea nitrogen (BUN) 32.1 mg/dL, creatinine 0.6 mg/dL, and *estimated glomerular filtration rate* (eGFR) 102.9 mL/min/1.73m^2. The patient's abdominal ultrasonography (USG) and *magnetic resonance imaging* (MRI) results showed no renal abnormalities.

The patient said that she had been taking vitamin D supplementation of 1x2000 IU per day for the past 1 year to improve immunity. The patient did not know exactly which form of vitamin D contained in the supplementation. The patient led a sedentary lifestyle and was rarely exposed to sunlight while she was healthy. These conditions had worsened since the patient was diagnosed with early *stage of* endometrial cancer. The patient was now prone to feeling tired and motivation for outdoor activities had decreased even further. In addition, due to food preferences, the patient rarely consumed *dairy products* (eggs, milk, cheese, etc.) and fish which were the source of vitamin D. The patient read that one of the possible risks of long-term vitamin D supplementation was nephrolithiasis. The patient asked the doctor if continuing her current dosage of vitamin D supplementation for a long term could cause the patient to develop nephrolithiasis in the future.

CLINICAL QUESTION

"Does long-term (≥ 1 year) vitamin D supplementation of 2000 IU/day in adult patients lead to increased risk of nephrolithiasis?"

P: Adults taking regular vitamin D supplements

I: Long-term (≥ 1 year) vitamin D supplementation

C: Placebo

O: Increased incidence of nephrolithiasis

INTRODUCTION

Nephrolithiasis is a common disease found in daily practice. The prevalence of the disease is 13% for men and 7% for women.[1] There are many contributing factors including lifestyle and diet. The type of kidney stones varies but is generally dominated by calcium stones (calcium oxalate and calcium phosphate stones).[1,2] The most common abnormality is increased excretion in the urine (hypercalciuria).[1] A study by Patel, et al[3] showed that people with nephrolithiasis have a decreased quality of life mainly due to pain and urinary problems. In addition, nephrolithiasis has a high recurrence rate of 35-50% within 5 years after the first kidney stone event and 75% within 20 years.[1,2]

Based on previous studies, it is known that vitamin D consumption plays a role in calcium metabolism and can increase hypercalciuria.[4] There are only 2 sources of vitamin D, namely diet (food or supplements) and sunlight.[4] To date, the relationship between long-term vitamin D supplementation and the incidence of nephrolithiasis still varies between studies. Previous studies have looked at the association of calcium supplementation with or without vitamin D supplementation with the incidence of nephrolithiasis.[5,6] In this case study, we will discuss the role of long-term vitamin D supplementation with the incidence of kidney stones.

METHODS

Searching strategy

The literature search was conducted through *advanced searching* on 3 large databases namely PubMed, Cochrane Library, and EMBASE on March 17th 2025. A combination of *MeSH Term*, *Title/Abstract/Key*, and *Text word* or *All text* was used in the search and PICO search was used in EMBASE. The keywords used were *"vitamin D", "vitamin D2, vitamin D3", "cholecalciferol", "ergocalciferol, "supplementation", "supplements", "kidney calculi", "kidney stones", "renal calculi", "nephrolithiasis"*. The literature search

strategy is presented in Table 1. The retrieved articles then screened for duplication and asessed for the suitability with PICO in this review. Articles that fit the clinical question were included for critical appraisal using tools from Oxford-CEBM (Centre for Evidence Based Medicine).

Eligibility Criteria

Inclusion Criteria: 1) adult population (age ≥ 18 years to <60 years); 2) population with subjects taking vitamin D2 or D3 supplementation ≥1 year; 3) studies with kidney stone outcomes; 4) articles in English; 5) *Systematic Review/Meta-analysis* (SR/MA)-Randomized *controlled trial (RCT*)-cohort-case control research design. In RCTs, it can be seen in the control/non-intervention group.

Exclusion Criteria: 1) articles not accessible in *full text*; 2) studies with research subjects taking supplementation other than vitamin D; 3) subjects already suffering from kidney stones before the study; 4) research subjects involving pregnant women; 5) research subjects involving the elderly (≥60 years old); 6) research subjects with vitamin D supplementation <2000 IU/day.

To avoid duplication of studies, if a SR/MA has been included in this review, then RCT, cohort and case control studies included in that SR/MA will be excluded from the review. After determining the studies used, the authors conducted a critical review of each study using *appraisal tools* according to the research design and determined the *levels of evidence* based on *Evidence Based Medicine Oxford.* (https://www.cebm.ox.ac.uk/resources/ebm-tools/critical-appraisal-tools).

