Retrospective Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
49(5) 1–8

DOI: 10.1177/03000605211012231
journals.sagepub.com/home/imr
SAGE

Relationship between serum vitamin D3 concentration and anaemia in patients with chronic kidney disease in China

Meng Li[1,2,#], Jun Xu[3,#], Qin Wan[4], Qiang He[5], Yan Ma[3], Ying-Qian Tang[6] and Hong-Ying Peng[3]

Abstract

Objective: In the present study, we aimed to investigate the relationship between serum vitamin D3 concentration and anaemia in patients with chronic kidney disease (CKD) in China, to assist understanding of the effects of vitamin D treatment in such patients.

Methods: A total of 225 patients with CKD were enrolled and a range of laboratory parameters were measured. The participants were allocated to three groups, according to their serum 25-hydroxyvitamin D3 concentration: a severe deficiency group, a deficiency group, and a sufficiency group. The prevalences of anaemia in the three groups were assessed, and the factors associated with anaemia in patients with CKD were analysed using logistic regression.

Results: The prevalences of anaemia were 79.5% in the severe deficiency group, 63.5% in the deficiency group, and 48.0% in the sufficiency group. The prevalence of anaemia gradually increased with the severity of vitamin D3 deficiency. The prevalences of anaemia in participants with stages 1 to 5 CKD were 21.1%, 30.4%, 39.5%, 78.7%, and 94.6%, respectively.

Conclusion: Vitamin D3 deficiency may increase the risk of anaemia in patients with CKD.

[1]Department of Pneumology, Bijie Hospital of Traditional Chinese Medicine, Guizhou, China
[2]Guizhou Medical University, Guizhou, China
[3]Department of Nephrology, Affiliated Baiyun Hospital of Guizhou Medical University, Guizhou, China
[4]Department of Nephrology, Qianxi County People's Hospital, Guizhou, China
[5]Department of Nephrology, Pingba County People's Hospital, Guizhou, China
[6]Department of Nephrology, Affiliated Hospital of Guizhou Medical University, Guizhou, China

[#]These authors contributed equally to this work.

Corresponding author:
Hong-Ying Peng, Department of Nephrology, Affiliated Baiyun Hospital of Guizhou Medical University, 108 Gangyu Street, Baiyun District, Guizhou 550004, China.
Email: phypeng78@163.com

Keywords
Chronic kidney disease, anemia, vitamin D3 deficiency, estimated glomerular filtration rate, parathyroid hormone, hemoglobin

Date received: 20 December 2020; accepted: 29 March 2021

Introduction

Vitamin D supplementation can ameliorate anaemia by increasing the expression of erythropoietin receptors, stimulating the production of erythropoietin, reducing the secretion of pro-inflammatory mediators, and increasing sensitivity to erythropoietin.[1–4] Therefore, vitamin D deficiency may increase the risk or severity of anaemia in patients with CKD. However, to date, few studies have examined the effects of vitamin D on CKD-associated anaemia around the world.[5,6] In the present study, we have determined the relationship between serum 25-hydroxyvitamin D3 (25 (OH) D3) and anaemia in patients with CKD to better understand the effects of vitamin D treatment such patients.

Methods

Participants

Patients were enrolled who had been diagnosed with stages 1 to 5 CKD in the Affiliated Hospital of Guizhou Medical University or Baiyun Hospital of Guizhou Medical University, both in China, between March 2017 and February 2018. All the participants provided their verbal informed consent. The study was approved by the Ethics Committee of the Affiliated Baiyun Hospital of Guizhou Medical University.

The exclusion criteria were: (1) a history of blood transfusion in the preceding 3 months because the life of a red blood cell is approximately 120 days; (2) the use of erythropoietin in the preceding month because it usually takes 2 to 6 weeks for the haemoglobin (Hb) concentration to rise after the use of erythropoietin; (3) the use of an active vitamin D3 preparation in the preceding 2 months because 25 (OH) D3 has a long half-life of up to 2 months; and (4) gastrointestinal bleeding or other acute blood loss in the preceding 2 months because Hb concentrations return to normal 6 to 8 weeks after the blood loss ceases.

