The Association of Vitamin D Status and Vitamin D Replacement Therapy with Glycemic Control, Serum Uric Acid Levels, and Microalbuminuria in Patients with Type 2 Diabetes and Chronic Kidney Disease

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Keywords

Type 2 diabetes · Chronic kidney disease · Vitamin D status · Vitamin D replacement therapy · Glycemic control · Serum uric acid · Microalbuminuria

Abstract

Objective: To evaluate the relationship of vitamin D status and vitamin D replacement therapy with glycemic control, serum uric acid (SUA) levels, and microalbuminuria (MAU) in patients with type 2 diabetes (T2DM) and chronic kidney disease (CKD). **Subjects and Methods:** A total of 1,463 patients with T2DM and CKD (aged 14–88 years), 927 females and 536 males, were included in this study. The serum data of 25-hydroxyvitamin D, i.e., 25(OH)D, level, SUA, hemoglobin (Hb) A_{1c}, creatinine, estimated glomerular filtration rate, and urine albumin-to-creatinine ratio (UACR) were obtained from the medical records. The Mann-Whitney U test, the χ^2 test, the Mantel-Haenszel test, and linear regression models were used for data analysis. **Results:** Vitamin D deficiency and insufficiency were evident in 770 (52.0%) and 357 (24.0%) patients, respectively. Median HbA_{1c} levels (7.3 [IQR 3.9] vs. 6.5 [IQR 2.3]%; $p < 0.01$) were significantly higher in patients deficient in vitamin D than in those with a normal vitamin D status. A significantly low level of vitamin D was

noted with a high UACR ($\beta -0.01$; 95% CI -0.01 to -0.001 ; $p = 0.017$) and HbA_{1c} ($\beta -1.1$; 95% CI -1.6 to -0.6 ; $p < 0.001$), but with low levels of SUA ($\beta 1.3$; 95% CI 0.5 – 2.2 ; $p = 0.002$). Vitamin D replacement was associated with a significantly low level of HbA_{1c} (7.4 [2.7] vs. 6.7 [1.9]%; $p < 0.001$). **Conclusion:** In this study, there was a high prevalence of hypovitaminosis D among T2DM patients with CKD, with a higher UACR, higher HbA_{1c}, and lower SUA being noted as playing a role in predicting a decrease in vitamin D levels and potential benefits of vitamin D replacement therapy on glycemic control in T2DM management.

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Introduction

In calcium-phosphate homeostasis and bone physiology, it is well known that vitamin D status is associated with a number of nonskeletal functions including glucose homeostasis, pathophysiology, and the progression of type 2 diabetes mellitus (T2DM) [1–3]. The serum 25-hydroxyvitamin D, i.e., 25(OH)D, level is considered to be the most stable and reliable indicator of vitamin D status [4, 5]. It reflects vitamin D exposure based on the sum of endogenous synthesis and dietary intake from foods, for-

tified products, and/or supplements [4, 5]. Most patients with T2DM have low 25(OH)D levels, while high levels are associated with a lower risk of incident diabetes [6, 7]. Reduced nephron mass and/or 1- α hydroxylase enzyme activity has been shown to be associated with a decline in 1.25 dihydroxyvitamin D, i.e., 1.25(OH)₂D, levels in patients with chronic kidney disease (CKD) [8]. Hence, it has been suggested that renal status be considered in studies involving vitamin D status among T2DM patients [7].

Serum uric acid (SUA) has been shown to be associated with reduced levels of 1.25(OH)₂D via the inhibition of 1- α hydroxylase activity [9, 10] as well as with microalbuminuria (MAU) [11]. This seems notable, since MAU is considered to be a biomarker for diagnosing diabetic kidney disease, and is a predictive factor for the progression to end-stage renal disease (ESRD) and increased cardiovascular risk among diabetic patients [12, 13].

Vitamin D supplementation for diabetic patients is of particular interest, with regard to its role in glucose homeostasis and thus its use as a potential cost-effective adjunct therapy in T2DM management [14, 15]. However, data on the impact of maintaining an adequate vitamin D status or supplementing with vitamin D on clinical outcomes in diabetic patients are inconsistent, probably reflecting the differences across studies in baseline vitamin D levels and replacement therapy dosage [14–16]. This study was therefore designed to evaluate the relationship of vitamin D status and vitamin D replacement therapy with glycemic control, SUA levels, and MAU in patients with T2DM and CKD.

