Prevalence of Primary Hyperparathyroidism and Vitamin D Status Among Urinary Tract Stone Formers in Maiduguri, Nigeria.

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ABSTRACT

Background: A lot of attention has been drawn to primary hyperparathyroidism (PHPT) and vitamin D as risk factors of urolithiasis due to their association with calcium metabolism and stone formation. This study intends to assess the Vitamin D status of stone formers and prevalence of primary hyperparathyroidism amongst them in Maiduguri, Nigeria. A cross-sectional descriptive study was conducted in the University of Maiduguri Teaching Hospital from February 2018 to January, 2019. Eighty five stone formers who consented were recruited. ELISA technique and autoanalyzer (Cobas C311, ISN) was used for sample analysis. IBM SPSS version 26.0 was used for statistical analysis. The prevalence of PHPT in the stone formers was 8.2%. The most common site where stones were found is the kidney (68.2%). A total of 45 (52.9%) have vitamin D3 deficiency or insufficiency, 29 (34.1%) had optimal vitamin D3 levels and 1 (1.2%) had hypervitaminosis D3. Twelve patients had hypoalbuminemia, 24 patients had elevated inorganic phosphate, 8 patients had hypercalcaemia, 17 had hypocalcaemia, while 21 had hyperuricaemia. Given the high incidence of vitamin D deficiency/insufficiency in PHPT in this study and previous findings, evaluating vitamin D and calcium levels could be beneficial for a thorough assessment of urinary tract stone formers.

Keywords: Urolithiasis, Primary hyperparathyroidism, Vitamin D3 status.

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Introduction

The aetiology of nephrolithiasis is multifactorial, although hypercalciuria, detected in 30–60% of adults with nephrolithiasis[1,2] remains the most prevalent and consistent metabolic abnormality found in kidney stone formers. Increased urine calcium excretion in urinary tract stone formers was demonstrated in a previous study in Maiduguri.[3] Duvie et al[4] showed a higher incidence of urolithiasis in Maiduguri compared to other parts of Nigeria,[5] and nephrolithiasis remains a prominent health issue imposing significant burden to human health with a considerable financial expenditure.[6] Primary hyperparathyroidism is the most common cause of hypercalciuria in surveys,[7] hypercalciuria can also result from enhanced production of 1,25-dihydroxyvitamin D_3 (calcitriol), the active form of vitamin D.[8] Consequently, hyperparathyroidism and hypervitaminosis D_3 are cardinal in considering the aetiology of urinary tract stones. [8]

Although less than 1% of stone formers in the community setting have primary hyperparathyroidism, higher prevalence (1.65-13.3%) is encountered in referral centers. [9] In early series in developed countries, the incidence of urolithiasis in primary hyperparathyroidism was 80%, however, due to frequent medical checkup and

early diagnosis it has been reduced to 7 - 20% and usually those who developed stones have higher urinary calcium excretion. [10,11]

Patients with primary hyperparathyroidism typically form calcium complexes with phosphate, oxalate, or mixed calcium stones but approximately 80% of kidney stones contain calcium.[12] Similarly, a high percentage of calcium containing urinary tract stones (77%) was demonstrated in a previous study in Maiduguri.[3] Currently in Maiduguri analysis of parathyroid hormone or vitamin D_3 has not been institutionalized as part of routine evaluation of urinary stone formers and there is little evidence that the two disorders have been established as the causes of urinary tract stone in Nigeria and Africa at large. Hence, this study determines prevalence of primary hyperparathyroidism and hypervitaminosis D_3 in urinary stone formers in this environment.

Methods

A prospective cross-sectional descriptive study was conducted in the Departments of Chemical Pathology, Surgery and Medicine, University of Maiduguri Teaching Hospital, Maiduguri, Nigeria over a period of 12 months (February, 2018 to January, 2019). Maiduguri is a cosmopolitan city with temperature ranges between 31^{o}C and 43^{o}C; with 43^{o}C in most parts of the year, **(www.bornostate.gov.org).**

Patients attending Urology unit of Surgery Department, University of Maiduguri Teaching Hospital who are diagnosed with urinary tract stone disease, consented to participate in the study. Due to financial constraints, we recruited two patients per week (the first two who consented, without consideration of gender or age). Ten milliliters (10ml) venous blood was collected aseptically with minimal stasis and allowed to clot at room temperature. The samples were centrifuged at 5000 revolutions per minute (rpm) for 10 minutes. Serum for vitamin D_3 and parathyroid hormone were extracted and stored at -20^{o}C for batch analysis. Other parameters such as calcium, albumin and inorganic phosphate were analyzed immediately.