Table 1. Literature search strategy

Database	Search Strategy	Hits	Selected Articles
PubMed 17/3/2025	((((((((((vitamin d[MeSH Terms]) OR (vitamin d 3[Text Word])) OR (vitamin D3[Title/Abstract])) OR (vitamin D3[Text Word])) OR (cholecalciferol[MeSH Terms])) OR (cholecalciferol*[Text Word])) OR (ergocalciferols [MeSH Terms])) OR (ergocalciferol*[Text Word])) OR (vitamin D2[Text Word])) OR (vitamin d 2[Text Word])) AND (((((dietary supplements[MeSH Terms]) OR (supplement[Title/Abstract])) OR (supplement*[Text Word])) OR (supplementation[Title/Abstract])) OR (supplementation*[Text Word]))) AND ((((((((((kidney calculi[MeSH Terms]) OR (kidney calculus[Text Word])) OR (kidney stone*[Text Word])) OR (kidney stone[Title/Abstract])) OR (kidney stones[Title/Abstract])) OR (renal calculi[Text Word])) OR (renal calculus[Text Word])) OR (nephrolith[Text Word])) OR (nephrolithiasis[MeSH Terms])) OR (nephrolithiasis[Text Word]))	146	4
Cochrane Library 17/3/2025	#1 MeSH descriptor: [Vitamin D] explode all trees #2 ("vitamin D") OR ("vitamin D2") OR ("vitamin D3") OR (vitamin D3): ti, ab, kw #3 MeSH descriptor: [Cholecalciferol] explode all trees #4 ("cholecalciferols") OR ("cholecalciferol") OR (cholecalciferol): ti, ab, kw OR (cholecalciferols): ti, ab, kw #5 MeSH descriptor: [Ergocalciferols] explode all trees #6 ("ergocalciferol") #7 #1 OR #2 OR #3 OR #4 OR #5 OR #6 #8 MeSH descriptor: [Dietary Supplements] explode all trees #9 ("supplementation"): ti, ab, kw OR ("supplement"): ti, ab, kw OR ("supplementation") OR ("supplement") OR (supplements) #10 #8 OR #9 #11 MeSH descriptor: [Kidney Calculi] explode all trees #12 ("kidney stone") OR ("kidney stone"): ti, ab, kw OR ("renal calculi") OR ("kidney stones") OR (kidney stones): ti, ab, kw #13 MeSH descriptor: [Nephrolithiasis] explode all trees #14 ("nephrolithiasis"): ti, ab, kw OR ("nephrolithiasis")	138	2

	#15 #11 OR #12 OR #13 OR #14 #16 #7 AND #10 AND #15		
EMBASE 17/3/2025	('adults'/exp OR 'adults' OR 'grown-ups'/exp OR 'grown-ups' OR 'grownup'/exp OR 'grownup' OR 'grownups'/exp OR 'grownups' OR 'adult'/exp OR 'adult') AND ('vitamin d'/exp OR 'vitamin d' OR 'colecalciferol'/exp OR 'colecalciferol' OR 'ergocalciferol'/exp OR 'ergocalciferol' OR 'vitamin d3'/exp OR 'vitamin d3' OR 'vitamin d2'/exp OR 'vitamin d2' OR 'cholecalciferol'/exp OR cholecalciferol OR 'cholecalciferols'/exp OR cholecalciferols) AND ('placebo'/exp OR 'placebo') AND ('nephrolithiasis' OR 'nephrolithiasis'/exp OR nephrolithiasis OR 'kidney stone'/exp OR 'kidney stone' OR 'kidney stones'/exp OR 'kidney stones' OR 'kidney calculi'/exp OR 'kidney calculi')	89	0

