ORIGINAL ARTICLE

Serum vitamin D levels among immunoglobulin A nephropathy patients and the associated parameters

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ABSTRACT

Introduction: Low serum 25-hydroxyvitamin D is associated with chronic kidney disease progression, and there are limited data on the vitamin D levels in patients with Immunoglobulin A nephropathy. This study was conducted to determine the level of 25-hydroxyvitamin D in a stable immunoglobulin A nephropathy patient and its association with other parameters.

Materials and Methods: We performed a cross-sectional study involving 70 patients with biopsy-proven immunoglobulin A nephropathy with a stable estimated glomerular filtration rate and urinary albuminuria. Their demographic profiles were documented, and blood samples were taken for serum 25-hydroxyvitamin D, highly sensitive C-reactive protein, urine albuminuria and other routine blood tests.

Results: We found nine patients (12.9%) had sufficient 25-hydroxyvitamin D [25(OH)D] levels of more than 30ng/mL and the rest of the patients; 61 (87.1%) had serum 25(OH)D levels below 30 ng/ml. Amongst those with low vitamin D, 38 (62.3%) had serum 25(OH)D between 15–30 ng/mL (insufficient), and the remaining 23 (37.7%) had serum 25(OH)D below 15 ng/ml (deficient). Their mean level of serum 25(OH)D was 19.92 ± 9.04 ng/mL with a serum creatinine of 106.23 ± 38.56 µmol/L and mean estimated glomerular filtration rate (eGFR) at 68.11± 27.65 mL/min/1.73 m^2. There was no association between urinary albuminuria, highly sensitive C-reactive protein, estimated glomerular filtration rate or systolic blood pressure with serum 25(OH)D level.

Conclusion: Low vitamin D (insufficiency and deficiency) are indeed prevalent in stable immunoglobulin A nephropathy patients. We found no correlation between the vitamin D levels with albuminuria, renal function and highly sensitive C-reactive.

KEYWORDS:
25-hydroxyvitamin D; vitamin D insufficiency; vitamin D deficiency; immunoglobulin A nephropathy; urine albumin creatinine ratio

INTRODUCTION

IgA nephropathy (IgAN) was first described in 1969 and is one of the most common forms of glomerulonephritis in many countries. In Asia, it accounts for approximately 30–40% of patients undergoing renal biopsy compared to 15–20% in Europe, and 5–10% in North America.[1] In Malaysia, the report from 6th Malaysian Registry of Renal Biopsy 2017 showed that IgAN is the third commonest primary glomerulonephritis at 23.3% after minimal change disease and focal segmental glomerulosclerosis, which contributed about 29.2% and 29.8%, respectively.[2] IgAN is defined histologically by the presence of glomerular immunoglobulin A (IgA) deposits accompanied by a variety of histopathology lesions.

Therefore, the pathogenesis of IgAN appears to be due to mesangial deposition of IgA, causing activation of the mesangial cells. In human, IgA is produced in two forms, IgA1 and IgA2, and is secreted from different mucosal surfaces. There is emerging evidence showing a molecular abnormality in IgAN patients that involves defects in glycosylation of the IgA1 hinge region. Bindings of IgA to mesangial cells are associated with mesangial cells expansion, apoptosis and increased synthesis of extracellular matrix components that can further potentiate glomerular injury. It does also activate complement to enhance the inflammatory cascade and potentiate further glomerular injury in IgA nephropathy.

Vitamin D has been shown to express non-calcaemic effects which are beyond the regulation of calcium and phosphorus. These effects are mediated by the vitamin D receptor (VDR), which includes the regulation of kidney and cardiovascular functions as well as immune systems. Studies have shown that low level of serum 25-hydroxy-vitamin level [25(OH)D] has been significantly associated with a severe decrease in estimated glomerular filtration rate (eGFR) in chronic kidney diseases (CKD).[3,4] Indeed, Framingham study also showed vitamin D deficiency is associated with cardiovascular diseases, and it has consistently shown that vitamin D deficiency increases the risk of myocardial infarction, and independent of classical risk factors such as diabetes and hypertension.[5] Nutrition Examination Survey (NHANES III) cohort showed that individuals with serum 25(OH)D levels lower than 15 ng/ml had a higher risk for all-cause mortality despite adjustments for potential confounders.[6]