Standardized and validated ELISA technique was used for the estimation of both Intact-Parathyroid hormone and Vitamin D (25(OH)D3) using the technique as described by Monobind Inc., USA (Accu-Bind, 100 North Pointe Drive, Lake Forest, California 92630 USA). Based on the instructions of the manufacturer, PTH is said to be raised when the value is ≥94ng/ml. This cut off value was used in this study because there are no local reference values established in this locality. The rest of the parameters were analyzed using the autoanalyzer (Cobas C311, ISN, Roche, Germany) in the Department of Chemical Pathology UMTH. The data generated in this study was analyzed using IBM SPSS version 26.0. The results were expressed in charts, tables, means and simple percentages.

Results

A total of 85 patients were recruited, 23 (27%) females and 62 (73%) males, with a male: female ratio of 2.7: 1. Seventeen (20%) are children ≤ 18 year, including a 2-year-old child, while 68 (80%) were adults. Those in the 21-30-year-old age group constituted the majority, followed by children less than 10 years old; with 65 (76.5%) being aged 50 years and below. The commonest site of stone formation in the study patients is the kidney (68.2%), more on the right than the left and bilateral in 6.9%. in 11 (12.9%), the stones were found in the ureter, more on the left than right, 11.8% was found in the bladder and 2.4% in the urethra.

Thirty (35%) of the subjects studied had raised PTH; 18(60%) of them being males with a male: female ratio of 1:1.5. Two of those with raised PTH were below 10-years old, majority were between 20 and 50 years old with a surge between 61-70years. Among the 30 patients who had raised PTH, 7 had hypercalcaemia, 23 had normocalcaemia, while none had hypocalcaemia.

Table 2 and 3 showed how serum concentration of 25 (OH) D_3 is categorized according to the manufacturer. Using this categorization 45 (52.9%) either had vitamin D_3 deficiency or insufficiency, 29 (34.1%) had optimal vitamin D_3 level and 1 (1.2%) had hypervitaminosis D_3, though 5 (5.9%) had upper normal and 5 (5.9%) had overdose values. Twenty (66.7%) patients with raised serum PTH had deficient/insufficient serum vit D_3 and 5 (16.7%) had optimal values and 1 (3.3%) had hypervitaminosis D_3. Hypovitaminosis D_3 is common among patients with raised PTH (66.7%) compared to the total number of patients (53.0%).

Only 12 of all the patients studied had hypoalbuminaemia, five of whom had raised PTH. 24 patients had elevated inorganic phosphate, 21 had hyperuricaemia, 29 had urea above upper limit of normal but only 8 had values >10 mmol/L, 12 patients had raised creatinine. 10 patients had simultaneous increased inorganic phosphate, uric acid, urea and creatinine with various degrees of increases. Out of these, 7 had urea above 10 mmol/L and double upper limit of serum creatinine, 3 of whom had raised PTH among who 1 had hypervitaminosis D_3. Seven (7) patients are likely to have some degree of renal insufficiency, due to increased calcium and raised parathyroid hormones levels

Table 1: Sites of stone formation among patients studied

Sites	Frequency (%)		Frequency (%)
Renal	58(68.2%)	Rt	31(53.5%)
		Lt	23(39.7%)
		Bilateral	4(6.9%)
Ureter	11(12.9%)	Rt	5(45.5%)
		Lt	6(54.5%)
Bladder			10(11.8%)
Urethra			2(2.4%)
Site not identified			4(4.7%)

Table 2: Classification of vitamin D_3 status by values (based on manufacturer's instruction)

Vitamin D values(ng/ml)	Status
≤20	Vitamin D deficiency
21-30	Sub-optimal (Insufficiency)
31-50	Optimal
51-70	Upper normal
71-150	Over-dose but not toxic
>150	Hypervitaminosis

Table 3: Showing distribution of vitamin D_3 status among all patients and patients with raised PTH