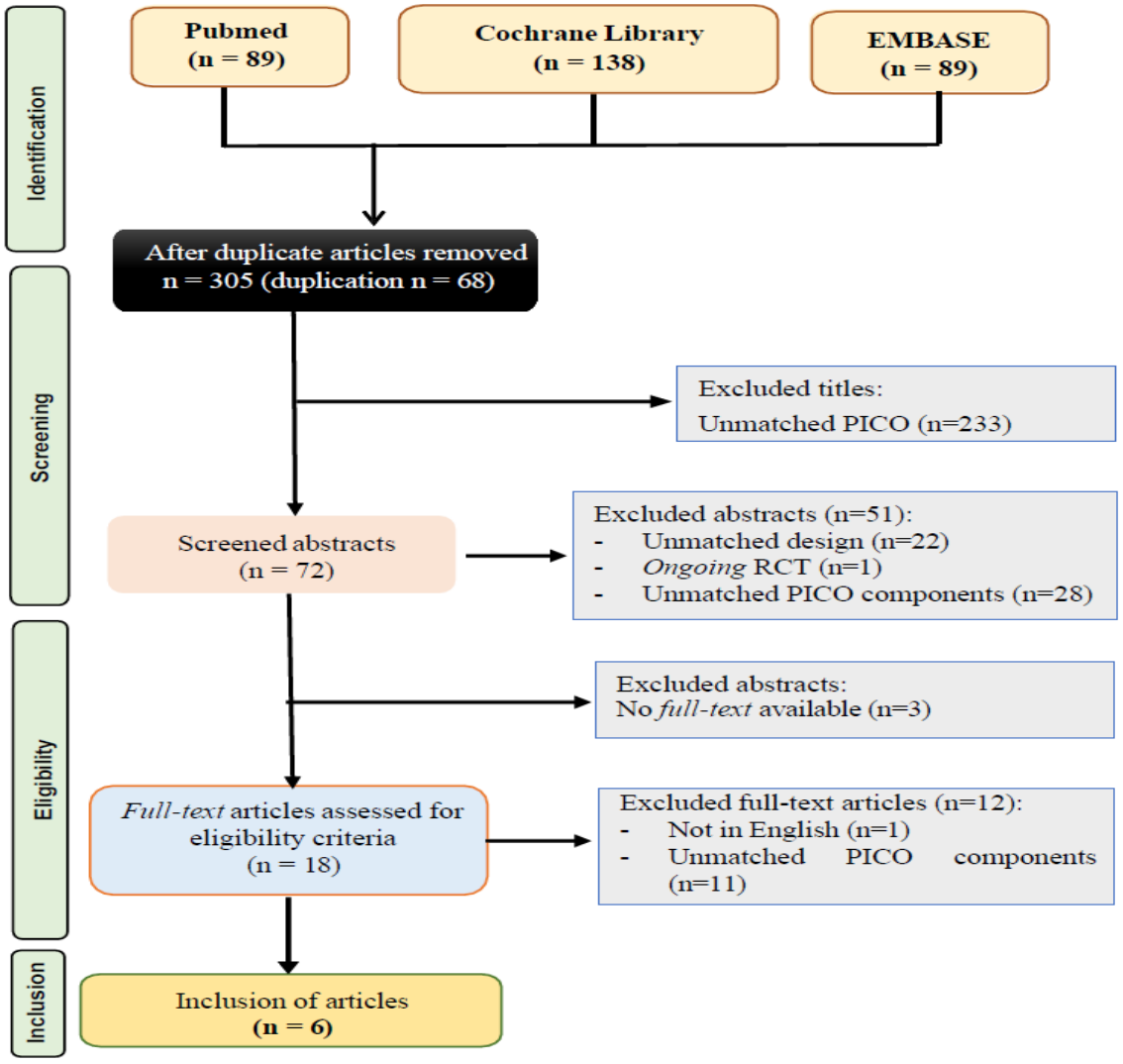

Figure 1. The flow diagram of literature search

RESULT

The flow diagram of literature search is illustrated in Fig.1. From 3 databases, 305 articles were initially identified. After removing 68 duplicates, 72 articles were screened for eligibility based on abstract and full text. Finally, 6 full text articles of 2 SR-MA, 2 RCT, and 2 cohort studies were selected for the critical appraisal. The characteristics of selected articles are presented in Table 2. The selected articles were critically appraised to review the validity, importance and applicability. Summary of critical appraisal result of each article is presented in Table 3 and 4.