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An interesting finding is that vitamin D also has a role in protecting the podocytes in the kidney glomerular and downregulate the renin-angiotensin-aldosterone-system (RAAS).[7] Podocytes were found to express VDR, and experimental animal studies showed that vitamin D has a renoprotective function in the podocytes.[8] These findings can potentially bring the therapeutic value of vitamin D therapy in IgAN, focussing on podocytes and mesangial cell regulation. Clinical studies by Szeto and Liu have shown that supplementation of calcitriol, a vitamin D analogue have been proven beneficial in reducing proteinuria in IgAN.[9,10] With this understanding, it would be interesting to explore the vitamin D levels in IgAN patients and potentially to understand the effect of 25(OH)D therapy in these group of patients. To date, limited studies are exploring issues as mentioned earlier. Therefore, we embarked in this study to evaluate vitamin D levels in a stable IgAN and to correlate the findings with other clinical parameters.

MATERIALS AND METHODS

Biopsy-proven IgAN patients were recruited from the Nephrology Clinic at Hospital Canselor Tuanku Muhriz (HCTM), Universiti Kebangsaan Malaysia Medical Centre (UKMMC). The Research and Ethics Committee, UKMMC approved the study with Research Grant (FF-2018-361). We included patients aged between 18 and 75 years with eGFR more than 30 ml/kg/1.73m^2, whom on a stable dose of immunosuppression and anti-proteinuric medications. Their urinary albumin creatinine ratio (UACR) is between 3 and 300 mg/mmol. We excluded those with active IgAN with nephrotic or nephritic syndrome, acute renal failure, chronic liver disease, malabsorption syndromes, uncontrolled diabetes with glycosylated haemoglobin (HbA1C) > 7.5%, granulomatous disease, pregnant or lactating women and patients who were on medications known to affect vitamin D absorption or metabolism.

The equation of CKD Epidemiology Collaboration (CKD EPI) 4 variables was used to measure eGFR during the study period. Ten millilitres of fasting venous blood were collected for measurement 25(OH)D, highly sensitive C-reactive protein (hs-CRP), and other routine blood tests. Urine was collected for urine dipstick, microscopy, and UACR.

Urinary Albuminuria Measurement and Definition

UACR is a ratio between urine albumin and urine creatinine. UACR was measured using Abbott Architect c8000 analyzer available in UKMMC pathology laboratory according to the manufacturer's protocol as described below. It is classified based on KDIGO CKD guideline 2012; normal to mildly increased (< 3 mg/mmol); moderately increased (3–30 mg/mmol) and severely increased (> 30 mg/mmol).

Serum 25-Hydroxyvitamin D Measurement and Definition

25(OH)D was measured using an electro-chemiluminescent immunoassay (ECLIA) with an Elecsys® Vitamin D total system (Roche Diagnosis Elecsys) according to the manufacturer's protocol. For analysis, 25(OH)D concentration was categorised based on current Kidney Disease Outcomes Quality Initiative guidelines (K/DOQI guidelines, 2003) as; sufficiency (> 30ng/mL); insufficiency (15–30ng/mL) and the deficiency (< 15 ng/mL).

Serum hs-CRP Measurement

Serum hs-CRP value was analysed using immune-turbidometry methods with hsCRP ELISA kits (EU59151) from Hamburg Germany by IBL International Gmb-H company according to the manufacturer's protocol.

Statistical Analysis

Data were analysed using the Statistical Package for Social Science (SPSS) software version 25. Continuous variables were reported as mean ± standard deviation. Categorical variables were reported as frequencies and percentages. To determine the difference between groups, the Pearson Chi-Square test was used for all categorical data. For continuous data, Independent t-test and paired t-test were used. Pearson correlation was used for correlation analysis. Multivariate analyses were performed using binary logistic regression. All statistical tests were two-sided, and an unadjusted p-value of <0.05 was considered significant.

