

The frequency of vitamin D deficiency in chronic kidney disease and its relation with baseline mineral bone markers

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Abstract

Objective: To assess the frequency of Vitamin D deficiency in chronic kidney disease and its association with baseline mineral bone markers in patients visiting nephrology clinics.

Method: The observational study was conducted at the Indus Hospital, Karachi, from January 2017 to January 2018, and comprised patients of either gender aged >16 years diagnosed with chronic kidney disease stage I-V. The patients were divided into two groups on the basis of severity of vitamin D deficiency. Severe vitamin D deficiency was defined as <10ng/ml, and moderate deficiency as 10-25ng/ml. Data was analysed using SPSS 21.

Results: Of the 267 patients, 146(54.7%) were males and 189(70.8%) had vitamin D deficiency. Vitamin D-deficient patients were younger than those with normal levels ($p=0.044$). Serum creatinine was raised in the deficient patients compared to those with normal vitamin D level ($p=0.042$). Females and currently employed patients were at a higher risk of having vitamin D deficiency ($p=0.048, 0.009$). There was no significant association between disease stage and vitamin D deficiency ($p=0.311$).

Conclusion: Vitamin D deficiency was found in a significant proportion of chronic kidney disease patients irrespective of the disease stage. Females, currently employed and young patients were more prone to having vitamin D deficiency.

Keywords: CKD, Vitamin D deficiency, Mineral bone markers. (JPMA 70: 432; 2020).

<https://doi.org/10.47391/JPMA.0302411>

Introduction

Vitamin D (Vit-D) is acquired both through nutritional means (10-20%) and by the cutaneous synthesis under the action of sunlight (80-90%).¹ When we take vitamin D3/D2 (cholecalciferol / ergocalciferol) from dietary sources, it undergoes hydroxylation in the liver (25-hydroxyvitamin D; 25[OH]D) and subsequently undergoes hydroxylation in the kidney under the influence of 1- α hydroxylase enzyme to yield the biologically active, 1,25 dihydroxylated form of Vit-D. The second hydroxylation occurring in the kidney diminishes progressively with the loss of renal function to the limit where mineral bone disease manifestation starts. And this starts with low bone mass, bone fractures, vascular calcification and greater mortality.²

Vit-D deficiency has emerged as a pandemic.^{3,4} In a normal population, the prevalence of Vit-D varies between 30% and 90% in different studies.^{5,6} In the presence of such

high Vit-D deficiency prevalence in the normal population, chronic kidney disease (CKD) is an added factor to depress its level further as CKD patients are often anorexic and have increased pigmentation which cause decreased synthesis of vitamin D.⁷ The use of ergocalciferol / cholecalciferol has received relatively little attention because of an earlier held concept of the kidney as the only site of 1- α hydroxylation of calcidiol and, in the failure of that, serum 25(OH)D was of less value. Recent data suggests a potential role for 25(OH)D in a number of tissues irrespective of renal conversion.⁸

In clinical practice, the treatment of CKD patients is often suboptimal or not well-targeted. Many doctors and general practitioners use active Vit-D to treat mineral bone disease (MBD) in CKD patients irrespective of the stage of the kidney disease. This may be partly the right approach if the patient happened to be advanced CKD stage, but along with active Vit-D deficiency, there may be a deficiency of nutritional Vit-D (an inactive form of vitamin D) as well.⁹ In that case, nutritional Vit-D (cholecalciferol / ergocalciferol) should also be replaced after ensuring its

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level in serum. Another benefit of treating with nutritional Vit-D is providing more substrate for $1-\alpha$ hydroxylation not only in the diseased kidney, but in other sites of a body too.^{10,11}

In CKD, supplementation with 25(OH)D is recommended at the inception of the disease, with the addition of calcitriol replacement beginning in stage III.¹² By incorporating the role of nutritional Vit-D, we can reduce the cost of avoiding unnecessary use of active Vit-D which is not only costly, but also causes a dynamic bone disease if used inappropriately.

The current study was planned to assess the frequency of Vit-D deficiency in CKD and its association with baseline mineral bone markers.

Patients and Methods

The observational study was conducted at the Indus Hospital, Karachi, from January 2017 to January 2018.