Table 2. Characteristic of selected articles

Article	Study Design	Population	Determinants (Indicator and Comparison)	Outcome
Malihi Z, et al (2019)[7]	SR/MA of RCTs	15 RCTs (n=3150) from Medline Ovid, Cochrane, EMBASE databases covering studies up to March 2018.	Vitamin D2 or D3 supplementation of ≥ 2800 IU/day for ≥ 1 year compared to placebo or control (vitamin D dosage between 0-600 IU/day)	Four outcomes were measured: incidence of nephrolithiasis, hypercalcaemia, hypercalciuria, and total adverse events
Malihi Z, et al (2016)[4]	SR/MA of RCTs	48 RCTs (n=19,833) from 3 databases: Pubmed, EMBASE, and Cochrane library. Including studies up to October 28th 2015	Vitamin D supplement with or without calcium compared to placebo or lower dose of vitamin D, or calcium at the same dose as the intervention	The three outcomes measured were hypercalciuria, hypercalcaemia and incidence of nephrolithiasis
Ginde AA, et al (2017)[8]	Double-blinded RCT	107 of elderly (≥ 60 years old) living in nursing homes in Colorado during 2010-2014.	The high-dose group received vitamin D3 supplements of 100,000 IU/month or equivalent to 3000-4000 IU/day. The standard-dose group took vitamin D equivalent to 400- 1000 IU/day (according to the daily routine dose).	The primary outcome was the incidence of ARI during the 12 months of exposure. Secondary outcomes included nephrolithiasis
Malihi Z, et al (2019)[9]	Double-blinded RCT	5110 adult subjects (50-84 years old) living in Auckland during the 3–4-year study period (2011-2015).	The intervention group received vitamin D3 supplementation of 100,000 IU/month in capsule form. The control group received placebo capsules.	Incidence rate of nephrolithiasis after supplementation of median 3.3 years.
Ferraro PM, et al (2017)[10]	Prospective cohort	3 populations (n=193,551) 1. HPFS cohort (1986-2012): A total of 51,529 male health workers aged 40-75 years old 2. NHS Cohort I (1976-2012): 121,700 females nurses aged 30-55 years. 3. NHS Cohort II (1989-2011): 116,430 females nurses aged 25-42 years.	Participants of all three cohorts completed questionnaires on lifestyle, medical history, medication and food intake validated on the NHS I and HPFS.	Incidence of nephrolithiasis
Sha S, et al (2024)[11]	Prospective cohort	The UK Biobank data was divided into several outcome groups. Kidney stone outcomes with (n) 439,189 adults' subjects aged 40-69 years who had data on serum 25(OH)D levels, were divided into the following 3 groups: - Non-vitamin D supplement group (n=330,625) - Multivitamin supplement group (n=89,638) - Vitamin D supplement group (n=18,926)	Serum vitamin D (25(OH)D) status at *baseline* and vitamin D supplementation for a mean of 12.8 years compared with no vitamin D supplementation and multivitamin supplementation including vitamin D	One of the outcomes is the risk of hypercalcaemia and incidence of nephrolithiasis

Table 3. Summary of critical appraisal results of a SR-MA article Malihi Z, et al (2019)[7]

	Study Design	Question	Find	Appraise	Inclusion	Total Up	Heterogeneity	Result	Applicability	Level of Evidence
Malihi Z, et al (2019)[7]	SR-MA	+	+	+	+	+	+	A	+	Level 1a

A: In renal stone outcomes, 5 of 15 studies (n=1336) reported the incidence of renal stones in large-dose and long-term vitamin D supplementation versus placebo, the cumulative RR was not increased (RR=1.26; 95%CI 0.35-4.58) with homogeneous results between studies (I^2 0%, p heterogeneity =0.78).

Table 4. Summary of critical appraisal results of a SR-MA article Malihi Z, et al (2016)[4]

	Study Design	Question	Find	Appraise	Inclusion	Total Up	Heterogeneity	Result	Applicability	Level of Evidence
Malihi Z, et al (2016)[4]	SR-MA	+	+	+	-	+	+	B	+	Level 1a

B: In renal stone outcomes due to vitamin D supplementation, 9 of 48 studies (n=9619) whose cumulative RR was not increased (RR=0.66; 95%CI 0.41-1.09) with more detail were described in subgroups of long-term vitamin D use or by dose. The heterogeneity results between studies in this study were homogeneous (I^2 0%, p heterogeneity =0.98).

Table 5. Summary of critical appraisal results of an RCT article Ginde AA, et al (2017)[8]

	Study Design	Randomisation	Similarity	Equally treated	Intention to treat analysis	Blinding	Result	Applicability	Level of Evidence
Ginde AA, et al (2017)[8]	Double- blinded RCT	+	+	+	+	Double blind	C	+	Level 1b

C: There was no hypercalcaemia or kidney stones in either the high dose or standard dose group in this study, suggesting that routine vitamin D supplementation of 400-4000 IU/day for 12 months does not increase the risk of kidney stones.