RESULTS

Seventy patients were enrolled in our study, and their baseline demographic data were summarised in Table I. Nearly 88% of our patients were already on RAAS blockade as their treatment which concurred with the current guideline to use this agent as part of IgAN treatment. We found only 9 (12.9%) had sufficient 25(OH)D levels of more than 30ng/mL and the rest of the patients; 61 (87.1%) had serum 25(OH)D levels ≤ 30 ng/mL. Amongst those with low vitamin D (n=61), 38 (62.3%) of them had serum 25(OH)D between 15 and 30 ng/mL (insufficient) and the remaining 23 (37.7%) had serum 25(OH)vitamin D below 15 ng/mL. The mean level of 25(OH)D in this study was 19.92 ± 9.04 ng/mL.

The correlation between serum 25(OH)D and other parameters

In our study, we grouped patients according to the levels of 25(OH) D; > 30 ng/mL (sufficient), 15–30 ng/mL (insufficient) and < 15 ng/mL (deficient). We summarised the relationship between these three groups with their clinical parameters in Table II. There was no difference in their UACR, renal function, blood pressure and hs-CRP (Table II) in the various levels of serum 25(OH)D. Figure 1 illustrates those patients with sufficient 25(OH)D levels has lower UACR compared to those with low serum 25(OH)D levels (insufficient and deficient), but it was statistically not significant (p=0.25). Further analysis on the percentage of those with severely increased UACR (> 30 mg/mmol), there were no differences if we stratified them according to the degree of vitamin D levels (Figure 2). Fifty-six (80%) of our patients has hs-CRP above ≥1mg/ml that would indicate moderate to high risk of inflammation.

Serum 25(OH)D levels did not show any correlation with UACR, eGFR and hs-CRP, but interestingly it has a weak positive correlation with serum creatinine. Meanwhile, only systolic blood pressure (SBP) correlates with eGFR, serum creatinine and hs-CRP (Table III).

DISCUSSION

Vitamin D deficiency is highly prevalent among CKD patients. The prevalence of serum 25(OH)D deficiency in IgA nephropathy was less studied. Our study in this group of

Table I: Baseline characteristics of IgA nephropathy patients (n=?)

Age (years)	49.31 ±12.90
Sex (n, %)	
• Male	23 (32.9)
• Female	47 (67.1)
Race (n, %)	
• Malay	42 (60.0)
• Chinese	24 (34.3)
• Indian	4 (5.7)
Serum 25(OH)D (ng/mL)	19.92 ± 9.04
25-OHD (ng/mL), (n, %)	
-Sufficiency (>30 ng/mL)	9 (12.9)
-Insufficiency (15–30 ng/mL)	38 (54.3)
-Deficiency (<15 ng/mL)	23 (32.8)
UACR (mg/mmol)	74.30 ± 93.98
Albuminuria (n, %)	
-Moderately increased (3–30 mg/mmol)	27 (38.6)
-Severely increased (>30 mg/mmol)	43 (61.4)
Creatinine (µmol/l)	106.23 ± 38.56
eGFR (ml/min/1.73 m2)	68.11± 27.65
Serum albumin (mg/dl)	39.23 ± 3.31
Serum calcium(mmol/l)	2.37 ± 0.01
Serum hs-CRP (mg/ml), n (%)	3.41 ± 4.15
< 1	14 (20.0)
1–3	37 (52.9)
> 3	19 (27.1)
Treatment (n, %)	
• RAAS blockers	62(88.6)
• Immunosuppressant	28(40)

Data are presented as mean ± SD. UACR= urine albumin creatinine ratio, eGFR; estimated glomerular filtration rate; IgAN; IgA nephropathy; RAAS; renin–angiotensin–aldosterone system