Vitamin D_3 Categories(ng/ml)	Deficiency ≤20	Insufficiency 21-30	Optimal 31-50	Upper normal 51-70	Overdose (Not toxic) 71-150	Hypervitaminosis D_3 >150
All patients (85)	25 (29.4%)	20 (23.5%)	29 (34.1%)	5 (5.9%)	5 (5.9%)	1 (1.2%)
Patients with PTH ≥94ng/ml (30)	12 (40.0%)	8 (26.7%)	5 (16.7%)	2 (6.7%)	2 (6.7%)	1 (3.3%)

Table 4: Distribution of biochemical parameters analyzed in the study

Variables	All patients studied			Patients with PTH ≥94ng/ml		
	Decreased	Normal	Raised	Decreased	Normal	Raised
Alb	12	73	0	5	25	0
Inorg. phosphate	0	61	24	0	22	8
Uric acid	0	64	21	0	26	4
Urea	0	56	29	0	22	8
Creatinine	0	73	12	0	24	6

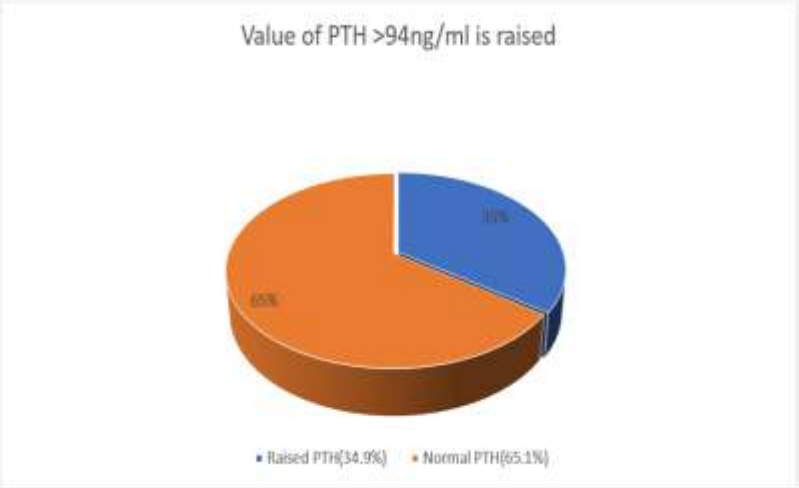

Fig 1: Showing percentage of patients with PTH ≥94ng/ml (raised)

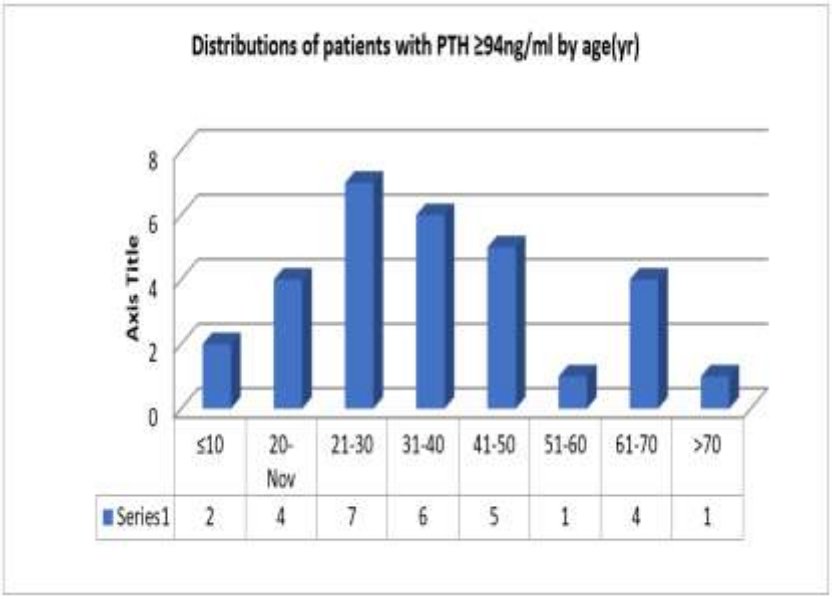

Fig 2: Age ranges (years) Distribution of patients with raised PTH (≥94ng/ml)