Table 6. Summary of critical appraisal results of an RCT article Malihi Z, et al (2019)[9]

	Study Design	Randomisation	Similarity	Equally treated	Intention to treat analysis	Blinding	Result	Applicability	Level of Evidence
Malihi Z, et al (2019)[9]	Double- blinded RCT	+	+	+	+	Double blind	D	+	Level 1b

D: Monitoring with a median of 3.3 years of exposure showed 158 subjects reported incidence of kidney stones (76 in the vitamin D group and 82 in placebo). *The hazard ratio* (HR) for the incidence of first kidney stone in the vitamin D group compared to placebo was 0.90 (95%CI: 0.66-1.23; p = 0.51) which also showed no statistically or clinically significant difference.

Table 7. Summary of critical appraisal results of a prospective cohort study Ferraro PM, et al (2017)[10]

	Study Design	**A clearly focused issue**	**Acceptable cohort recruitment**	**Accurate measurement of exposure to minimise bias**	**Accurate measurement of outcome to minimise bias**	**Identification of all important confounding factors**	**Control of confounding factors**	**Complete follow-up of subjects**	**Enough duration of follow-up**	**Level of Evidence**
Ferraro PM, et al (2017)[10]	Prospective Cohort	+	+	+	+	+	+	+	+	Level 2b

Results: In the HPFS study, there was no association between vitamin D intake and the incidence of kidney stones (HR of supplement ≥1000 IU/day and <100 IU/day 1.08, 95%CI 0.8-1.47, p value = 0.92). In the NHS I study, there was no association between vitamin D intake and the incidence of kidney stones (HR 0.99, 95%CI 0.73-1.35, p value = 0.7). In the NHS II study, a higher risk was found (HR 1.18, 95%CI 0.94-1.48, p value = 0.02). Not statistically significant.

Table 8. Summary of critical appraisal results of a prospective cohort study Sha S, et al (2024)[1(1)]

	Study Design	**A clearly focused issue**	**Acceptable cohort recruitment**	**Accurate measurement of exposure to minimise bias**	**Accurate measurement of outcome to minimise bias**	**Identification of all important confounding factors**	**Control of confounding factors**	**Complete follow-up of subjects**	**Enough duration of follow- up**	**Level of Evidence**
Sha S, et al (2024)[1](1)	Prospective Cohort	+	+	+	+	+	+	+	+	Level 2b

Results: There were 5,097 incident (1.1%) kidney stones during *follow-up*, with twice the ratio of males to females (1.6% vs 0.8%), p>0.05. The HR of the multivitamin group was slightly higher than that of vitamin D supplementation alone at 0.96 (95%CI 0.89-1.03) and 0.95 (95%CI 0.82-1.10), respectively. Not statistically significant.

DISCUSSION

Nephrolithiasis is a common disease found in daily medical practice, with an incidence prevalence of 13% in men and 7% in women.[1] Furthermore, the recurrence rate of nephrolithiasis is quite high at 35-50% within 5 years and 75% within 20 years from the first occurrence and can cause decrease in quality of life of the patients.[1-3] Some etiologies of nephrolithiasis include lifestyle and diet.[4] Vitamin D supplementation is one of the micronutrients that plays a role in calcium metabolism. Based on the results of several previous studies, it can increase the incidence of hypercalciuria hence can lead to increasing the risk of nephrolithiasis.[4] However, results mainly vary from study to study and thus inconclusive due to a great variability in vitamin D dosage, duration of studies, as well as study populations. The mechanism of how vitamin D causes hypercalciuria is still unclear. The current hypothesis links it to the genetic VDR that makes a person more sensitive to vitamin D metabolism, causing idiopathic kidney stones.[12]

In this article, 6 studies were critically reviewed, including 2 SR/MA from RCTs, 2 double-blinded RCTs, and 2 prospective cohorts. All six studies had similar subjects and eligibility criteria. The determinant (both in the exposure/intervention and control groups) was long-term vitamin D supplementation at a dose between 0-5000 IU/day consumed ≥ 1 year.[4,7-11] All six studies showed consistently similar results, i.e. no significant increase in the incidence of nephrolithiasis between subjects who received long-term vitamin D supplementation at a large dose (3000-5000 IU/day), maintenance dose (400-1000 IU/day), or no supplementation (placebo).[4,7-11] Clinically, the incidence of kidney stones was consistent in both the exposure group and the control group.[4,7,9-11] The differences in result of studies were not statistically significant as the 95%CI value always crossed 1 in all of these studies in both the primary and cumulative relative risk (RR) in the SR/MA.[4,7-11]

