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Vitamin D Deficiency in Smokers a Potential Risk Factor for Kidney Stone

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Abstract

Nephrolithiasis is a major cause of concern for the clinicians due to its growing incidents globally. However, the risk of developing kidney stone is high in case of smokers. The present study describes the plausible mechanisms smoking-induced nephrolithiasis. Literature survey is done with tobacco smoking, kidney stone formation, vitamin D deficiency, and molecular mechanisms. PubMed, Web of Science, Google Scholar, Embase, Scopus are used to search articles up to March 2025. Peer reviewed full articles in English language are taken into consideration. Several reports claim that both active and passive smoking are involved in the vitamin D deficiency. Vitamin D deficiency results in the elevation of calciuria followed by CaOx and CaP stone formation. It causes the activation of ROS-dependent signalling pathways and inflammation. These alterations lead to renal tubular epithelial cell injury. Vitamin D supplementation may be beneficial in this regard so that the normal level may be maintained.

Keywords: Nephrolithiasis; Kidney stone; Renal calculi; Smoking; Vitamin D.

Introduction

Kidney stone disease or nephrolithiasis also called as urolithiasis is one of the common diseases in medical science. Increasing cases of prevalence of kidney stone disease becomes a major health issue and cause of concern for the physicians. Kidney stones often known as calculi are the coalition of minerals, which may exist as free or attach with renal papillae. The prevalence of kidney sone disease is gradually rising. According to a recentcross-sectional observational study conducted in United States, the prevalence of kidney stone is estimated to be 9.9%.[1] The incidence of kidney stone is comparatively more in male than female.[2-4]

The mechanism of kidney stone formation is complex and poorly understood. Supersaturation of minerals in urine leads to the formation of crystals of calcium oxalate (CaOx) mixed with calcium phosphate (CaP). Renal calculi can be made up of calcium, uric acid, oxalate, phosphate, cystine, and xanthine. Instead of this, stones may be formed due to the low level of urinary citrate or elevation of urinary acidity (pH<5.5).[5] The risk factors of kidney stones recurrence include diabetes,[6] family history of nephrolithiasis,[5] hypertension,[7] obesity,[8] Surgical intervention associated with the first or earlier stones,[5]uric acid urolithiasis,[9] white race,[10] prior personal history of urolithiasis,[11] younger age when diagnosed with nephrolithiasis.[12, 13] Some other factors which may be crucial to trigger renal calculi formation include urease producing bacteria for the formation of struvite and carbonate apatite stones formation,[14]Randall's plaques for calcium oxalate stones formation,[15] nanobacteria,[16] intestinal microbiota,[17] immunity and inflammatory response,[18] macrophage differentiation,[19] sex hormones.[20] Additionally, metabolic changes such as calcium, oxalate/ glyoxalate, calcium oxalate monohydrate/oxalate, oxalate/ estrogen, oxalate/Erβ (estrogen receptor β), oxalate/short-chain fatty acids, reactive oxygen species, etc. play pivotal roles in kidney stone formation. There are several therapeutic modalities are available for the prevention of kidney stone. Normally, fluid intake (2.5 to 3.0 litre/day) and diuresis (less than2.0to 2.5 litre/day) are recommended.[21] Moreover, life style modification, citrus fruitsintake, natural bioactive products such as caffeine, epigallocatechin gallate etc. and medicine such as thiazides, alkaline citrate, other alkalinizing agents etc. may be promising to control kidney stone formation.[22] There may be a high risk to develop nephrolithiasis in smokers with vitamin D deficiency. . However, there is a lack of research in this particular field. Hence, the present study focuses on the kidney stone formation in smokers, which may be further correlated with the risk of vitamin D deficiency.