Participant groups

Adult men with an Hb concentration of <130 g/L and adult women with an Hb of <120 g/L were assigned to an anaemia group, and adult men with an Hb of ≥ 130 g/L and adult women with Hb of ≥ 120 g/L were assigned to a normal group, according to the World Health Organisation (WHO) recommendations[7] According to the Application Guidelines for Vitamin D and Adult Bone Health,[8] participants with a serum 25 (OH) D3 concentration of <30 nmol/L were allocated to a severe deficiency group, those with a serum 25 (OH) D3 between 30 and 50 nmol/L were allocated to a deficiency group, and those with a serum 25 (OH) D3 of ≥ 50 nmol/L were allocated to a sufficiency group. Estimated glomerular filtration rate (eGFR) was calculated as $186 \times (\text{serum creatinine concentration}) - 1.154 \times \text{age}$ (years) $- 0.203$ ($\times$ 0.72 for women).

Statistical analysis

Quantitative data are summarised as means and standard deviations. Differences in normally distributed quantitative data between groups were analysed using Student's *t*-test and non-normally distributed quantitative data were analysed using Wilcoxon's rank sum test. Categorical data are described as rates or proportions and were compared using the chi-square test. $P < 0.05$ was considered as indicating statistical significance. Multivariate analysis was conducted using binary logistic regression. Data were stored in MS Excel 2007 for Windows (Microsoft Corp., Redmond, WA) and data analysis was conducted using SPSS 19.0 (IBM Corp., Armonk, NY, USA).

Results

General characteristics of the participants

A total of 225 patients were recruited to the present study, of whom 134 were male (59.6%) and 92 were female (40.4%). The general characteristics of the sample are shown in Table 1. In total, 153 of the participants had anaemia (68%) and 72 did not (normal group; 32%). One hundred and twelve participants had severe vitamin D3 deficiency (50%), 63 had vitamin D3 deficiency (28%), and 50 had sufficient concentrations of vitamin D3 (22%) (Tables 1 and 2).

Aetiology of the CKD in the participants

Of the participants, 140 had chronic glomerulonephritis (62.2%), 65 had diabetic nephropathy, (28.9%), 14 had hypertensive nephropathy (6.2%), two had obstructive nephropathy (0.9%), and four had gouty nephropathy (1.8%). With regard to the stage of CKD in the participants, 19 had stage 1 CKD (8.4%), 23 had stage 2 CKD (10.2%), 43 had stage 3 CKD (19.1%), 47 had stage 4 CKD (20.9%), and 93 had stage 5 CKD (41.3%).

Prevalences of anaemia in participants with stages 1 to 5 CKD

We next compared the prevalences of anaemia in participants with stages 1 to 5 CKD and found that they significantly differed (21.1% for stage 1, 30.4% for stage 2, 39.5% for stage 3, 78.7% for stage 4, and 94.6% for stage 5; $\chi^2 = 82.95$, $P<0.001$, Figure 1).

Prevalences of anaemia in the vitamin D3 groups

The prevalences of anaemia were next compared between the participants with severe deficiency, deficiency, and sufficiency, and we found that these significantly differed (79.5% in the severe deficiency group, 63.5% in the deficiency group, and 48.0% in the sufficiency group; $\chi^2 = 16.544$, $P<0.001$, Figure 2). A pairwise comparison of the prevalence of anaemia among vitamin D3 groups was then conducted using the Bonferroni correction, and the results revealed significant differences in the prevalence of anaemia between the severe deficiency and deficiency groups, between the severe deficiency and sufficiency groups, and between the deficiency and sufficiency groups ($P<0.0167$; Table 3). The prevalence of anaemia decreased with increasing vitamin D3 concentration ($P<0.001$, Table 2).