Table II: The association between 25(OH)D level and other parameters

Variables	Serum 25-hydroxyvitamin (ng/mL)			*p* value
	>30 (n=9)	15-30 (n=38)	<15 n=23)	
Age (years)	59.00 ±15.19	48.39 ± 11.21	47.04 ± 13.46	0.13
Race (n, %)				
Malay	2(22.2)	24(63.2)	16(69.6)	
Chinese	7(77.8)	13(34.2)	4(17.4)	0.013
Indian	0 (0)	1(2.6)	3(13.0)	
Sex (n, %)				
Male	4(44.4)	13(34.2)	6(26.1)	0.59
Female	5 (55.6)	25(65.8)	17(73.9)	
UACR (mg/mmol)	67.81 ± 64.99	69.97 ± 74.45	90.59 ± 128.18	0.36
Serum albumin (mg/dl)	38.67 ± 2.29	39.68 ± 3.35	38.70 ± 3.59	0.27
Creatinine(µmol/l)	114.60 ± 30.09	111.46 ± 42.22	94.30 ± 33.23	0.41
Mean eGFR (ml/min/1.73 m^2)	57.11 ± 25.05	65.92 ± 26.64	76.04 ± 29.20	0.35
eGFR (n, %)				
CKD stage 1	2(22.2)	12(31.6)	11(47.8)	
CKD stage 2	1(11.1)	7(18.4)	4(17.4)	0.51
CKD stage 3	1(11.1)	7(18.4)	4(17.4)	
CKD stage 4	5(55.6)	12(31.6)	4(17.4)	
hs-CRP (mg/ml)	1.78± 1.84	3.56 ± 4.32	3.80 ± 4.49	0.38
hs-CRP (n, %)				
<1	4(44.5)	6(15.8)	4(17.4)	
1-3	2(22.2)	22(57.9)	13(56.5)	0.28
>3	3(33.3)	10(26.3)	6(26.1)	

UACR= urine albumin creatinine ratio, eGFR = estimated glomerular filtration rate, CKD= chronic kidney disease, hs-CRP= highly sensitive C-Reactive protein.

patients showed 87.1% of our IgAN patients had vitamin D levels ≤ 30ng/ml and only 12.9% were sufficient. This raised the concern of the possibility that low vitamin D is genuinely prevalent in our healthy population. Rozita et al. conducted a study in our institution to explore vitamin D levels among CKD patient compared to a healthy population, and she found 100% of the study participants including the healthy individuals had low serum 25(OH)D (< 30mg/dl).[11]

Nonetheless, Khor et al. who also studied the prevalence of vitamin D deficiency among Malaysians population demonstrated the prevalence of vitamin D insufficiency was

Table III: Pearson correlation coefficients between various parameters in IgAN patients

	25(OH)D	hs-CRP	SBP	DBP
UACR	r = -0.12; p=0.29	r = 0.25; p=0.83	r = 0.34; p=0.05	r = 0.14; p=0.24
eGFR	r = -0.28; p=0.18	r = -0.171; p=0.16	r = - 0.26; p=0.03	r = 0.10; p=0.40
Creatinine	r = 0.31; p=0.01	r = 0.17; p=0.16	r = 0.28; p=0.02	r = 0.23; p=0.85
hs-CRP	r = -0.15; p=0.22	-	r = 0.34; p=0.01	r = 0.14; p=0.24
25(OH)D	-	r = -0.15; p=0.22	r = -0.95; p=0.44	r = -0.83; p=0.49

UACR= urinary albumin creatinine ratio, eGFR= estimated glomerular filtration rate, hs-CRP= highly sensitive C-reactive protein, SBP- systolic blood pressure, DBP – diastolic blood pressure