Subjects and Methods

Study Population

A total of 1,463 patients with T2DM and CKD (age range 14–88 years), 927 females and 536 males, who had their serum 25(OH)D levels measured during follow-up at our diabetes outpatient clinic between January 2010 and January 2015, were included in this retrospective study. Exclusion criteria were an age of <18 years, pregnancy, a change in antidiabetic treatment during the study, and no data on concomitantly assessed vitamin D levels.

The study was conducted in full accordance with the local Good Clinical Practice guideline and current legislation, and permission was obtained from the Institutional Ethics Committee for the use of patient data for publication purposes.

Study Assessments

Data on patient demographics, laboratory parameters including analysis for 25(OH)D, SUA, HbA_{1c}, creatinine, estimated glomerular filtration rate (eGFR), and urine albumin-to-creatinine ratio (UACR) were obtained from medical records. Demographic

characteristics and laboratory parameters were evaluated with respect to vitamin D status, while estimators of baseline vitamin D levels and the effect of vitamin D replacement therapy on the vitamin D, glycemic, and renal function parameters were also analyzed. Overall, 383 of 1,463 patients received vitamin D replacement therapy (75,000 units weekly). Pretreatment and posttreatment laboratory parameters were compared in these patients.

Blood Biochemistry Analysis

25(OH)D, creatinine, uric acid, HbA_{1c}, and hemogram were measured using a central laboratory biochemistry analyzer (ICT [ISE] Module of ARCHITECT c16000, Abbott Laboratories, Abbott Park, IL, USA). 25(OH)D levels were measured using high-performance liquid chromatography, and were classified as deficient (<20 ng/mL), insufficient (20–30 ng/mL) or optimal (>30 ng/mL) [17].

Estimation of the Glomerular Filtration Rate

The GFR was estimated according to the Modification of Diet in Renal Disease (MDRD) equation, which includes 4 variables: $\text{eGFR (mL/min/1.73 m}^2\text{)} = 175 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female})$ (conventional units) [18]. The patients were then classified into 5 CKD stages: stage 1 (eGFR >90 mL/min/1.73 m²); stage 2, mild CKD (eGFR 60–89 mL/min/1.73 m²); stage 3, moderate CKD (eGFR 30–59 mL/min/1.73 m²); stage 4, severe CKD (eGFR 15–29 mL/min/1.73 m²); and stage 5, end-stage CKD (eGFR <15 mL/min/1.73 m²).

Statistical Analysis

Categorical variables were summarized as *n* (%) and continuous variables as median (IQR) due to nonnormal distribution patterns. Baseline vitamin D level groups were compared by means of the Mann-Whitney U test for continuous variables, the χ^2 test for nominal variables, and the Mantel-Haenszel test for ordinal variables. The estimators of baseline vitamin D levels were evaluated by using univariate and multivariate (adjusted for age and gender) linear regression models. The effect of vitamin D replacement therapy during follow-up was evaluated by the Wilcoxon or McNemar-Bowker test depending on the variables. Type 1 error level was set at 5% and the Bonferroni adjustment for a type 1 error was used, where appropriate. Statistical analysis was conducted with Statistical Package for the Social Sciences software (v21.0, released 2012, IBM Corp., Armonk, NY, USA).

Results

Demographic Characteristics and Laboratory Findings

The median (IQR) 25(OH)D level was 18.1 (15.5) ng/mL; vitamin D deficiency and insufficiency were evident in 770 (52.6%) and 357 (24.4%) patients, respectively. Stage 1–2 CKD was noted in 1,308 (91.9%) patients. The median (IQR) level of HbA_{1c} was 7.0 (3.9%) and that of uric acid was 4.9 (1.9) mg/dL in the overall study population (Table 1).