Comparisons of the anaemia group and the normal group

Student's *t*-test and the rank sum test were used to analyse the differences in vitamin D3, parathyroid hormone (PTH), high-sensitivity C-reactive protein (CRP), eGFR, transferrin saturation, folate, and

Table 1. Characteristics of the participants.

	CKD1	CKD2	CKD3	CKD4	CKD5
Sex (male/female)	9/10	17/6	34/9	28/19	46/47
Age (years)	46.7±12.0	51.6±15.0	50.1±15.0	54.8±13.9	49.8±14.4
BMI (kg/m^2)	23.6±14.8	25.7±4.1	24.4±3.4	23.2±2.9	24.2±11.9
Vitamin D3 (nmol/L)	41.8±24.3	28.3±24.0	41.3±24.8	32.5±21.0	30.0±19.0
PTH (pmol/L)	4.01±1.24	5.69±7.15	6.81±4.15	12.48±9.60	30.87±24.16
High sensitivity C-reactive protein (nmol/L)	32.7±26.8	26.6±33.7	76.8±115.9	58.8±98.6	85.2±162.2
Albumin (μmol/L)	584.7±91.6	506.0±170.0	576.3±103.2	549.7±92.2	554.8±93.1
Hb (g/L)	135.2±22.6	132.9±26.9	130.0±21.0	105.1±25.0	91.5±20.8
eGFR (ml/min. 1.73 m^2)	107.65±18.44	75.76±9.00	42.14±6.98	21.97±4.04	8.37±3.13
Transferrin saturation	0.35±0.07	0.42±0.30	0.27±0.08	0.29±0.13	0.28±0.15
Ferritin (pmol/L)	549.7±293.9	575.7±409.9	475.1±288.3	505.8±326.5	522.7±375.5
Folate (nmol/L)	17.73±5.59	16.32±5.93	18.54±8.04	19.65±11.30	20.37±11.49
Vitamin B12 (pmol/L)	267.8±112.5	285.4±108.7	396.2±251.8	405.6±286.1	430.9±331.7

Data are mean ± SD or numbers.
CKD1–5, chronic kidney disease stages 1–5; BMI, body mass index; PTH, parathyroid hormone; Hb, haemoglobin, eGFR, estimated glomerular filtration rate.

Table 2. Prevalences of anaemia in the vitamin D3 groups.

	Presence of anaemia			
Vitamin D3 group	Yes, n (%)	No, n (%)	χ^2	p
Severe deficiency	89 (79.8)	23 (20.2)	16.54	<0.001
Deficiency	40 (63.1)	23 (36.9)		
Sufficiency	24 (49.0)	26 (51.0)		

The results of chi square testing are shown.

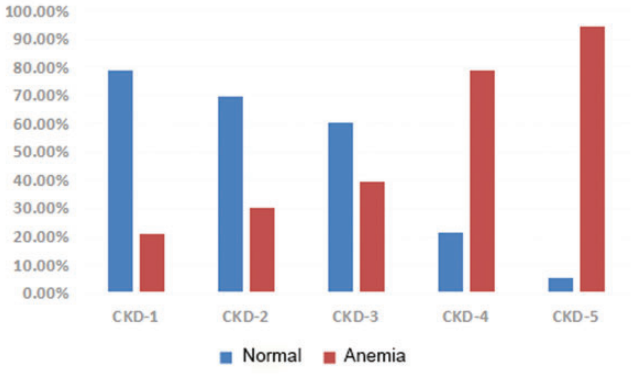

Figure 1. Distribution of the prevalence of anaemia in different grades of chronic kidney disease.