After approval from the institutional review board, the sample size was calculated using OpenEpi software while assuming confidence interval (CI) of 95%, desired precision 6%, and the prevalence of Vit-D deficiency in CKD patients 50.8%.¹³ All patients aged >16 years of either gender with established CKD (pre-dialysis) on regular follow-up consenting to participate were included. All patients on

dialysis, with chronic liver disease, and already on Vit-D or calcium (Ca)-containing drugs or at least stopped such medications for the preceding one month were excluded. Detailed demographic and clinical history was obtained from each subject and general physical examination was conducted.

Routine renal and other biochemical investigations, including serum creatinine (mg/dl), serum calcium (mg/dl), serum phosphorus (mg/dl), serum alkaline phosphatase, intact parathyroid hormone (IPTH) level (pg./ml), Vit-D level, serum albumin (mg/dl), were carried out as per the standard method used in the biochemistry laboratory of the hospital. Estimated glomerular filtration rate (eGFR) was calculated using the four-variable modification of diet and renal disease (MDRD) equation. The patients were divided into two groups on the basis of severity of Vit-D deficiency. Severe Vit-D deficiency was defined as level <10ng/ml, and moderate deficiency as 10-25ng/ml.

Data was analysed using SPSS 21. Mean $\pm$ standard deviation (SD) / Median with interquartile range (IQR) were calculated, as appropriate, for quantitative variables age, height, weight, body mass index (BMI), serum albumin, serum calcium, serum phosphate, alkaline phosphate, and IPTH. Independent sample t-test / Mann-Whitney U test / Kruskal Wallis were applied, as

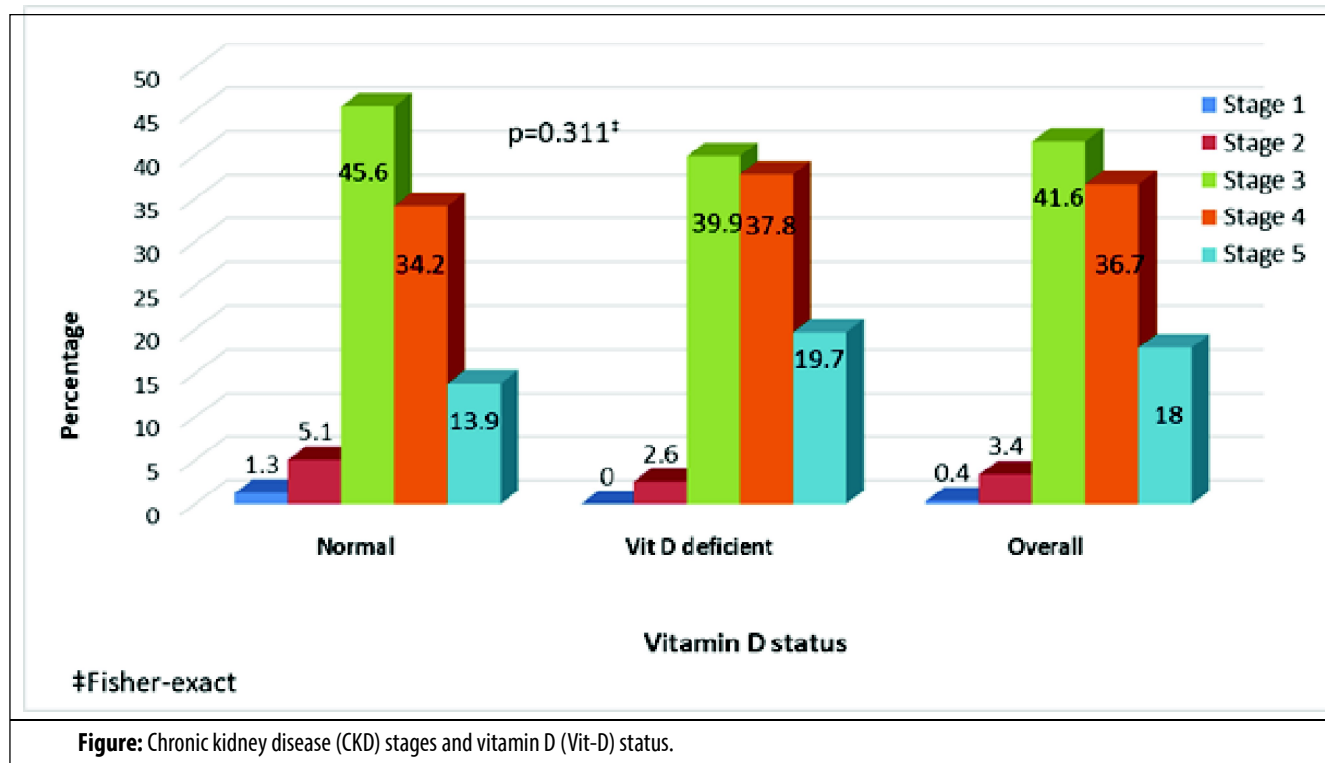


Table-1: Baseline characteristics of the study population.

