

## STUDY OF IDIOPATHIC CALCIUM NEPHROLITHIASIS AND VITAMIN D DEFICIENCY

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### ABSTRACT

#### BACKGROUND

Vitamin D deficiency is a worldwide health concern. It prevails in epidemic proportions all over the Indian subcontinent with a prevalence of 70%-100% in the general population. Vitamin D is important in maintaining calcium and phosphorus homeostasis, but its role in kidney stone disease and its effect on stone formation are still not clear.

#### AIMS AND OBJECTIVES

In the present study, association between levels of Vitamin D and nephrolithiasis were studied.

#### MATERIALS AND METHODS

50 patients with nephrolithiasis were selected and were compared with 50 controls matched in terms of age and sex. 25-OH Vitamin D levels were measured in both groups.

#### RESULTS

25-OH Vitamin D levels were low in patients with nephrolithiasis when compared to controls.

#### KEYWORDS

25-OH Vitamin D, Nephrolithiasis, Calcium, Hypovitaminosis D, Parathyroid hormone.

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**INTRODUCTION:** Hypovitaminosis D is a worldwide health concern that nowadays has acquired the proportion of a pandemic.<sup>1</sup> Vitamin D is strongly involved in metabolism of calcium and phosphorus and its effects on bone health have been particularly emphasised. However, the role of vitamin D in Idiopathic Calcium Nephrolithiasis (ICN) is still controversial.<sup>2</sup> Some studies have demonstrated that the active metabolite, 1,25-dihydroxyvitamin D is associated with a higher calcium excretion and symptomatic onset of stones.<sup>3-7</sup> On the other side, hypercalciuric idiopathic calcium nephrolithiasis seems to be associated with higher serum concentrations of 25-hydroxyvitamin D (25-OH-D), the precursor and the laboratory gold standard for assessment of vitamin D status.<sup>8</sup> More recently, the association between serum pool of vitamin D and urinary calcium excretion in Stone Formers (SF) has been questioned.<sup>9</sup> While data from a population-based Swiss survey show that there might be gender-related differences in calciuric response to endogenous vitamin D.<sup>10</sup> Moreover, epidemiological data from a large cross-sectional study show that 25-OH-D levels seem to be unrelated to the prevalence of nephrolithiasis.<sup>11</sup>

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In contrast with the assumption that vitamin D promotes calcium nephrolithiasis. There are also data indicating that vitamin D deficiency is similarly and highly represented in patients with and without Idiopathic calcium nephrolithiasis.<sup>11-13</sup> Moreover, vitamin D2 supplementation does not seem able to increase the lithogenic risk.<sup>14</sup> In this scenario, it is still unclear whether, and possibly how, hypovitaminosis D influences idiopathic calcium nephrolithiasis onset and urinary factors of lithogenic risk. The primary aim of the present study was to investigate whether vitamin D deficiency (25-OH-D) is more prevalent in patients with Idiopathic Calcium Nephrolithiasis than in non-stone-forming controls.

**MATERIALS AND METHODS:** This cross-sectional study was done on 50 cases of nephrolithiasis and age and sex matched 50 controls from February 2015-December 2015 in P. K. Das Institute of Medical Sciences. The clinical records of all patients evaluated with kidney stones in our outpatients clinic from February 2015 to December 2015. Inclusion criteria were age  $\geq 18$  year's old, well-documented personal history of calcium nephrolithiasis (radio-opaque images at plain abdomen x-ray or stone fragments with at least 80% calcic composition at laboratory analysis) and presence of one recorded serum concentration of calcium, phosphorus, parathormone (PTH) and 25-OH-D. To avoid confounders patients with severe acute or chronic comorbidities, secondary causes of calcium nephrolithiasis (such as primary hyperparathyroidism), infectious nephrolithiasis, recurrent urinary tract infections, renal or



urinary anatomical abnormalities (such as medullary sponge kidney), previous urological and gastrointestinal surgery, chronic bowel inflammatory disease or gastrointestinal malabsorption syndromes, epilepsy, moderate or severe chronic kidney disease were excluded. All 25-OH-D tests were performed on both cases and controls in Central Lab of Biochemistry at PKDIMS using paramagnetic particle chemiluminescent immunoassay.