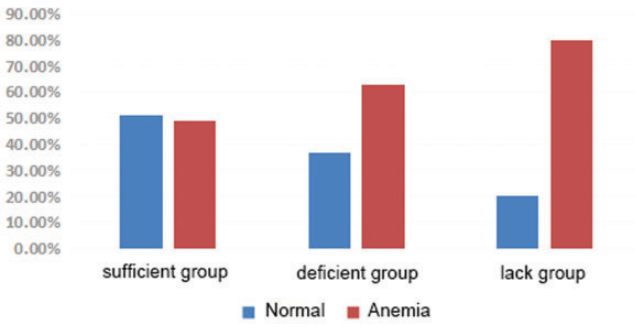

Figure 2. Prevalence of anaemia among different vitamin D3 groups.

Table 3. Comparisons of the prevalences of anaemia between the vitamin D3 groups.

	Pearson chi-square statistic	Degrees of freedom	*p*
Deficiency *vs.* Severe deficiency	5.997	1	0.014
Severe deficiency *vs.* Sufficiency	16.016	1	<0.001
Deficiency *vs.* Sufficiency	5.668	1	0.015

Bonferroni correction ($\alpha' = 0.05/3 = 0.0167$) and a pairwise comparison of the prevalences of anaemia among the vitamin D3 groups was performed.

Table 4. Comparisons of the characteristics of the participants with and without anaemia (n = 225).

Groups	Anaemic (n)	Non-anaemic (n)	F/Z	*p*
n	153	72	–	–
Sex (male/female)	83/74	52/21	–	–
Age (years)	51.8±14.1	49.4±15.7	0.284	0.595
BMI (kg/m^2)	23.89±9.55	25.08±3.786	0.246	0.620
Vitamin D3 (nmol/L)	30.0±19.3	40.2±25.6	−3.426	0.001
PTH (pmol/L)	22.74±21.67	8.76±12.09	−6.97 (z)	<0.001
High-sensitivity C-reactive protein (nmol/L)	77.9±145.2	52.0±82.0	−1.58 (z)	0.115
Albumin (μmol/L)	593.1±100.8	537.2±103.8	0.71 (z)	0.401
eGFR (ml/min. 1.73 m^2)	18.42±17.32	46.46±22.58	−8.86 (z)	<0.001
Transferrin saturation	0.28±0.18	0.33±0.11	−4.1 (z)	<0.001
Ferritin (pmol/L)	525.2±365.2	458.0±261.8	5.631	0.064
Folate (nmol/l)	19.93±11.12	17.88±7.72	−0.43 (z)	0.665
Vitamin B12 (pmol/l)	417.1±312.1	360.6±217.3	−0.88 (z)	0.378

Data are mean ± SD or numbers. The groups were compared using Student's *t*-test or the Wilcoxon rank sum test, as appropriate.
BMI, body mass index; PTH, parathyroid hormone; Hb, eGFR, estimated glomerular filtration rate.

vitamin B12 between the anaemia and normal groups. The groups showed homogeneity of variance with respect to age, BMI, albumin and ferritin. We identified significant differences in serum vitamin D3, PTH, eGFR, and transferrin saturation between the anaemia and normal groups (all $P<0.05$, Table 4).

Table 5. Results of the multivariate regression analysis of factors potentially influencing anaemia.

	B	S.E.	Wals	df	*p*	OR	95% CI
Vitamin D3	−0.059	0.021	7.874	1	**0.005**	0.943	(0.905, 0.983)
eGFR	−0.045	0.008	29.703	1	**<0.001**	0.956	(0.941, 0.972)
Transferrin saturation	−0.006	0.007	0.859	1	0.354	0.994	(0.981, 1.007)
PTH	0.002	0.002	1.062	1	0.303	1.002	(0.998, 1.005)
Constant	3.282	0.686	22.882	1	<0.001	26.623	

S.E., standard error of the mean; df, degrees of freedom; OR, odds ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate, PTH, parathyroid hormone.

Multivariate analysis to identify factors associated with anaemia

The parameters used the regression model were vitamin D3, eGFR, and transferrin saturation (Table 5). Vitamin D3 and eGFR were found to be independently associated with a lower prevalence of anaemia ($P<0.05$, odds ratio (OR) = 0.943 and $P<0.001$, OR = 0.956, respectively), but PTH and transferrin saturation were not independently associated with anaemia.