Nephrolithiasis and tobacco smoking

In addition to the above-mentioned etiology and risk factors, tobacco smoking contributes to the formation of kidney stones. It is reported that 26.5% of nephrolithiasis patients are linked to current cigarette smoking.[23] Moreover, data are also available, which depict that second-hand or passive smoking is also associated with kidney stone disease.[24] It is in this context that both active and passive tobacco smoking is correlated with the risk of vitamin D deficiency.[25] Besides, the risk of vitamin D deficiency increases with time of smoking if an individual does not take vitamin D supplementation.[26]

As mentioned earlier, tobacco smoking is readily associated with kidney stone formation.[27]A study conducted by Tamadon et al.[28] has demonstrated that 26.5% of patients having kidney stones are linked to tobacco smoking. In this study, it has been shown that the age group between 30 to 39 years are largely associated withnephrolithiasis.[34,3] Another study has shown that high level of serum cotinine is associated with risk of kidney stone formation.[29] Cotinine is the chemical compound produced through nicotine metabolism. The concentration of cotinine is related to cigarette smoking. It is shown that serum cotinine concentrations of 0.05 to 2.99 ng/ml and ≥ 3.00 ng/ml have high risk of developing renal calculi. As mentioned earlier, second-hand smoke also the risk factor of developing kidney stone. It has been reported that 3.3% of never-smokers with second-hand smoke exposure is associated with kidney stone disease.[24] Smoking significantly increases reactive oxygen species and oxidative stress in urine, which may lead to the development of renal injury. It is experimentally shown through gas chromatography that isopr0ostane, a biomarker of lipid peroxidation, is elevated in the urine sample of smokers. However, the level of isoprostane may be less in ex-smokers with age.[30] This may suggest that the frequency of the formation of kidney stone may be reduced with time of quitting smoking. It is reported that damage and dysfunction of kidney epithelial cell result in the supersaturation in the interstitium, which in turn leads to the formation of Randall's plaques.[31]

Tobacco smoking and vitamin D deficiency

Vitamin D is a very important micronutrient that helps our body perform biological functions.Vitamin D deficiency causes many diseases and disrupts many molecular functions.[32]Vitamin D is synthesized by our skin cells when sunlight falls directly on the skin.Vitamin D is basically of two types, Vitamin D_2 and Vitamin D_3.Vitamin D_2 is called as ergocalciferol and vitamin D_3 is called as cholecalciferol. Many intermediates are formed through carboxylation processes, such as 25-\\

hydroxyvitamin D or 25(OH)D in the liver and 1,25-dihydroxyvitamin D or calcitriol in the kidneys. 25(OH)D is a very important hormone and a very good parameter by which the serum vitamin D is measured.

A study conducted on US population has revealed that both active and passive cigarette smoking are significantly responsible for vitamin D deficiency.[33] It has been reported that serum vitamin D concentrations are 54.7 nmol/L in active smokers and 58.3 nmol/L in passive smokers.[34] Cigarette smoking causes VDR (vitamin D receptor) gene polymorphisms, which have already been reported.[35] An experiment shows that cigarette smoking exposure causes lung injury and significantly reduced vitamin D receptors (VDR) in male Wister rats. Mitogen-activated protein kinase (MAPK) becomes active as a result of VDR depletion.[36] In context, it is reported that activation of ROS/Akt/p38 MAPK signalling pathway is directly associated with calcium oxalate crystal formation and damage of tight junction of distal renal tubular epithelial cells (Figure 1).[37,38] However, multiple studies have reported the vitamin D status in case of active and passive tobacco smoking as described in Table 1.

Figure.1 The effect of tobacco smoking in nephrolithiasis. Smoking is significantly associated with vitamin D deficiency, which in turn regulates multiple biological events in order to development of the renal calculi and renal tubular epithelial cell injury.