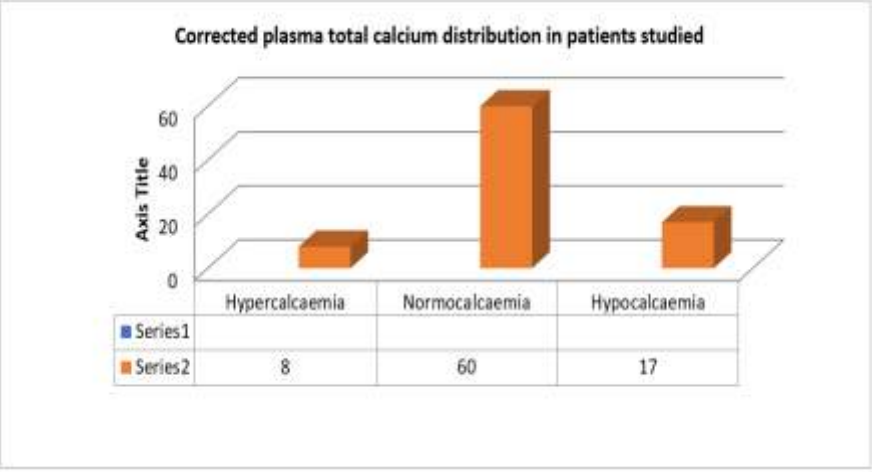

Fig 3: Plasma total calcium distribution among patients studied

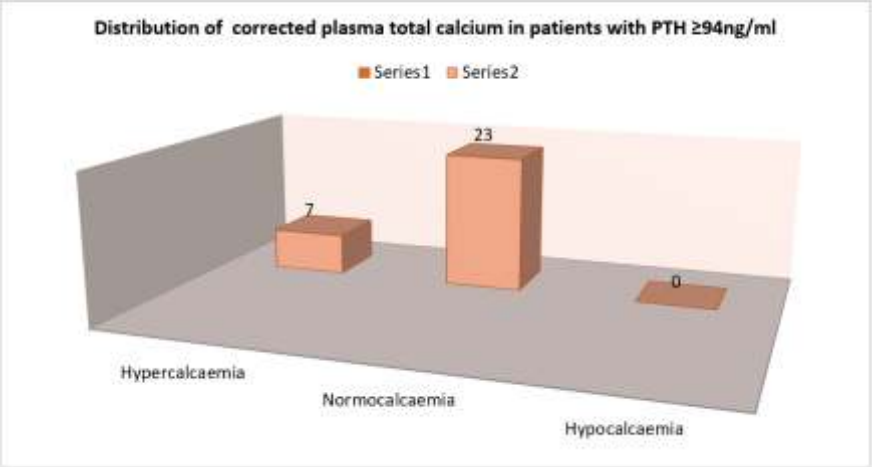

Fig 4: Distribution of plasma total calcium among patients with raised PTH (≥94ng/ml)

Discussion

Primary hyperparathyroidism is one of the most common causes of hypercalcaemia and should be considered in individuals with elevated serum calcium level; therefore, unless another cause of the hypercalcemia is obvious, the first step is the measurement of serum PTH. High values of PTH in the presence of hypercalcaemia confirms the diagnosis. A total of 85 patients were recruited with a male: female ratio of 2.7:1. A male preponderance was also noted in a study in Nigeria,[13] with male: female ratio of 6.1:1 and a ratio of 4.93:1 was noted in Iran,[14] 2:1 in Ghana,[15] 2.4:1 in Germany, [16] 2.5:1 in Iraq,[17] and 5:1 in Saudi Arabia.[18] A kidney stone typically affects men approximately 2 to 3 times more frequently than women.[19] This may be attributed to the fact that African men are more engaged in outdoor as well as physical activities than their female counterparts. Restricted water intake, dehydration, reduced urine volume during the physical activities and dietary habits leading to hyper crystalluria and calculi formation may suggest the increased tendency of renal stone disease in this environment similar to reasons suggested in the United Arab Emirates and Saudi Arabia.[20]