	Vitamin D (Vit-D) Status						
	Normal (n=78)			Vit-D deficient (n=189)			
	Mean ± SD	Min-Max	Median (IQR)	Mean ± SD	Min-Max	Median (IQR)	p-value
Age (year)	55.52 ± 17.465	17 - 104	58 (51 - 67)	53.3 ± 13.9	15-91	54 (46.2-62.8)	0.044†
Height (m)	1.6 ± 0.16	1.2-1.8	1.6 (1.55 - 1.66)	1.8±1.9	1.22-19.8	1.6 (1.5-1.7)	0.410†
Weight (kg)	65.8± 17.6	36-102	64 (56-69)	63.6 ± 14.7	29-112	62 (54-72)	0.792†
BMI (kg/m2)	23. 3± 3.5	19.2-30.3	23.3 (19.9-24.8)	26.3 ± 7.6	11.4-52.9	25 (21-29.7)	0.276†
Serum Calcium (mg/dl)	9.3± 0.9	5.9-11.5	9.3 (8.8-9.9)	9.1 ±0.86	5.7-11	9.3 (8.6-9.6)	0.039*†
Serum Creatinine (mg/dl)	2.5 ± 1.3	0.78- 6.5	2.1 (1.7-3)	3 ± 1.8	0.8-13	2.4 (1.8-3.7)	0.042*†
Phosphate (mg/dl)	4.2 ± 0.98	1.7-8.1	4.1 (3.6-4.6)	4.2 ± 1.1	2.1-9.5	4.1 (3.5-4.7)	0.994†
Alkaline phosphate	131 ± 155	34-1172	101 (78-124)	131.9 ± 93.6	41-802	104 (80-142)	0.162†
Albumin (mg/dl)	3.9 ± 0.47	2.7-4.8	4 (3.7-4.3)	3.8 ± 0.6	1.2-4.9	3.9 (3.5-4.2)	0.023*†
IPTH (pg./ml)	108.1 ± 115.6	11.4-610	76 (43-119.5)	181 ± 165.2	13-1115	131 (72-233)	0.000***†

*p-value<0.05, **p-value<0.0001, †Mann-Whitney U test. IQR: Interquartile range; BMI: Body mass index; IPTH: Intact parathyroid hormone.

Table-2: Gender and occupation distribution.

	Vitamin D (Vit-D) Status		Total	OR (95%CI)	p-value
	Normal	Vit-D deficient			
Gender					
Female	28(35.4)	93(49.5)	121(45.3)	1.73 (1.01-3.0)	0.036*†
Male	51(64.6)	95 (50.5)	146(54.7)		0.048*†
Total	79 (100)	188(100)	267 (100)		
Occupation					
Working	5 (6.6)	36 (19.7)	41 (15.8)	3.4 (1.3-9.1)	0.009*†
Not Working	71 (93.4)	147(80.3)	218(84.2)		0.009*†
Total	75 (100)	184 (100)	259 (100)		

*P-value<0.05, **P-value<0.0001, † Chi-square test, † Logistic regression, OR: Odds ratio; CI: Confidence interval

appropriate, to assess the significant difference in quantitative variables between Vit-D and CKD stages. Chi-square / Fisher-exact tests were applied, as appropriate, to find significant association of various categorical variables, like gender, CKD stage, co-morbid, with Vit-D

Table-3: Distribution of comorbid between Vitamin D (Vit-D) statuses.