**Reference Ranges:**

- Deficient - <20 ng/mL.
- Upper safety level - >100 ng/mL.

Venous blood samples were obtained from all patients and controls after taking informed consent. For statistical analysis, descriptive data are expressed as Mean±SD. All statistical analysis were performed after entering data into SPSS 15.0 using Mann-Whitney’s U test. Statistical significance was inferred at P value <0.05.

**RESULTS:** The study population was composed of 50 patients with idiopathic calcium nephrolithiasis (20 males, 30 females, mean age±females, 59±15). After stratification for age group and sex and independently of Age, Difference in 25-OH Vitamin D between stone formers and controls was statistically significant in females, males younger than 45 years and in males older than 55 years. Comparison of 25-hydroxyvitamin D concentrations (expressed in ng/mL, median and interquartile range) between Stone Formers and Controls.

Age Category	Stone Formers	Controls	Age Adjusted P Value Using Mann-Whitney’s U test
<45 yrs.	15±5	22±5	<0.01
45-55 yrs.	14±4	21±4	0.04
>55 yrs.	16±4	20±5	<0.01

**Table 1: Females**

Age Category	Stone Formers	Control	Age Adjusted Mann-Whitney’s U test
<45 yrs.	16±4	23±6	0.02
45-55 yrs.	17±4	19±6	0.3
>55 yrs.	15±5	18±7	0.03

**Table 2: Males**

**DISCUSSION:** Vitamin D, the sunshine vitamin, is now recognised not only for its importance of bone health in children and adults, but also for other health benefits like reducing risk of chronic diseases including autoimmune diseases, cancer and cardiovascular diseases.<sup>15</sup> Vitamin D is an essential nutrition component, which has a unique metabolism and physiological effects compared to other vitamins; in fact, it is more suitable to be classified as a hormone.<sup>16</sup> Circulating 25-hydroxyvitamin-D concentrations are considered as an indicator of vitamin D status.<sup>17</sup>

The endogenous source (80-90%) is the main source of vitamin D, which is synthesised in the skin with the help of ultraviolet lights.<sup>18</sup> Exogenous source (10-20%) is through food. There are two main forms of vitamin D-Ergocalciferol (Vitamin D<sub>2</sub>) and Cholecalciferol (Vitamin D<sub>3</sub>). Ergocalciferol is derived from plant sources while cholecalciferol is of animal origin.<sup>19</sup> 7-dehydrocholesterol (an intermediate of cholesterol metabolism, which accumulates in the skin) is acted upon by ultraviolet B rays (UVB) of wavelength 290 nm to 315 nm and is converted to previtamin D<sub>3</sub>, secosterol. The cis double bond between 5<sup>th</sup> and 6<sup>th</sup> carbon atoms is then isomerised to a trans double bond to give rise to vitamin D<sub>3</sub> or cholecalciferol. Orally ingested and endogenously formed vitamin D is transported to the liver and is there converted to 25-hydroxyvitamin D (25(OH)D). 25(OH)D is rapidly released by the liver into the blood where it circulates with a biological half-life of approximately 12-19 d. It is bound to “Vitamin D binding protein” (an alpha-2 globulin).