In this study 20% of patients were aged ≤ 18 years, similar findings were noted in many studies where children accounted for 2-10% in developed countries [21] but can be as high as 15% in developing countries.[22] Generally, children are engaged in labour work more often assisting their parents in this environment. In Poland, however, 23-43% of children with urolithiasis are younger than 1 year of age.[21,22] In young children, the disease is usually a result of congenital/genetic or acquired metabolic defects associated with hyper crystalluria (hypercalciuria, hyperuricosuria, hyper phosphaturia, hyperoxaluria, cystinuria, distal renal tubular acidosis, familial hypomagnesaemia with hypercalciuria and nephrocalcinosis, or Lesch-Nyhan syndrome). Another significant risk factor in children is a urinary tract defect with urinary retention.[23]

Several uncommon genetic disorders also cause hyperparathyroidism, patients with familial hypocalciuric hypercalcaemia type 1 (an autosomal dominant condition that produces PTH-dependent hypercalcaemia) have heterozygous loss-of-function mutations in the calcium sensing receptor and lifelong modest elevations in serum calcium with low calcium excretion in the urine.[24]

These patients generally do not require treatment. Hyperparathyroidism due to four gland hyperplasia is seen in multiple endocrine neoplasia type 1 and 2 syndromes.

However, PHPT is usually uncommon among children and adolescents; when it occurs, the levels of calcium in serum are often higher and germ line mutations more frequently than among adults.[25]

49.4% of patients were between 21 - 50 years (the most productive age group) which is similar to Trinchieri [26] study who found the highest incidence

to be between the age of 20 and 40years. A study in Nepal found 71.9% to be 60 years and below. [19] Similarly, Gadzama noted in Kano that stones were rare in patients older than 65years. [13] There is generally more involvement of the most productive age group in kidney stone formers, particularly in the developing countries.

In this study the commonest site of stone is the kidney (68.2%), more on the right than the left and was bilateral in 6.9%, a significant property of primary hyperparathyroidism and ureteric stone was found in 12.9%. This concurs with the study in Nepal [19] where kidney stone constituted 68.7% and ureteric 13.6%. However other studies found ureteric stone accounting for up to 20% while bladder stone only 1.7% compared to 11.8% in this study.

Gadzama in Kano, [13] found lower urinary tract to be the commonest site accounting for 55.7% (bladder stone accounting for 38.6% and ureteric lithiasis 21.4%) while the upper tract 44.3%. This contrasts with the findings in this study and that from Nepal. [19] Also, where stones are detected early, upper tract stones are more, the incidence of upper urinary tract stone disease has increased steadily in most countries over the past 100 years. [27] Urinary tract Infection (UTI) also contributes significantly to factors causing lower tract stones.

30(35%) of the subjects studied had raised PTH, 12 were females and 18 were males. Seven (8.2%) also presented with hypercalcemia, 23 (27.1%) had normocalcaemia. Primary hyperparathyroidism is considered to be present when serum calcium is elevated and PTH is increased or inappropriately normal. Therefore, in this study the prevalence of primary hyperparathyroidism is 8.2%. This is similar to the 7% noted by Sunil Kota *et al*., in 2013. [28] The routine evaluation of serum biochemistry in the developed countries has led to the origin of a new entity, 'asymptomatic normocalcaemia hyperparathyroidism', thus representing a change in the clinical spectrum of hyperparathyroidism. [29] Therefore, primary hyperparathyroidism in this study appears to be more than the 8.2% stated above because a raised PTH in the presence of normocalcaemia may also be considered as primary hyperparathyroidism. This is reported in 27.1% of patients studied similar to findings in Pakistan 21.88% [30] and Saudi Arabia (23.9%). [31] Patients with normocalcaemia hyperparathyroidism are not spared the renal complication of the disease. [32] In the past, PHPT was characterized by severe skeletal and renal complications and apparent mortality. This is still the case in many developing countries including Nigeria, [33-35] because there is a dearth of published reports of PHPT in asymptomatic patients in Nigeria. In the developed countries the prevalence of stone disease has declined from around 80% in early series to 7-20% in more recent series [36] and more than 80% of patients with primary hyperparathyroidism present with vague constitutional and nonspecific symptoms suggestive of asymptomatic primary hyperparathyroidism as the developed countries have moved from a clinical diagnosis to a chemical diagnosis because of the availability of routine serum chemical screening. [36] Although renal stone disease is considered a less frequent complication of primary hyperparathyroidism by some investigators, particularly those in developed countries, others have reported that up to 75% of patients undergoing surgical treatment for primary hyperparathyroidism present with nephrolithiasis.[37] This emphasizes the importance of screening for primary hyperparathyroidism in every patient diagnosed with urinary tract stone disease.