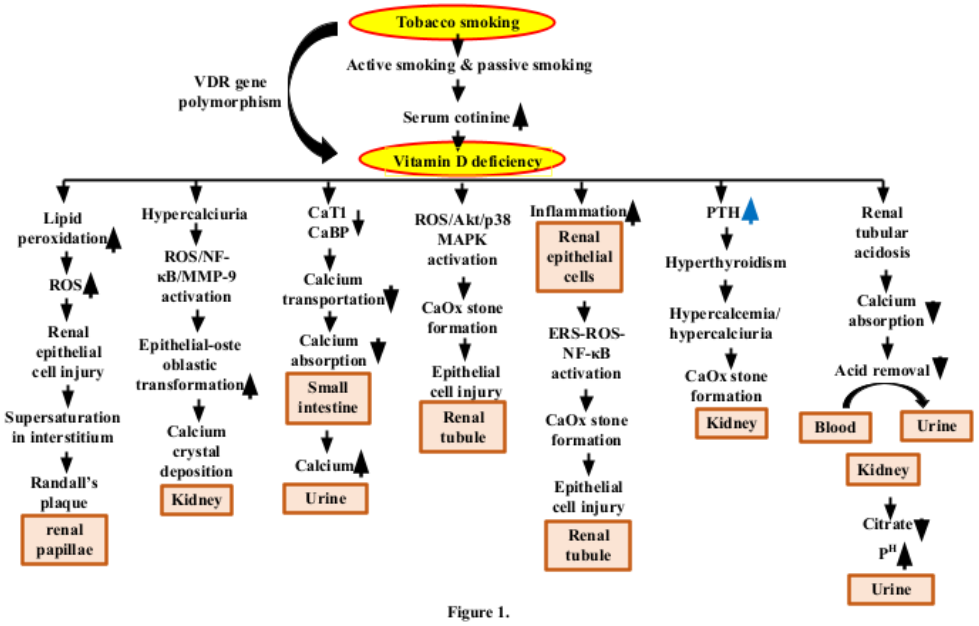

Figure 1.

Table 1: List of studies indicating the levels of serum 25(OH)D in smokers and non-smokers population.

Number of participants (N)		Age (years) (range or mean)	Method of vitamin D estimation	Serum 25(OH)D*		References
Smokers	**Non-smokers**			**Smokers**	**Non smokers**	
254	256	45 to 58	Radioimmunoassays	22.1ng/mL	25.0ng/mL	Brot et al., 1999.[39]
270	188	50 and above	Enzymeimmunoassay	54.7 ± 15.4nmol/L	58.3 ±17.2nmol/L	Jiang et al. 2016.[40]
4593#	Not reported	1.5 and 2	Liquid chromatography–tandem mass spectrometry (LC-MS/MS)	<20ng/mL	≥20ng/mL	Yang et al., 2022.[41]
626	Not reported	21 to 80	ChemiluminescenceImmunoasaay	< 20 ng/mL	Not reported	Lange et al., 2012.[42]
25	515	40.5	Chemiluminescence Immunoassay	51.4 ± 26.2nmol/L	63.4 ± 26.2nmol/L	Klingberg et al., 2015.[43]
825	1181	50.6	Radioimmunoassays	24.1 ± 12.1ng/mL	25.8 ± 12.3ng/mL	Hermann et al., 2000.[44]
32	29	30.13	Radioimmunoassays	23.9 ± 8.7ng/mL	29.9 ± 11.6 ng/mL	Diaz-Gomez et al., 2007.[45]
71	105	47	Chemiluminescence Immunoassay	22.82 ± 10.33ng/mL	24.66 ± 6.94ng/mL	Cutillas-Marco et al., 2012.[46]
64	117	34.69	e liquid chromatography–tandem mass spectrometry (LC-MS/MS)	17 ± 6.83ng/mL	21.36 ± 6.56ng/mL	Kassi et al., 2015.[47]
22	52	32.26	Radioimmunoassays	16.77 ± 9.9ng/mL	31.94 ± 15.1ng/mL	Supervia et al., 2006.[48]
9	12	46.29	Enzyme-Linked Immunosorbent Assay	25.32 ± 20.99ng/mL	46.6 ± 16.18ng/mL	Mulligan et al., 2014.[49]
21	29	40.64	Chemiluminescence Immunoassay	27.1 ± 2.49ng/mL	28.49 ± 6.38ng/mL	Alam et al., 2018.[50]
46	313	27.06	Chemiluminescent Microparticle Immunoassay	32.1 ± 14.6	41.6 ± 19.5	Lokki et al., 2020.[51]
86	320	51.9	Liquid chromatography–tandem mass spectrometry	31 ± 12	34.8 ± 13	Jorde et al., 2019.[52]
124	22	57	Elecsys	23.2 ± 9.4ng/mL	22.3 ± 8.9ng/mL	Sturmer et al., 2015.[53]