In the kidney, 25(OH)D is enzymically converted to the vitamin D hormone 1,25-dihydroxyvitamin D (Calcitriol). Renal synthesis of Calcitriol is homeostatically controlled by Parathyroid Hormone (PTH). Vitamin D plays a key role in calcium homeostasis. It has been shown that vitamin D regulates calcium metabolism through its endocrine function. The non-classic actions of vitamin D can be categorised into three general effects: regulation of hormone secretion, regulation of immune function and regulation of cellular proliferation and differentiation. Serum 25(OH)D level is a better indicator of vitamin D status than 1,25(OH)<sub>2</sub>D.<sup>17</sup> There are several reasons for this. The circulating half-life of 1,25(OH)<sub>2</sub>D is only 4-6 hours and is present in pg/pmol and is therefore very hard to measure and ideally needs sophisticated techniques such as liquid chromatography-tandem mass spectrometry (LC-MS). Moreover, the titres of this product are highly variable and depend on the activity of cytochrome P450, family 27, subfamily B, polypeptide 1 (CYP27B1), the enzyme in the kidneys responsible for the 1-hydroxylation. This enzyme is under the control of parathyroid hormone.<sup>20</sup> As a patient becomes vitamin D deficient, there is a decrease in intestinal calcium absorption, which lowers ionised calcium transiently.

This signal is recognised by the calcium sensor in the parathyroid glands to increase the production and secretion of parathyroid hormone. PTH regulates calcium metabolism by increasing tubular reabsorption of calcium in the kidney, increasing mobilisation of calcium from the skeleton and by increasing the renal production of 1,25(OH)<sub>2</sub>D. Circulating levels of 25(OH)D are a thousand fold more than 1,25(OH)<sub>2</sub>D and is present in millimoles per litre range, which makes it easier to measure. It is a direct reflection of vitamin D reserves in the body as the enzymes responsible for 25-hydroxylation in liver (CYP27A1 and at least three others) will convert all vitamin D that comes into the body into 25(OH)D in a non-rate-limiting way. These levels are quite stable over several days or weeks and fluctuate typically with vitamin D intake and UVB exposure (seasonal variation).<sup>21</sup>

Therefore, circulating 25(OH)D concentrations are considered an indicator of vitamin D status. Hypovitaminosis D is widespread and is re-emerging as a major health problem globally. More recently, studies carried across different countries in South and South East Asia showed with few exceptions, widespread prevalence of hypovitaminosis D in both sexes and all age groups of the population.<sup>22</sup> The total amount of calcium in the human body varies between 1000 and 1300 grams, 99% of which is in the bone tissue, while the remaining 1% is in the intra and extracellular spaces. In physiological conditions, serum calcium is maintained within a narrow concentration range (8.5-10.4 mg/dL or 2.1-2.6 mmol/L). About 50% is free ionised calcium, while 10% is bound to bicarbonates, citrates, lactates and phosphates. These two fractions represent the so called "ultrafilterable calcium." The remaining 40% is bound to plasma proteins, mainly to albumin and to a lesser extent (5-10%) to globulins. In physiological conditions, only a fraction of the calcium binding sites on albumin are saturated. Therefore, the increase or decrease of the fraction of calcium bound to plasma proteins is able to buffer the effects of a rapid increase or decrease of calcaemia.

The hematic pH represents the most important factor able to affect the calcium binding to plasma proteins: Alkalosis increases the binding, while acidosis has the opposite effect.<sup>23,24</sup> In physiological conditions, serum calcium concentration is maintained strictly constant. This regulation occurs mainly thanks to two hormones, Parathyroid Hormone (PTH) and the active form of vitamin D, 1,25(OH)<sub>2</sub>D<sub>3</sub>, acting mainly on the skeleton, gut and kidney. The causes of calcium nephrolithiasis remain largely unknown. Research shows that it is a disease with multifactorial pathogenesis with several genetic and dietary predisposing factors. The main metabolic anomalies that are often associated with calcium nephrolithiasis are: hypercalciuria, hyperoxaluria and hypocitraturia. The causative role of these anomalies is suggested by the fact that they increase the risk of calculosis as well as being more frequent in patients with calculosis.<sup>25</sup> The increased calcium urinary excretion increases the risk of lithiasis via at least two known mechanisms: by increasing the saturation state of the urinary calcium salts (Calcium Oxalate, Calcium Phosphate) and by chemical bound with inhibitors (citrates) with consequent reduction in their activity.<sup>26</sup>