Discussion

Kim *et al.*[9] revealed a positive correlation between serum vitamin D concentration and Hb concentration in patients with end-stage renal disease, and vitamin D was shown to be an independent risk factor for anaemia in such patients. In addition, Sonkar *et al.*[10] showed that patients with CKD and low Hb concentrations had higher circulating PTH concentrations, and noted a positive correlation between their vitamin D and Hb concentrations. These results suggest that a lack of vitamin D and secondary hyperparathyroidism may be closely associated with renal anaemia. Furthermore, Hb has been shown to positively correlate with vitamin D and negatively correlate with the erythropoietin resistance index in patients undergoing maintenance haemodialysis.[11] However, to date, there have been few studies around the world that have aimed to determine the relationship between vitamin D and anaemia in patients with CKD. In the present study, we have explored the relationship between anaemia and serum vitamin D3 in patients with CKD, to aid understanding of the therapeutic efficacy of vitamin D in such patients. A logistic regression analysis of factors that might influence the prevalence of anaemia showed that vitamin D3 concentration was associated; specifically, as the vitamin D3 level concentration, the prevalence of anaemia gradually decreased. These data suggest that vitamin D deficiency may represent a novel risk factor for CKD-associated anaemia. However, further longitudinal studies are required to determine whether vitamin D administration in patients with CKD might reduce their risk of anaemia.

In the present study, the participants had stages 1 to 5 CKD and were not undergoing haemodialysis, whereas in previous studies,[6,9] the participants were mainly in the early stages of CKD or were undergoing maintenance haemodialysis. We analysed the relationship between vitamin D and anaemia after excluding a number of factors that are known to affect the development of anaemia.[12–15] Patients from various parts of Guizhou Province were studied and they were categorised by their serum 25 (OH) D3 concentration, according to the Vitamin D and Adult Bone Health Application Guidelines.

Although vitamin D status seems to be associated with anaemia, the mechanism underlying this association remains unclear. Previous studies have suggested that the mechanism whereby vitamin D might influence Hb concentration in patients with CKD is through a downregulation of pro-inflammatory factors and an inhibition of transcription from the *HAMP* gene, which encodes hepcidin.[16] There is also evidence that vitamin D can reduce the risk of anaemia by increasing the production of red blood cells and reducing resistance to the actions of erythropoietin.[2,3] In addition, PTH has also been shown to influence the formation of red blood cells, and vitamin D may further prevent anaemia by reducing serum PTH[17,18].

The present study has several limitations. First, owing to its cross-sectional design, conclusions regarding causality in the relationship between vitamin D and anaemia cannot be drawn. Second, the sample size was small; therefore, in future studies, more participants should be recruited to verify the identified relationship between vitamin D and anaemia, as well as with other potential risk factors for anaemia. Third, vitamin D status is affected by obesity, age, sex, skin colour, duration of sunlight exposure, exercise, and other factors;[19,20] and therefore differences in these parameters among the participants may have affected the findings.

Conclusion

Vitamin D3 is associated with anaemia in patients with CKD. A deficiency of vitamin D3 may increase the risk of anaemia.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This work was supported by a Guiyang Bureau of Science and Technology Greater Health Cooperation Project (Zhu Ke Contract [2018] 1-73).