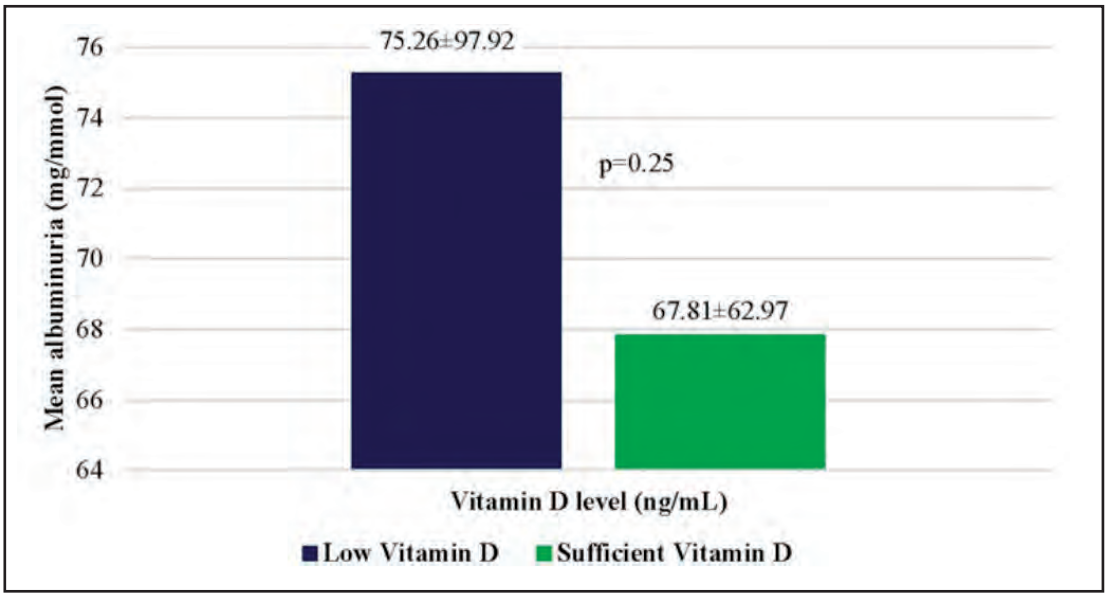

Fig. 1: Albuminuria levels between low vitamin D (< 30 ng/mL) and sufficient vitamin D (> 30 ng/mL)

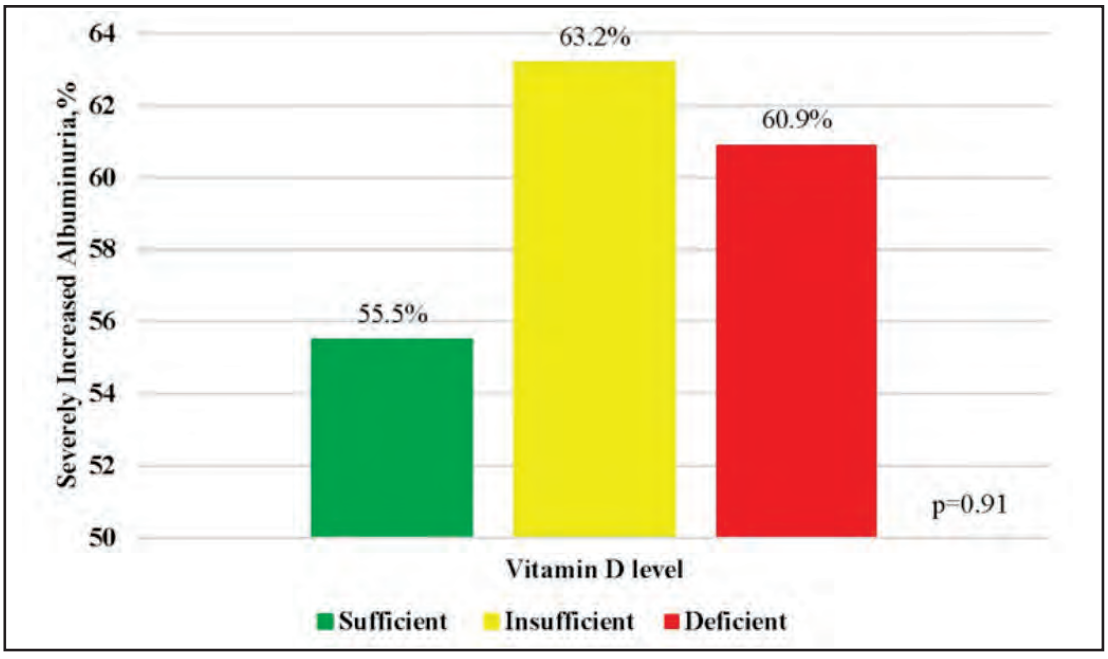

Fig. 2: Percentage of severely increased albuminuria amongst various groups of vitamin D levels

73% among obese primary school children aged 7–12 years old, whereas, Rahman et al. found in post-menopausal women aged 50 to 65 years showed significantly lower in the post-menopausal Malay women (71%) compared to Chinese (11%).[12,13] These are alarming evidence that the prevalence of low vitamin D is high in the general population. As expected, those with CKD also will be at risk, including those with IgAN.