A high or even inappropriately normal value of PTH in the presence of hypercalcaemia confirms the diagnosis of Primary hyperparathyroidism. Hypercalciuria, consequent to hypercalcaemia, is a common finding in primary hyperparathyroidism, observed in up to 30% of patients, and has been implicated in the formation of renal stone. Subsequently, nephrolithiasis and nephrocalcinosis remain the most frequent complication of PHPT, occurring in about 20% of the patients and among patients with urinary tract stones PHPT is classified as the cause of stone formation in about 3% to 8% of the cases. In recent series however, stone disease is registered in 20% to 30% of the cases referred for surgery. [38] Primary hyperparathyroidism is a well-known risk factor for urolithiasis and nephrocalcinosis and urolithiasis is considered to be the most common presentation of the disease. Furthermore, there was a 10-fold increase in the prevalence of PHPT among patients with urolithiasis following the recommendation of

Albright to routinely measure serum calcium in patients with kidney stones. [39] Interestingly, although the reported prevalence of urolithiasis has increased over the last decades in the general population, [40] it is less commonly reported among patients with PHPT in recent times due to early detection of hypercalcaemia as a result of routine biochemical measurement of serum calcium by auto-analyzers in the Western population that detects asymptomatic patients with PHPT. [41] However, unlike in the Western countries, report from India still showed a persistently higher prevalence (20-30%) of urolithiasis in patients with PHPT. [42]

Nevertheless, PHPT is the only surgically correctable risk factor among the various predisposing factors for urolithiasis, and unless treated, may contribute to recurrent urolithiasis and renal failure. [43]

Urolithiasis is a recurring disease. In a study, recurrence is identified within 5 years in 50% of patients and within 10 years' recurrence occurred in 80-90% of patients. The younger the patient at diagnosis, the greater the risk of recurrence, almost 100% risk for recurrence stone formation, [44] the more frequent the complications, and the more difficult the treatment. Appropriate evaluation, including routine screening for hypercalcaemia and PTH estimation should be necessary to reduce recurrence. Subsequently, one strategy to reduce the recurrence rate is to screen for primary hyperparathyroidism. Patients with kidney stones and PHPT classically present with hypercalcaemia and hypercalciuria, which raised the risk for stone formation by increasing urine supersaturation for calcium oxalate or phosphate.

Also, lack of PTH testing in patients with kidney stones and hypercalcaemia in this environment suggests that clinicians are missing an opportunity to prevent recurrent kidney stones by diagnosing and treating PHPT despite the guidelines by the American Urological Association and European Association of Urology that recommend PTH testing. Also, patients with recurrent nephrolithiasis and nephrocalcinosis may develop urinary tract obstruction, infection, and loss of renal function. [45]

The implication of not doing routine screening for hypercalcaemia of all medical cases in Nigeria and other low-income countries, is that many patients who have PHPT remain undiagnosed until they present with nephrolithiasis as a complication. Another implication of the under-diagnosis is that the medical community may falsely be laying claim that PHPT is a rare endocrine disorder. Primary Hyperparathyroidism may not, after all, be a rare endocrine disorder in Nigeria. Under-diagnosis as well as underreporting may be responsible for its apparent rarity in Nigeria and other low/middle income countries. There is need to encourage laboratory services in Nigeria for screening of hypercalcaemia in all medical cases. Thus, PHPT may be reduced in Nigeria like in USA, Canada and Europe.

Vitamin D is acquired both through nutritional means (10-20%) and by the cutaneous synthesis under the action of sunlight (80-90%). Serum $25(OH)D_3$ is considered the best marker for assessing vitamin D status and said to be reliably reflecting the free fractions of the vitamin D metabolites. A range of below 75nmol/L (30ng/ml) of serum/plasma 25(OH)D concentration is considered vitamin D deficiency by most authors. However, the clinical practice guidelines of the Endocrine Society Task Force on Vitamin D [46] have defined a cutoff level of 50nmol/L (20ng/ml) as vitamin D deficient. Worldwide, many countries report very high prevalence of low vitamin D status including Nigeria. [47] Vitamin D ($25(OH)D_3$ levels<30nmol/L(12ng/ml) in >20% of the population are common in India, Tunisia, Pakistan, Afghanistan, including Nigeria. For example, about 490 million individuals are vitamin D deficient in India. [48]