Calcium nephrolithiasis (CaNL) accounts for more than 70% of all renal stones and its prevalence has increased in the last decades. Under this definition are included patients passing stones, composed of calcium oxalates and/or calcium phosphates. Current views of the pathogenesis of CaNL are based on the role of metabolic abnormalities, which concur to render urines more conducive to crystallisation. Therefore, the diagnostic approach is aimed at detecting these abnormalities and the medical treatment assumes that a decrease in the risk of lithogenesis will result in remission or improvement of recurrences. The workup of the patients with CaNL begins with the analysis of passed stones and x-ray, sonography or other imaging techniques.

Eligible patients, that is, both recurrent active stone formers and single-stone formers with individual risk factors are considered for a metabolic evaluation by which a number of blood and urine parameters are measured and others calculated. These include estimates of urine state of saturation with calcium and uric acid salts, net gastrointestinal alkali absorption, renal threshold of phosphate and other renal clearances and net acid and total nitrogen excretions. The present study shows that patients with idiopathic calcium nephrolithiasis have significantly lower serum 25-OH-cholecalciferol levels than non-stone-forming subjects. Vitamin D deficiency (25-OH-D <20 ng/mL) is found to be independently associated with an increased risk of idiopathic calciuric nephrolithiasis. According to a study done by Elkoushy et al, hypovitaminosis D was found to be in 80 percent of the 101 subjects with different types of nephrolithiasis.<sup>13</sup>

According to classical physiopathological models, vitamin D may also increase the risk of kidney stones by promoting excretion of urinary calcium. Thus, on this basis, it has been hypothesised that vitamin D deficiency maybe protective against this risk. However, data that is currently available in literature are found to be conflicting. Some studies show significant associations between hypovitaminosis D and various urinary lithogenic risk factors including hypercalciuria and some others deny such associations. As a matter of fact, vitamin D repletion in subjects with a deficiency status does not alter urinary calcium excretion in healthy women.<sup>27</sup> However, experts claim caution in prescribing vitamin D repletion in patients with idiopathic calcium nephrolithiasis.<sup>28</sup> This caution is mainly due to the results of a large randomised controlled trial where co-administration of vitamin D and calcium supplements led to an increased incidence of nephrolithiasis.<sup>29</sup> A small prospective observational study, however, it was demonstrated that pharmacological vitamin D repletion in stone formers does not influence the excretion of urinary calcium during a 3-month followup period.<sup>14</sup>

An increase in the threshold of calcium reabsorption from filtrate to blood or mild parathyroid hormone elevations could also be involved in this case.<sup>30</sup> Vitamin D deficiency could also cause a state of systemic phosphorus depletion with a secondary rise in excretion of urinary calcium and a decreased responsiveness to parathyroid hormone.<sup>31</sup> It could also promote the onset of incomplete distal renal tubular acidosis, a condition frequently linked to rickets in children and osteoporosis in adults<sup>32</sup> and whose pathophysiology and genetic background has been recently described.<sup>33</sup> Recurrent calcium nephrolithiasis maybe associated with incomplete distal renal tubular acidosis, although often unrecognised because of difficulties in diagnosis.<sup>34</sup> Interestingly, a recent study on animal models of nephrolithiasis shows that vitamin D and calcium supplementation may lead to a decrease rather than increase of urinary calcium suggesting that Vitamin D deficiency could actually play a role in stone formation.<sup>35</sup>

**CONCLUSION:** It is clear that Vitamin D levels were related with idiopathic calcium nephrolithiasis. Statistical analysis showed that Vitamin D levels were lower among females and in males <45 years and >55 years of age who were stone formers. This study included only subjects without a known history of nephrolithiasis in the control group. However, the presence of clinically silent calculi could not be completely excluded given the absence of specific imaging addressing this issue. Even though, it is evident that lower Vitamin D levels were associated with nephrolithiasis, studies which include covariates, chronic co-morbidities and extended study material are necessary for making the study precise and conclusive.

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