Vitamin D deficiency was associated with a significantly higher number of females (*n* = 527; 68.4% vs. *n* = 197; 58.6%; *p* = 0.003) and higher (median [IQR]) HbA_{1c}

Table 1. Demographics, medical characteristics, and laboratory findings in the overall study population and according to baseline vitamin D status

	Deficiency (<i>n</i> = 770)	<i>p</i> value	Insufficiency (<i>n</i> = 357)	<i>p</i> value	Normal (<i>n</i> = 336)	All patients (<i>n</i> = 1,463)
Demographics						
Age, years	54.0 (17.0)	1.000 ^a	52.0 (17.0)	0.205 ^a	54.0 (20.0)	54.0 (17.0)
Female gender, <i>n</i>	527 (68.4%)	0.003 ^b	203 (56.9%)	1.000 ^b	197 (58.6%)	927 (63.4%)
Medical characteristics^d						
CKD stage, <i>n</i>						
Stage 1	446 (59.5%)	1.000 ^c	212 (60.4%)	1.000 ^c	193 (59.9%)	851 (59.8%)
Stage 2	239 (31.9%)		112 (31.9%)		106 (32.9%)	457 (32.1%)
Stage 3	59 (7.9%)		25 (7.1%)		23 (7.1%)	107 (7.5%)
Stage 4	6 (0.8%)		1 (0.3%)		0 (0%)	7 (0.5%)
Stage 5	0 (0%)		1 (0.3%)		0 (0%)	1 (0.1%)
Laboratory findings^d						
Serum creatinine, mg/dL	0.8 (0.2)	0.122 ^a	0.8 (0.2)	1.000 ^a	0.8 (0.2)	0.8 (0.2)
eGFR, mL/min/1.73 m ²	92.4 (31.9)	1.000 ^a	92.8 (28.7)	1.000 ^a	92.8 (29.2)	92.7 (30.4)
UACR, mg/mmol	14.9 (42.9)	0.006 ^a	15.2 (41.7)	0.033 ^a	9.5 (19.6)	13.9 (40.0)
SUA, mg/dL	4.7 (2)	0.001 ^a	4.7 (1.7)	0.001 ^a	5.1 (1.9)	4.9 (1.9)
HbA1 _c , %	7.3 (3.2)	<0.001 ^a	6.8 (3.0)	0.305 ^a	6.5 (2.3)	7.0 (3.9)

Values are expressed as median (IQR), unless otherwise indicated. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HbA1_c, glycated hemoglobin A1_c; SUA, serum uric acid; UACR, urine albumin-to-creatinine ratio. Deficiency: a serum vitamin D level <20 ng/mL; insufficiency: a serum vitamin D level ≥20 and <30 ng/mL; normal: a serum vitamin D level ≥30 ng/mL.

^a Comparisons made by Mann-Whitney U test and results adjusted by the Bonferroni method.

^b Comparisons made by χ^2 test and results adjusted by the Bonferroni method.

^c Comparisons made by Mantel-Haenszel test and results adjusted by the Bonferroni method.

^d Data for some patients are missing, so results are based on available data.

levels (7.3 [3.2] vs. 6.5 [2.3]%; $p < 0.01$) compared with normal vitamin D status. Patients with vitamin D deficiency and insufficiency had significantly lower levels for SUA (4.7 [2.0] and 4.7 [1.7] vs. 5.1 [1.9] mg/dL, respectively; $p < 0.001$ for each), and higher UACR (14.9 [42.9] and 15.2 [41.7] vs. 9.5 [19.6] mg/mmol; $p < 0.01$ for each) when compared to patients with a normal vitamin D status (Table 1).

Estimators of Baseline Vitamin D Levels

Univariate linear regression analyses revealed lower vitamin D levels with higher UACR ($\beta -0.01$; 95% CI -0.01 to -0.001 ; $p = 0.017$) and HbA1_c ($\beta -1.1$; 95% CI -1.6 to -0.6 ; $p < 0.001$) levels but lower SUA ($\beta 1.3$; 95% CI 0.5 – 2.2 ; $p = 0.002$), even after adjusting for age and gender ($p = 0.023$, $p = 0.013$, and $p < 0.001$, respectively; Table 2).

Effect of Vitamin D Replacement Therapy on Laboratory Findings

Among patients who had vitamin D replacement therapy ($n = 383$), after a median (IQR) 6.0 (5.0) months,

there was a significant increase in (median [IQR]) 25(OH) D levels (from 18.1 [15.5] ng/mL pretreatment to 25.5 [19.1] ng/mL posttreatment; $p < 0.001$) and the percentage of patients with normal vitamin D status (from 19.8 to 37.1%; $p < 0.001$) (Table 3).