In the SR/MA by Malihi Z, et al[7] the strength of the study was supported by the wide variety of RCTs that had studied vitamin D supplementation, thus obtaining a study with a large sample of population and being able to specifically study large doses and long-term vitamin D supplementation. In addition, this study was controlled for the confounding factor of calcium so as to assess the safety aspect of vitamin D alone without calcium and in accordance with component I of this study's PICO. The selected RCTs were of high quality and had low risk of bias with a critical review of each study looking at random sequence, allocation masking, and *blinding*.[7] All RCTs included in this study were published within the last 10 years so there was sufficient information on design including *blinding*, randomisation, baseline characteristics, and measurement of outcome.[7]

Limitations of this SR/MA include literature search method, which was carried out using three largest databases for RCTs plus the results of a previous *systematic review* by Malihi Z, et al (2016)[4], yet the included studies were limited to the articles published in English hence there was a possibility of a language bias even though all studies analysed in this SR/MA showed consistent results. In addition, the search strategy for unpublished studies was not explained so there might have been studies that had not been included, despite using Cochrane as a central *clinical trial registry.* Another limitation is that the subjects in the included studies involved both sick and healthy subjects, so the authors of the study suspected that this might have an impact on increasing heterogeneity between studies as the 95%CI range was quite wide even though the heterogeneity value in this study was not statistically significant and subgroup analyses had been conducted. Similar limitations were also found in the 2016 SR/MA. During the study period, the outcomes of hypercalcaemia and nephrolithiasis were still small and overall, the results were deemed inconclusive.

The strengths and weaknesses of the 2019 and 2016 SR/MA by Malihi Z, et al[4,7] was overall similar. Slight difference with the 2016 SR/MA in which the initial limit of article retrieval was not set.[7] In the conclusion, it was written that insufficient data had not been collected to reach a conclusion hence the study was repeated.7

In the RCT by Ginde AA, et al[8] involving 107 subjects monitored for 12 months, no incidence of nephrolithiasis was found in either the high-dose or standard-dose group so it was not continued to the analysis stage. This suggests that vitamin D3 supplementation for 12 months at either high-dose (3000-4000 IU/day equivalent) or standard-dose (400-1000 IU/day) does not increase risk of nephrolithiasis. These results are also similar and consistent with the results from the RCT by Malihi Z, et al[9] which also studied kidney stone outcomes in vitamin D supplementation of 100,000 IU/month versus placebo in 5110 adult subjects. Results from monitoring at a median of 3.3 years of exposure showed that there was no significant difference in the incidence of nephrolithiasis due to long-term large-dose supplementation in either the vitamin D or placebo group, either statistically or clinically.

The strength of these two RCTs is that they can demonstrate the effect of high-dose, long-term vitamin D supplementation compared to maintenance-dose independent of the effect of calcium supplementation.[8,9] In addition, the RCT by Malihi Z, et al[9] had a large sample size which increased the precision of the results to be applied to real populations. It can be seen from the 95%CI margin that is quite narrow although the difference in effect on the results is not statistically significant. Both RCTs also applied a good randomisation process from recruitment to group allocation. *Blinding* was done to all subjects involved in the study from the intervention to analysis.[8,9] The limitation of these two RCTs is that the measurement/collection of nephrolithiasis data was through interviews and *self-reported* questionnaires so that there was possibility of measurement bias and kidney stone outcomes that might not be reported.[8,9] In these studies, this was controlled through *blinding* of group allocation and collecting more objective data through examination results by health workers and diagnosis of nephrolithiasis from hospitalization data the Ministry of Health.[8,9]

The study results of Ferraro, et al[10] are in line with the other four studies in which there was no association between vitamin D supplementation and the incidence of nephrolithiasis. The slight difference in results in NHS II may be influenced by age factor, although it is not statistically proven. The strength of this cohort study lies in the very large number of participants, with a fairly long *follow-up* time (22-36 years).[10] The study had also considered many confounding factors, rendering the results of the study more precise to be applied in clinical practice. Some limitations include the observational method of this study and that the majority of participants were white. In addition, the lack of information regarding the type of stones suffered by the participants, the indications for vitamin D supplementation, and drop-outs also made up the limitations of this study.