	Normal	Vit-D deficient	Overall	P-value
DM	33(41.8)	124(67.8)a	157(34.20)	0.000***†
HTN	54(68.4)	152(83.1)a	206(44.8)	
IHD	22(27.8)b	23(12.6)	45(9.8)	
Nephrolithiasis	12(15.2)b	11(6)	23(5)	
HCV	3(3.8)b	1(0.5)	4(0.87)	
HEP B	0(0)	1(0.5)a	1(0.2)	
Others	13(16.5)b	5(2.7)	18(3.9)	
No comorbid	3(3.8)	2(1.1)	5(1.1)	

*P-value<0.05, **P-value<0.0001, †Chi-square test

Results are based on two-sided tests with significance level .05. For each significant pair, the key of the category (a=DM, b=HTN, c=IHD, d=Nephrolithiasis, e=HCV, f=Hep B, g=others and h=No comorbid) with the smaller column proportion appears under the category with the larger column proportion.

DM: Diabetes mellitus; HTN: Hypertension; IHD: Ischaemic heart disease; HCV: Hepatitis C virus; EP B: Hepatitis B

status. P<0.05 was considered significant.

Results

Of the 267 patients, 146(54.7%) were males and 121 (45.3%) were females; 189(70.8%) were Vit-D-deficient and 78(29.2%) had normal Vit-D levels. Among the deficient patients, 106(56.1%) were severely deficient and 83(43.9%) were moderately Vit-D deficient. Vit-D deficient patients were younger than the patients who had normal Vit-D levels (p=0.044). In addition, Vit-D deficient patients had significantly low level of serum calcium (p=0.03), low albumin (p=0.02), high creatinine (p=0.04), and high IPTH (p<0.0001). There was no significant difference in height, weight and BMI between the groups (Table-1). Females and currently employed patients were at higher risk of Vit-D deficiency (Table-2). No significant association

Table-4: Comparison of Vit-D, IPTH and phosphate level among CKD stages.

	CKD stages				p-value
	Stage ≤2	Stage 3	Stage 4	Stage 5	
Vit-D					
Mean ± SD	21.8 ± 9.6	20.1 ± 18.1	18.8± 16.6	12.8±11.1	0.014*
Min-Max	7-33	3-131	3-70	3-38	
Median (IQR)	25.9 (13.5-31)	15 (8.7-28.2)	12 (6.5-29.8)	7.7 (3.6-21.2)	
IPTH (pg./ml)					
Mean ± SD	89.22± 63	96.7± 78.8	184.4± 169.5	267 ±196.6	0.000**
Min-Max	31-220	11-454	13-1115	58-962	
Median (IQR)	69(44-136)	71.5(43.7-119)	135(75-226)	207.5(134-314)	
Phosphate (mg/dl)					
Mean ± SD	3.93±0.64	3.92± 0.86	4±0.96	4.9±1.38	0.000**
Min-Max	3-4.7	2.4-8	1.7-6.6	2.4-9.5	
Median (IQR)	4(3-4.6)	3.8(3.4-4.4)	4.1(3.6-4.7)	4.9(4.2-5.6)	

**P-value<0.0001, Kruskal Wallis test, CKD: Chronic kidney disease;

SD: Standard deviation; IQR: Interquartile range; IPTH: Intact parathyroid hormone.

was observed in CKD stages and Vit-D deficiency ($p=0.31$). Majority of the patients had CKD stage III, followed by stage IV, stage V and stage I-II (Figure).

Overall, 206(44.8%) patients had hypertension, followed by diabetes 157(34.2%), while 5(1.1%) had no comorbid condition (Table-3). A higher proportion of diabetic and hypertensive patients were Vit-D-deficient compared to those with other co-morbidities ($p<0.05$). Patients with CKD stage IV and V had low Vit-D levels, high IPTH and phosphate levels (Table-4).

Discussion

Vitamin D is the major steroid hormone which ensures bone health in conjunction with calcium, phosphorus and IPTH. It helps in the absorption of calcium from the intestine and reabsorption from tubules of kidneys and in conjugation with calcium mobilisation from skeleton by IPTH.¹⁴ This delicate balance of Vit-D, calcium, phosphorus and IPTH is disturbed when CKD progresses and this leads to increased risk of not only bone disease but also cardiovascular disease.¹⁵

As part of the typical lifestyle, humans have a combination of vitamins D2 and D3 available from ambient ultraviolet (UV) rays, habitual dietary intake of vitamin D3-rich foods (egg yolks and oily fish), fortified foods like margarine and breakfast cereals which generally have vitamin D2 fortification.¹⁶ The prolonged deficiency of 1,25 dihydroxy vitamin D together with parathyroid abnormality leads to renal osteo-dystrophy (ROD) and CKD-mineral bone disorder (CKD-MBD), which can be manifested by any one or combination of abnormalities of calcium, phosphorus, PTH, and Vit-D metabolism, leading to increase in secondary hyperparathyroidism, bone disease, vascular or soft tissue calcification.^{9,17}