When compared to pretreatment values, posttreatment values showed a significant decrease (median [IQR]) in HbA1_c (7.4 [2.7] vs. 6.7 [1.9]%; $p < 0.001$) and eGFR (92.3 [30.3] vs. 91.4 [30.4] mL/min/1.73 m²; $p < 0.001$). Analysis of data adjusted for follow-up duration also revealed a significant decrease in mean (95% CI) HbA1_c levels from baseline to follow-up (7.8 [7.6–8.0] vs. 7.1 [6.9–7.2]%; $p < 0.001$) (Table 3).

Discussion

Our findings in a cohort of patients with T2DM and CKD revealed a high prevalence (approx. 70%) of hypovitaminosis D, particularly among females, in cases of vitamin D deficiency. Higher levels of HbA1_c and UACR,

Table 2. Estimators of baseline vitamin D levels

	Univariate		Adjusted ^a	
	β (95% CI)	<i>p</i> value	β (95% CI)	<i>p</i> value
Serum creatinine, mg/dL	1.3 (−2.9 to 5.5)	0.541	−1.2 (−5.9 to 3.6)	0.629
eGFR, mL/min/1.73 m ²	−0.03 (−0.07 to 0.02)	0.212	−0.02 (−0.07 to 0.03)	0.372
UACR, mg/mmol	−0.01 (−0.01 to −0.001)	0.017	−0.01 (−0.01 to −0.001)	0.023
SUA, mg/dL	1.3 (0.5–2.2)	0.002	1.1 (0.2–2.0)	0.013
HbA _{1c} , %	−1.1 (−1.6 to −0.6)	<0.001	−1.2 (−1.7 to −0.8)	<0.001

Data on some patients are missing, so the results are based on the available data. β, linear regression coefficient; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin A_{1c}; SUA, serum uric acid; UACR, urine albumin-to-creatinine ratio.

^a Results of linear regression model which was adjusted for patients' age and gender.

Table 3. Effect of vitamin D replacement therapy on renal function and glycemic parameters and vitamin D status

Parameters	Patients, <i>n</i>	At baseline	After treatment	<i>p</i> value ^a
Renal function ^b				
Serum vitamin D, ng/mL	383	18.1 (15.5)	25.5 (19.1)	<0.001
Serum creatinine, mg/dL	368	0.8 (0.2)	0.8 (0.2)	0.054
eGFR, mL/min/1.73 m ²	368	92.3 (30.3)	91.4 (30.4)	<0.001
SUA, mg/dL	72	4.8 (2.0)	5.0 (1.5)	0.470
HbA _{1c} , % ^b				
Mean (95% CI)	373	7.4 (2.7)	6.7 (1.9)	<0.001
		7.8 (7.6–8.0)	7.1 (6.9–7.2)	<0.001
Vitamin D status, <i>n</i> (%)				
Deficiency		224 (58.5)	140 (36.6)	<0.001
Insufficiency		83 (21.7)	101 (26.4)	
Normal		76 (19.8)	142 (37.1)	

eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin A_{1c}; SUA, serum uric acid; UACR, urine albumin-to-creatinine ratio.

^a Results of comparison to normal vitamin D group.

^b Median (IQR).

and lower levels of SUA were shown to predict lower vitamin D levels. Vitamin D replacement revealed an increase in patients with normal vitamin D status, along with a significant decrease in HbA_{1c} levels.

The high 76.0% prevalence of hypovitaminosis D in our cohort, particularly among females, in cases of vitamin D deficiency, was similar to the previously published data indicating, overall, a 73.0% prevalence of hypovitaminosis D (higher in females) among Turkish T2DM patients [19, 20].

This lower level of 25(OH)D among diabetic patients and higher HbA_{1c} in cases of hypovitaminosis D than with vitamin D sufficiency was also reported in other

studies on diabetic patients with various stages of CKD [7, 19, 21, 22]. Our findings also revealed a significant role of higher HbA_{1c} in predicting a decrease in vitamin D levels, in agreement with previous studies [7, 23, 24].

In this cohort, vitamin D replacement therapy enabled a significant improvement in HbA_{1c} levels. In an analysis of insulin-naïve T2DM patients with vitamin D deficiency who received vitamin D supplementation, all patients were reported to achieve serum levels of 25(OH)D >20 ng/mL, along with a significant reduction in fasting blood glucose, but nonsignificant reductions in HbA_{1c}, fasting insulin, and HOMA-IR [16].