Reports of vitamin D overdose are rare in the literature. Serum $25(OH)D_3$ usually exceeds 375nmol/L(150ng/ml), and factors such as high-calcium intake contribute to the risk of hypercalcaemia. [49]

Forty-five (52.9%) of patients studied either have vitamin D_3 deficiency or insufficiency compared with 66.7% of the 30 patients with raised serum PTH had vitamin D_3 deficiency or insufficiency and only 16.7% had optimal value. Vitamin D deficiency may be associated with a worsening primary hyperparathyroidism due to loss of the regulatory effects of 1,25-dihydroxyvitamin D_3 on the PTH gene and also frequent conversion of $25(OH)D_3$ to

$1,25(OH)_2D_3$ which has a short half-life. In addition, high circulating plasma PTH level decreases plasma 25-OHD by increasing metabolic clearance of 25-OHD via increased faecal excretion of vitamin D products. The association between hypersecretion of PTH in PHPT patients, with hypovitaminosis D causing normocalcaemic PHPT, has opened new possibilities for regional differences in the clinical manifestation of PHPT, which is linked to the prevalence of vitamin D_3 deficiency in the general population of that region. Similar reports with high prevalence of vitamin D_3 deficiency were noted in India, Pakistan and Jordan. [50,51] Due to the significant prevalence of vitamin D deficiency/insufficiency in individuals with PHPT, it is desirable to measure vitamin D_3 in all these patients and treating those with low levels, prior to making any management decisions regarding hyperparathyroidism. Concomitant vitamin D deficiency masks hypercalcaemia, related to elevated PTH levels, thus leading to a delay in diagnosis. Therefore, hypercalcaemia must not be used alone as a screening tool for PHPT. In addition, long-standing vitamin D deficiency may cause hyperplasia and/or adenoma of parathyroid glands due to PTH dysregulation. [52]

Efforts to correct this deficiency by vitamin D replacement in the face of hypercalcaemia and/or hypercalciuria can be risky. Normocalcaemia was said to be attributed by concomitant vitamin D deficiency, as population in Pakistan has a high prevalence of vitamin D deficiency/insufficiency, and it could be attributable to the similar findings in Saudi Arabia and this study. A study in Kano, Nigeria, found high prevalence of vitamin D_3 deficiency/Insufficiency (41.9%) among the general population. [47]

Missing a diagnosis of PHPT in patients with kidney stones is consequential for 2 reasons. First, thiazide and thiazide-type diuretics are commonly used to treat hypercalciuria, but they can increase plasma calcium concentration, particularly in patients with PHPT, and should not be used in these settings. Secondly, a diagnosis of PHPT is typically associated with parathyroidectomy, the definitive treatment that reduces urinary calcium excretion and risk of stone recurrence.[53] More broadly, parathyroidectomy in PHPT is associated with improved skeletal, cardiovascular, and neuropsychiatric outcomes. These advantages motivated the American Association of Endocrine Surgeons guideline recommendation that patients with kidney stones and biochemical evidence of PHPT be referred for parathyroidectomy.

Some of the limitations of this study include its sample size, single-center design, cross-sectional study design without longitudinal follow-up, and lack of control over factors that influence vitamin D status, such as vitamin D intake through diet and supplementation.

Conclusion

In conclusion, the outcomes of this study underscore the significance of promoting awareness regarding primary hyperparathyroidism (PHPT) screening as a pivotal approach for mitigating kidney stone formation and other complications stemming from hyperparathyroidism (HPT). Elevating consciousness regarding the magnitude or frequency of elevated serum calcium levels might correlate with heightened rates of parathyroid hormone (PTH) testing among individuals afflicted with kidney stones. Enhanced screening protocols for PHPT have the potential to augment detection rates and treatment interventions for PHPT, while concurrently diminishing the recurrence of stones linked to undetected or untreated PHPT.

Declarations

Ethical approval and consent to participate - Ethical approval was obtained from the Ethical Committee of the University of Maiduguri Teaching Hospital, Maiduguri, Borno State Nigeria. Also, all the participants consented to take part in the study.

Availability of data and material - available

Competing interests – No competing interests to declare.

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