Another cohort study by Sha S, et all[11] also support the results of previous ones. Contrary to the hypothesis, this study found that low 25(OH)D levels increased the risk of kidney stones. This result was statistically significant yet the association was considered to be weak. The strength of this study is that it is the largest study to date to examine the potential adverse effects of vitamin D supplementation in adult population with a long time period for outcomes to occur. The large amount of data provided sufficient statistical power to detect rare adverse effects of vitamin D supplementation in the general population. In addition, comprehensive adjustments were conducted to control for up to 50 covariates. A limitation of this study is that the majority of the subjects were healthy adults, hence potentially skewing the

observed disease prevalence. However, the RR derived from the exposure-outcome association is believed to be less affected by this bias due to the controlled confounding factors. Another limitation is that due to the self-report method, not all data were complete regarding the supplementation dose, frequency of consumption per day, and chemical content of multivitamin supplementation that may affect kidney stone outcomes.

Overall, the validity aspect of this critical review shows that each study included is valid, although some parts of the research methods are not perfect and there is still a possibility of bias. Regardless, the studies have provided explanations on how these biases were controlled. For *Importance* aspect, the results between studies are consistent and conclusive showing that long-term vitamin D supplementation at both maintenance and high doses (3-5 times the daily dose consumed by the patient in this case study) does not significantly increase the risk of nephrolithiasis, both clinically or statistically.[4,7-11] In addition, the studies in general have good enough precision so that they can be applied in the population.[4,7-11] For applicability, most of the research subjects from each study had similar characteristics to the patient in this case study, namely adult patient, not pregnant, generally without diseases or comorbidities associated with risk factors for kidney stones, daily routine of vitamin D supplementation for ≥ 1 year at a dose of 2000 IU/day (within the dose range studied) and no previous history of nephrolithiasis.[4,7-11] It is important to note that most of the study subjects were not or lived in Southeast Asia so there may be differences in daily vitamin D supplementation requirements and exposure to vitamin D from food sources, vitamin D fortified foods, and sunlight.

The recommendation based on the current evidence is that vitamin D supplementation for the patient in this case study, with lack of consumption of vitamin D-source in food and sun exposure, can be continued at the current maintenance dose (2000 IU/day) for the long term as it has not been shown to increase the risk of nephrolithiasis in the dosage between 0-5000 IU/day.[4,7-11] In addition, the patient was also advised to engage more in outdoor activities and increase the duration of morning sun exposure. When taking vitamin D capsules, the patient was advised to take them with unsaturated fat products such as olive oil or avocado to increase vitamin D absorption in the digestive tract and eat vitamin D-source food such as fatty fish and eggs.[13] The patient was also advised to have their serum vitamin D levels checked in the laboratory so that they can determine whether to increase or decrease the supplementation dose to avoid vitamin D deficiency or toxicity.[13]

The strength of this article is the search strategy method with good sensitivity using a combination of *Mesh terms*, *text words/all text*, and *title/abstract* on each PICO component and its synonyms to get high hits. In addition, it managed to get SR/MA from RCTs which is the highest *level of evidence* for the etiology study. The limitation includes the method of article search, which was conducted on large English-based databases only so that local studies which may have more suitable demographics with the patient in this case study might have been skipped.

It should be noted that the involved studies with vitamin D supplementation reviewed in this article measured a maximum dose of <8000 IU/day. However, over-the-counter vitamin D supplements may exceed this dosage.

The safety of taking high dose of vitamin D could be attributed to the fact that vitamin D is metabolically inactive and stored as such and requires a series of metabolic transformations to its active form to be utilized by target tissues.[14] After its hepatic synthesis, vitamin D3 in the form of calcidiol (25(OH)D) is secreted from the liver. The blood is the largest single pool of calcidiol, with 85–90% of 25(OH)D in the blood is bound to and transported by the vitamin D-

binding receptors (VDBP), about 10–15% is bound loosely to albumin, and <1% is free (unattached). Calcidiol in the blood has a half-life of about 2–3 weeks.[13] High intakes of the vitamin causes more vitamin D to be stored (most nonhydroxylated but also as calcidiol) in the liver and adipose tissue, causing saturation of VDBP.[14-15] Vitamin D is then released slowly from the storage to the blood stream. Individuals who are overweight or obese with higher-than-average amount of fat mass appear to store more of the vitamin in adipose tissue than those with less body fat. After release to the blood stream, calcidiol then transported to kidney and is hydroxylated into calcitriol, the active form of vitamin D, which is then transported to the rest of the body via VDBP, primarily to regulate calcium metabolism. The excess amount of ingested vitamin D in inactive form is not readily excreted from the body, but rather be stored to be released slowly upon necessity.[13-14]