Data were represented as mean/ mean ± standard deviation

Vitamin D is crucial for calcium homeostasis and vitamin D deficient state is considered when serum or plasma 25(OH)D level is less than 75 nmol/L (<30 ng/ml).[54] Calcium absorption takes place in the mammalian small intestine through transcellular active transport and paracellular passive transport mechanisms.Calcium transport protein (CaT1) and calcium binding protein (CaBP) play important roles in the calcium transportation process. In context, the biosynthesis of CaBP (100%) and CaT1 (90%) are $1,25(OH)_2D_3$(vitamin D)-dependant. Moreover, CaBP and CaT1 are downregulated once vitamin D is downregulated even after high calcium intake.[55]Hence, vitamin D deficiency leads to the less absorption of calcium in the small intestine (Figure 1). It is important to state that when vitamin D is low in the body, calcium absorption in the small intestine is reduced by 10% to 15%.Under normal conditions, when vitamin D level is adequate in the body regardless of dietary or supplemental source, calcium absorption in the small intestine is 30 to 40%.[56] Thus, leftover unabsorbed calcium excretes through urine, which may be more in case of vitamin D deficiency.[57] The condition of high concentration of calcium in urine is called as hypercalciuria. Coe et al. have shown that idiopathic hypercalciuria (calcium concentration >200 mg per day) is associated with nephrolithiasis.[58] In context, almost 85% of kidney stones are consisted with CaP and CaOx. Calcium stones may be differentiated as CaOx (50%), CaP (5%), and mixed (45%).[59]Besides, Vitamin D deficiency is linked with hyperparathyroidism.[60] A study conducted by Malik et al. have reported that vitamin D deficiency is linked with high level of parathyroid hormone (PTH)(75.66 ng/ml) in blood.[61] It is in this context that hyper parathy roidism is associated with renal stone formation. A controlled retrospective follow-up study shows that renal stone is associated with hyper parathy roidism, which may be reduced after parathyroid surgery.[62] It is shown that although vitamin D supplementation 50000IU/week for 8-12 weeks decreases serum PTH, it increases the 24 hours serum and urinary calcium level and it also increase CaOx and CaP in urine.[63] However, dietary factors may play crucial role in this case. Thus, proper vitamin D supplementation dose needs to be determined. However, the incidents of stone formation is 27 time more in preoperative patients compared to the post surgery. Moreover, glomerular filtration rate more than 60 ml / minute / 1.73 m^2 is recommended for parathyroid adenomectomy to manage renal stones.[64] In addition to the above-mentioned facts, it is also important to disclose that hypercalciuria is associated with renal tubular acidosis.[65-67] Renal tubular acidosis is the physiological condition, when renal calcium reabsorption decreases and kidney becomes unable to remove acids from blood into urine. Type I or distal renal tubular acidosis (dRTA) hypercalciuria is linked with high risk of kidney stone.[68, 69] In this condition, patients show CaP stones with low urinary citrate and elevated urine pH (pH >5.5). However, potassiumcitrate may be recommended for the treatment of this condition.[70] Vitamin D deficiency is linked to increased reactive oxygen species (ROS) production.[71] It has been reported that CaOx kidney stones formation is enhanced by the activation of ROS and the formation of oxidativestress.[72] Vitamin D deficiency is one of the key players to modulate inflammation. It is known that vitamin D deficiency is associated with elevated level of transcription factor NF-κB.[73] It also execrates endoplasmic reticulum stress (ERS), a possible triggering factor of chronic inflammation.[74] It is suggested by Ming et al. thatERS/ROS/NF-κB signalling plays a major role in the oxalate-induced injury of renal tubular epithelial cells, which may be a potential mechanism for kidney stone formation.[75] MMP-9 is an important factor for tissue remodelling. Moreover,it is shown that hypercalciuria induces epithelial–osteoblastic transformation and the calcium crystal deposition in renal tubule through the activation of ROS/NF-κB/MMP-9.[76]