Among the patients with different 25(OH)D levels, we found no significant differences in the severely increased albuminuria. This result is contrary to the previous study by Li et al. 2016, which showed there is an inverse correlation between vitamin D level and albuminuria.[14] Interesting to note in our study that those with low vitamin D (<30 ng/ml) compared to those with sufficient vitamin D levels (>30 ng/ml) showed no significant difference in the mean albuminuria levels; 75.26 ± 97.92 vs 67.81 ± 62.97 mg/mmol (p=0.25). This finding may suggest that the degree of vitamin D levels does not have any effects on the UACR in stable IgA nephropathy patients. Nonetheless, a study with a larger sample size would be needed.

Highly sensitive C-reactive protein (hs-CRP) serves as a marker for systemic inflammation, and it has emerged as the leading inflammatory marker in predictive ability importantly in coronary syndromes. Similarly, Want et al. showed that vitamin D deficiency is associated with incident cardiovascular disease.5 Several studies have also proposed vitamin D receptor (VDR) activation inhibits renal inflammation by promoting VDR-mediated sequestration of nuclear factor κB signalling.[15,16] There were studies which utilised hs-CRP as a marker of inflammation in IgAN; however, their results were inconsistent. Nelson et al. and Kaartinen showed increased hs-CRP levels in early IgAN, and it is a marker of kidney disease progression, but Baek et al. showed that hs-CRP was not elevated in IgAN.[17-19] In this study, we also measured hs-CRP as a biomarker of inflammation, and we found that 80% of our patients had hs-CRP of more than 1 mg/ml. Our result on hs-CRP concurred with Kaartinen at al. and Nelson et al.[17,18] Overall, the result indicates that generally, IgAN patients have increased systemic inflammation even though in our study population, their disease is in a stable state. These findings concurred with the notion that IgAN is an auto-immune disease and potentially also has an increased cardiovascular risk. Chronic inflammatory state in CKD patients is a topic of interest amongst many researchers. Mustafar et al.[20] also found raised hs-CRP in 70% of CKD patients with low serum 25(OHD). However, in this study population with IgAN, we did not find any significant association or serum 25(OH)D with the hs-CRP level.

Low level of serum vitamin D was consistently prevalent in CKD patients due to the reduced eGFR. However, in this study amongst the IgAN patients with mean eGFR > 60ml/min/1.73m^2, we found 87.1% had low serum 25(OH)D as well. A study by Li et al. suggested that the plasma 25(OH)D level at the time of initial diagnosis is a possible independent inverse-predictor of IgAN progression.[14] Another study also found that baseline level of 25(OH)D was significantly correlated with eGFR and showed an inverse correlation between the 25(OH)D level and proteinuria.[4] Additional to that, blood pressure showed an inverse relationship with 25(OH)D level in several epidemiological studies.[6,21] Our observation failed to show such correlations. We found there was no correlation among baseline eGFR, UACR, blood pressure, hs-CRP and 25(OH)D level. This could be due to our small sample size. SBP has shown a positive correlation with UACR, creatinine and hs-CRP. It showed a negative correlation with eGFR. These are the classical association that has been demonstrated by several kidney studies.

CONCLUSION

Our study has clearly shown the high proportion of low vitamin D in IgA nephropathy patients; however, we are not able to describe any significant correlation between the vitamin D levels with other parameters especially the albuminuria in this stable patient. The significance of low vitamin D in our patients may explain the chronic inflammatory state, and as shown in our result, 80% had serum hs-CRP of more or equal to 1mg/ml. It will be interesting to evaluate the effect of correcting low vitamin D levels in these patients' cohort and observing the improvement of disease progression indices. Given such a high prevalence of low vitamin D levels in our study population, our findings needed to be confirmed by another more extensive study. The effects of vitamin D replacement in reducing proteinuria will be interesting to explore, and it is beyond the scope of this paper.

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