ORCID iD

Hong-Ying Peng https://orcid.org/0000-0003-2814-9694

References

1. Zhang L, Wang F, Wang L, et al. Prevalence of chronic kidney disease in China: a cross-sectional survey. *Lancet* 2012; 379: 815–822.
2. Aucella F, Scalzulli RP, Gatta G, et al. Calcitriol increases burst-forming unit-erythroid proliferation in chronic renal failure. A synergistic effect with r-HuEpo. *Nephron Clin Prac* 2003; 95: c121–c127.
3. Alon DB, Chaimovitz C, Dvilansky A, et al. Novel role of 1,25(OH)(2)D(3) in induction of erythroid progenitor cell proliferation. *Exp Hematol* 2002; 30: 403–409.
4. Carozzi S, Ramello A, Nasini MG, et al. Ca++ and 1,25(OH)2D3 regulate in vitro and in vivo the response to human recombinant erythropoietin in CAPD patients. *Adv Perit Dial* 1990; 6: 312–315.
5. Kendrick J, Targher G, Smits G, et al. 25-Hydroxyvitamin D deficiency and inflammation and their association with hemoglobin levels in chronic kidney disease. *Am J Nephrol* 2009; 30: 64–72.
6. Patel NM, Gutiérrez OM, Andress DL, et al. Vitamin D deficiency and anemia in early chronic kidney disease. *Kidney Int* 2010; 77: 715–720.
7. KDIGO Clinical Practice Guideline Working Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int Suppl* 2012; 2: 279–335.
8. Xiangpeng L, Li ZC, Honghong Z, et al. Application Guideline for Vitamin D and Bone Health in Adult Chinese (2014 Standard Edition) Vitamin D Working Group of Osteoporosis Committee of China Gerontological Society. *Chin J Osteoporos* 2014; 20: 1011–1030. doi: 10.3969/j.1006-7108.

9. Kim YL, Kim H, Kwon YE, et al. Association between Vitamin D Deficiency and Anemia in Patients with End-Stage Renal Disease: A Cross-Sectional Study. *Yonsei Med J* 2016; 57: 1159–1164.
10. Sonkar SK, Singh HP, Sonkar GK, et al. Association of Vitamin D and secondary hyperparathyroidism with anemia in diabetic kidney disease. *J Family Med Prim Care* 2018; 7: 815–818.
11. Kiss Z, Ambrus C, Almasi C, et al. Serum 25 (OH)-cholecalciferol concentration is associated with hemoglobin level and erythropoietin resistance in patients on maintenance hemodialysis. *Nephron Clin Pract* 2011; 117: 373–378. doi: 10.1159/000321521.
12. McGonigle RJ, Wallin JD, Shadduck RK, et al. Erythropoietin deficiency and inhibition of erythropoiesis in renal insufficiency. *Kidney Int* 1984; 25: 437–444.
13. Erslev AJ, Besarab A. The rate and control of baseline red cell production in hematologically stable patients with uremia. *J Lab Clin Medicine* 1995; 126: 283–286.
14. Teruel JL, Marcen R, Ocaña J, et al. Clinical Significance of C-Reactive Protein in Patients on Hemodialysis: A Longitudinal Study. *Nephron Clin Prac* 2005; 100: c140–c145.
15. Panichi V, Migliori M, De PS, et al. C reactive protein in patients with chronic renal diseases. *Ren Fail* 2001; 23: 551–562.
16. Bacchetta J, Zaritsky JJ, Sea JL, et al. Suppression of iron-regulatory hepcidin by vitamin D. *J Am Soc Nephrol* 2014; 25: 564–572.
17. Gaweda A E, Goldsmith LJ, Brier ME, et al. Iron, Inflammation, Dialysis Adequacy, Nutritional Status, and Hyperparathyroidism Modify Erythropoietic Response. *Clin J Am Soc Nephrol* 2010: 5: 576–581.
18. Brancaccio D, Cozzolino M, Gallieni M. Hyperparathyroidism and anemia in uremic subjects: a combined therapeutic approach. *J Am Soc Nephrol* 2004; 15 Suppl 1: S21–S24.
19. Diamond TH, Eisman JA, Mason RS, et al. Vitamin D and adult bone health in Australia and New Zealand: a position statement. *Med J Aust* 2005; 182: 281–285.
20. Turer CB, Lin H, Flores G. Prevalence of Vitamin D Deficiency Among Overweight and Obese US Children. *Pediatrics* 2013; 131: 152–161.