However, hypervitaminosis D can occur when the concentration of vitamin D metabolites, such as 25(OH)D increase significantly, exceed the VDBP-binding capacity, and resulting in a release of free $1,25(OH)_2D$ to the blood stream. Toxicity is marked by serum 25(OH)D concentrations exceeding 150 ng/mL.[13-14] The exact amount of ingested dietary vitamin D that can cause this in adults is still unclear. The highest dose of vitamin D supplementation recorded in a study so far was an RCT (the Calgary study of vitamin D) at dosage of 10000 IU/day compared to 400 IU/day and 4000 IU/day. Hypercalcemia and hypercalciuria was common and occurred more frequently with 10000 IU/day (p=0.002 and 0.011, respectively) but were mild and transient.[15]

One case report showed a 58-year-old woman developing hypercalcemia and vitamin D supplement-induced toxicity after being prescribed vitamin D starting at 8000 IU/day, tapering to 2000 IU/day over 3 months.[16] Nephrolithiasis was also detected after 3 months of vitamin D therapy. However, further investigation revealed that the patient harbored a 25(OH)D-24-hydroxylase (cytochrome P450 [CYP]24A1) mutation, a key enzyme involved in the degradation of 25(OH)D and $1,25(OH)_2D$ into inactive metabolites, resulting in hypercalcemia, hyperphosphatemia, and nephrolithiasis in patients receiving vitamin D supplementation.[16] According to these studies, the current upper limit of vitamin D supplementation of <10000 IU/day is evidently safe. It is important to note that it is advisable to measure the serum level of vitamin D before prescribing >5000 IU/day for over 3 months.

It is also important to note that the studies reviewed in this article used populations with healthy renal function and no history of kidney stones to reduce the variability with the patient in this case study. From other studies of vitamin D supplementation in kidney stone formers, circulating calcitriol has been found to be increased, whereas higher plasma calcidiol seems to be present only in hypercalciuric patients.[17] Hypercalciuria is one of the risk factors for calcium kidney stone formation. Thus, available evidence might suggest that vitamin D administration worsens the risk for stone formation in patients predisposed to hypercalciuria.[17-18]

However, not all calcium stone formers have high serum calcitriol concentrations as different vitamin D receptor (VDR) polymorphisms were actually found to be associated with kidney stones in human patients, yet the pathogenic role of this association is yet to be determined.[17] One retrospective study of 26 patients with recurrent calcium kidney stones and vitamin D deficiency treated with 50000 IU vitamin D per week for 8-12 weeks showed increase in 24-h calculated relative supersaturations of calcium oxalate (CaOxSS) and calcium phosphate (CaPSS) through urine but the changes were not significant (p=0.177 and p=0.218, respectively).[18] This result is similar with another case report of two patients (a 74-year-old and a 52-year-old males) with long-term history of nephrolithiasis, recurrent renal crisis, and serum 25(OH)D deficiency, received high-

dose 25(OH)D supplementation of 50000 IU per week for 3 months.[19] At 3 months, both patients had no episodes of lithiasis renal crisis. The dosage then tapered to 50000 IU every 6 months for the elderly and every 4 months for the 52-year-old. Follow up after 4 years only showed renal microlithiasis. The study concluded that this megadose was safe for kidney stone formers without hypercalciuria.[19] Studies of vitamin D supplementation effect in risk of nephrolithiasis for renal insufficiency or chronic kidney disease (CKD) patients is still very limited. Regardless, current guideline from large trials for vitamin D supplementation suggests that there is no strong rationale for indiscriminate use of vitamin D supplements among patients with CKD.[20] Further evidence on side effects and safety aspects of taking higher doses of vitamin D than on these articles should be studied.

CONCLUSION

In this article, 6 studies were critically reviewed, including 2 SR/MA from RCTs, 2 RCTs, and 2 prospective cohorts. All six studies used similar subjects and eligibility criteria in accordance with PICO from this case study. The studies showed consistent and conclusive results, i.e. no significantly increased risk of nephrolithiasis between subjects receiving long-term supplementation of vitamin D at large doses (3000-5000 IU/day), maintenance doses (400-2000 IU/day), and non-supplementation (placebo), both statistically and clinically. Therefore, the patient in this case study can continue taking vitamin D supplementation at the current maintenance dose of 2000 IU/day for the long term, as it has been shown by the previous studies that it does not increase the risk of nephrolithiasis.

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