Vitamin D supplementation and nephrolithiasis

The relationship between vitamin D and kidney stones is very complex to understand.Vitamin D plays a very important role in the metabolic homeostasis of calcium and phosphorus.However, both excessive consumption and deficiency of vitamin D may increase the risk of kidney stone formation.[77]Vitamin D significantly increases calcium absorption in the kidneys, resulting in the regulation of calcium excretion into the urine. Vitamin D, particularly its active form1,25-dihydroxyvitamin D, plays an important role in the formation of kidney stones. Therefore, clinicians should consider more carefully when prescribing vitamin D supplementation and should consider the patient's genetic information, overall health status, and daily lifestyle before prescribing vitamin D supplementation. To ensure the effectiveness of the treatment, the patient should get adequate sunlight and should be aware of proper diet, exercise, and body weight. Vitamin D-mediated proper homeostasis of calcium and phosphorus may play a very important role in preventing kidney stones. So, it goes without saying that maintaining normal levels of vitamin D is very important for a person to prevent

kidney stones. It is recommended that intake of 25-hydroxyvitamin D in body should be 200, 400, 1nd 600 IU/day for young adults, person with age of 51-70 years, and >70 years respectively to achieve the normal level.[78]

Ferraro et al. have reported that vitamin D supplementation is not significantly associated with kidney stone formation.[79] Study conducted on 138 individuals with vitamin D mean dose 86 microgram (3440 IU) per day does not cause any incidents of hypercalcemia or hypercalciuria.[80] Similarly, Vieth et al. have demonstrated that supplementation of vitamin D_3 at a dose of 100 microgram/day does not cause the elevation of serum or urinary calcium excretion.[81] Besides, the population-based randomized controlled trial has revealed that vitamin D_3 supplementation of 100,000 IU/month for 3.3 years can reduce the incidence of kidney stones and also help reduce hyperglycemia.[82]

Study conducted on 204 osteoporosis patient aged 50-89 years shows that daily supplementation of calcium carbonate (600 mg) and alfacalcidol(0.5 µg) for 1 year elevate urinary calcium excretion and develop the risk of kidney stone formation.[83] However, the high prevalence of osteoporosis is inversely related to nephrolithiasis especially in elderly patients.[84] The similar type of observation has been reported by Sha et al., where it is shown that high 25(OH)D supplementation (i.e.≥ 100 nmol/L) is not associated with any adverse effect, however, it may increase the risk of hypercalcemia and kidney stone when calcium co-supplementation is advised.[85]

Conclusion

Smoking is significantly associated with the risk factor for kidney stone formation, especially CaOx/ CaP or their mixture. It is clear from the above-mentioned descriptions that both active and passive smoking result in the vitamin D deficiency. Various authorities have shown that vitamin D deficiency is linked to the elevation of urinary calcium concentration and CaOx stone formation in kidney. These mechanisms may play a crucial role in renal tubular epithelial cells injury. It is also reported that kidney stone formation may decrease with time of quitting tobacco smoking. It is also suggested that vitamin D is not the only predictor of the risk of kidney stone, however several other factors such as age, sex, race, education,marital and economical status, daily lifestyle, Smoking is significantly associated with the risk factor for kidney stone It is clear from the above-mentioned descriptions that formation, especially CaOx/ CaP or their mixture.

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Conflict of Interest

The author(s)declare no conflicts of interest.

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Authors' contribution

SS was involved in the data curation, study design, data compilation, conceptualization, interpretation, original draft writing, formatting, editing and review. MKS, RPS, and GB performed original draft editing and review.

Statements and Declarations

No potential conflict of interest was reported by the authors

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