In the current study, hypertension was noted as the most common comorbid followed by diabetes, ischaemic heart disease, and nephrolithiasis. Furthermore, Vit-D deficiency was found to be more in diabetic and hypertensive patients. Comparing the results with an earlier study, diabetes came as not only the most common causative agent of CKD but Vit-D deficiency was also seen in higher proportion in diabetics than in non-diabetics.¹³ In our study, serum calcium and serum albumin were significantly lower in Vit-D deficient group but phosphorus and alkaline phosphatase didn't show a significant change in either group in the study. Also, Vit-D-deficient patients had higher creatinine and mean IPTH level.

Mean IPTH remained above normal in all CKD stages and was higher in stage V. This signifies the development of secondary hyperparathyroidism when nephron mass declines. Phosphorus level also increased with the severity of CKD. Deficiency of Vit-D was seen in significant proportion (70.8%) as we defined the cut-off level at $<25\text{ng/ml}$. This was further categorised as moderate deficiency ($10\text{-}25\text{ng/ml}$) and severe deficiency ($<10\text{ng/ml}$). In this way, we found 57% who came in the severe deficiency group. This finding was comparable with studies done in Italian and Indian populations.^{14,18} One study found 87% Vit-D deficiency.¹⁹

In the Indian population,¹⁸ active Vit-D was also checked and was found to be more deficient ($>90\%$ population) which we could not check in our population. Active Vit-D is supposed to be more declined in advanced CKD as it is activated in functional renal tissue. The best laboratory indicator of Vit-D adequacy is serum $25(\text{OH})\text{D}$ concentration.²⁰ The Vit-D level declined significantly as CKD progressed from stage III to stage V in our study which is similar to an earlier finding.¹⁴ Females were found to have a 1.7 times higher likelihood of being Vit-D-deficient compared to males in our study which was in line with literature.^{13,21,22}

Although Vit-D deficiency was significant in CKD population, if we compare it with the prevalence in the general population of Pakistan, the results are not surprising as more than 50% deficiency has already been seen in the general population.²³⁻²⁵ This fact is also highlighted by a study which did not find significant difference in Vit-D deficiency in between CKD patients and the normal population.²⁴ We observed that the Vit-D-deficient group was relatively younger than the normal Vit-D group, indicating that there is relatively decreased Vit-D production in the skin of the elderly compared to the young.²⁶ A study found no difference in the severity of Vit-D deficiency in terms of age. This might be due to decreased Vit-D consumption in food and relatively less sun exposure.²⁷

Conclusion

Vitamin D deficiency was found in a significant proportion in CKD patients irrespective of the disease stage. Females, currently employed and young patients were more prone to having Vit-D deficiency.

Disclaimer: None.

Conflict of Interest: None.

Source of Funding: None.

References

1. Holick MF. Evolution, biologic functions, and recommended dietary allowances for vitamin D. Totowa, NJ: Humana Press, 1999; pp 1-16.
2. Bischoff HA, Stahelin HB, Urscheler N, Ehrensam R, Vonthein R, Perrig-Chiello P, et al. Muscle strength in the elderly: its relation to vitamin D metabolites. Arch Phys Med Rehabil 1999;80:54-8.
3. Masud F. Vitamin D levels for optimum bone health. Singapore Med J 2007;48:207-12.
4. Malabanan A, Veronikis IE, Holick MF. Redefining vitamin D insufficiency. Lancet 1998;351:805-6.
5. Cannata-Andia JB, Rodriguez Garcia M, Gomez Alonso C. Osteoporosis and adynamic bone in chronic kidney disease. J Nephrol 2013;26:73-80.
6. Andress DL. Adynamic bone in patients with chronic kidney disease. Kidney Int 2008;73:1345-54.
7. Garland FC, Garland CF, Gorham ED, Young JF. Geographic variation in breast cancer mortality in the United States: a hypothesis involving exposure to solar radiation. Prev Med 1990;19:614-22.
8. Zisman AL, Hristova M, Ho LT, Sprague SM. Impact of ergocalciferol treatment of vitamin D deficiency on serum parathyroid hormone concentrations in chronic kidney disease. Am J Nephrol 2007;27:36-43.
9. Martin KJ, Gonzalez EA. Metabolic bone disease in chronic kidney disease. J Am Soc Nephrol 2007;18:875-85.
10. Rostand SG. Ultraviolet light may contribute to geographic and racial blood pressure differences. Hypertension 1997;30:150-6.
11. Williams S, Malatesta K, Norris K. Vitamin D and chronic kidney disease. Ethn Dis 2009;19(Suppl 5):S5-8-11.
12. Qunibi WY, Abdellatif A, Sankar S, Hamdan Z, Lin FY, Ingle J, et al. Treatment of vitamin D deficiency in CKD patients with ergocalciferol: are current K/DOQI treatment guidelines adequate? Clin Nephrol 2010;73:276-85.
13. Kim SM, Choi HJ, Lee JP, Kim DK, Oh YK, Kim YS, et al. Prevalence of vitamin D deficiency and effects of supplementation with cholecalciferol in patients with chronic kidney disease. J Ren Nutr. 2014;24:20-5.
14. Aggarwal HK, Jain D, Mittal A, Pawar S, Ver R. The prevalence of vitamin D deficiency in pre-dialysis patients with chronic kidney disease. Medical Studies 2015;2:75-81.
15. Heaf JG, Joffe P, Marckmann P. Vitamin d and stage 5 chronic kidney disease: a new paradigm? Semin Dial 2012;25:50-8.
16. Tripkovic L, Lambert H, Hart K, Smith CP, Bucca G, Penson S, et al. Comparison of vitamin D2 and vitamin D3 supplementation in raising serum 25-hydroxyvitamin D status: a systematic review and meta-analysis. Am J Clin Nutr 2012;95:1357-64.
17. Coen G, Ballanti P, Bonucci E, Calabria S, Costantini S, Ferrannini M, et al. Renal osteodystrophy in predialysis and hemodialysis patients: comparison of histologic patterns and diagnostic predictivity of intact PTH. Nephron 2002;91:103-11.
18. Cupisti A, Vigo V, Baronti ME, D'Alessandro C, Ghiadoni L, Egidi MF. Vitamin D status and cholecalciferol supplementation in chronic kidney disease patients: an Italian cohort report. Int J Nephrol Renovasc Dis 2015;8:151-7.
19. Gonzalez EA, Sachdeva A, Oliver DA, Martin KJ. Vitamin D insufficiency and deficiency in chronic kidney disease. A single center observational study. Am J Nephrol 2004;24:503-10.
20. Institute of Medicine (US) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride. Washington DC: USA, National Academies Press; 1997.
21. Del Valle E, Negri AL, Aguirre C, Fradinger E, Zanchetta JR. Prevalence of 25(OH) vitamin D insufficiency and deficiency in chronic kidney disease stage 5 patients on hemodialysis. Hemodial Int 2007;11:315-21.
22. Jean G, Charra B, Chazot C. Vitamin D deficiency and associated factors in hemodialysis patients. J Ren Nutr 2008;18:395-9.
23. Guessous I, McClellan W, Kleinbaum D, Vaccarino V, Zoller O, Theler JM, et al. Comparisons of serum vitamin D levels, status, and determinants in populations with and without chronic kidney disease not requiring renal dialysis: a 24-hour urine collection population-based study. J Ren Nutr 2014;24:303-12.
24. Riaz H, Finlayson AE, Bashir S, Hussain S, Mahmood S, Malik F, et al. Prevalence of Vitamin D deficiency in Pakistan and implications for the future. Expert Rev Clin Pharmacol 2016;9:329-38.
25. Masood Z, Mahmood Q, Ashraf KT. Vitamin D deficiency-an emerging public health problem in Pakistan. J Univ Med Dent Coll 2010;1:4-9.
26. MacLaughlin J, Holick MF. Aging decreases the capacity of human skin to produce vitamin D3. J Clin Invest 1985;76:1536-8.
27. Nadeem Saqib MA, Rafique I, Hayder I, Irshad R, Bashir S, Ullah R, et al. Comparison of vitamin D levels with bone density, calcium, phosphate and alkaline phosphatase - an insight from major cities of Pakistan. J Pak Med Assoc. 2018;68:543-7.