In this cohort, the increase in median 25(OH)D level, from 18.1 to 25.5 ng/mL, along with an increase in the rate of normal vitamin D status, from 19.8 to 37.1%, due to the vitamin D replacement, could have produced extraskel-etal benefits of vitamin D as suggested previously [25].

The significant improvement in HbA_{1c} levels after vitamin D replacement therapy that we observed emphasizes the association of vitamin D levels with glucose hemostasis in T2DM, and the potential therapeutic implications of this association in achieving improved glycemic control in T2DM management [21]. Similar to our findings, the likely benefit of vitamin D substitution for a better T2DM prognosis was suggested in a 15-year longitudinal study among T2DM patients [26]. Clinical trials, however, have revealed inconsistent findings on the impact of maintaining adequate vitamin D status and/or high-dose vitamin replacement on long-term glycemic control in T2DM patients [14–16, 27]. Thus, the need for validation by further large-scale, cross-sectional, and interventional clinical studies is emphasized [15].

Given that renal status is a covariant influencing vitamin D status [7], it seems worth noting that the majority of our patients had stage 1–2 CKD and no difference was noted in the CKD stage of the patients with respect to vitamin D status.

A decrease in SUA was amongst the predictors of hypovitaminosis D in our study. This seems to contrast with past studies that indicated an association between hyperuricemia and hypovitaminosis D in gout, diabetes, and CKD patient populations [10, 19, 28]. In addition, no association was shown between reduced 25(OH)D levels and elevated SUA in premenopausal women, regardless of concomitant T2DM and hypertension [29]. This seems to indicate the likelihood of a multifaceted pathogenesis of the interaction between vitamin D status and SUA, with the contribution of several endocrine factors [9, 30].

In this cohort, higher UACR was shown to predict a decrease in vitamin D levels. This seems to support the

linear relation between vitamin D deficiency and progression of MAU reported in T2DM patients [13, 27], while also emphasizing the potential benefit of the normalization of vitamin D levels in the reduction of renal and cardiovascular risks associated with MAU in these patients [12, 13].

Certain limitations to this study include its retrospective, single-center design and thus an inability to generalize our findings to the overall diabetic population, the lack of data on parathyroid hormone levels and seasonal changes in vitamin D levels, and also the fact that there was no standard duration of vitamin D treatment.

Conclusion

Our findings in a cohort of patients with T2DM and CKD revealed a high prevalence (70%) of hypovitaminosis D, particularly among females, in cases of vitamin D deficiency. Higher UACR, higher HbA_{1c}, and lower SUA were shown to predict a decrease in vitamin D levels. Vitamin D replacement therapy had a beneficial effect on glucose hemostasis via a significant reduction in HbA_{1c}; this emphasizes the potential therapeutic implications of vitamin D supplementation as a promising preventative and therapeutic agent for improved glycemic control among T2DM patients with CKD. We recommend an evaluation of the relationship between hypovitaminosis D and SUA and of the impact of longer-term vitamin D replacement therapy on glycemic control and renal function among diabetic patients in a large-scale clinical study.

Disclosure Statement

There were no conflicts of interest.

References

- 1 Matyjaszek-Matuszek B, Lenart-Lipińska M, Woźniakowska E: Clinical implications of vitamin D deficiency. *Prz Menopauzalny* 2015; 14:75–81.
- 2 Adams JS, Hewison M: Update in vitamin D. *J Clin Endocrinol Metab* 2010;95:471–478.
- 3 Thomas GN, ó Hartaigh B, Bosch JA, et al: Vitamin D levels predict all-cause and cardiovascular disease mortality in subjects with the metabolic syndrome: the Ludwigshafen Risk and Cardiovascular Health (LURIC) Study. *Diabetes Care* 2012;35:1158–1164.
- 4 Ross AC, Manson JE, Abrams SA, et al: The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. *J Clin Endocrinol Metab* 2011;96:53–58.
- 5 Thacher TD, Clarke BL: Vitamin D insufficiency. *Mayo Clin Proc* 2011;86:50–60; review.
- 6 Pittas AG, Nelson J, Mitri J, et al: Plasma 25-hydroxyvitamin D and progression to diabetes in patients at risk for diabetes: an ancillary analysis in the Diabetes Prevention Program. *Diabetes Care* 2012;35:565–573.
- 7 Kajbaf F, Mentaverri R, Diouf M, et al: The association between 25-hydroxyvitamin D and hemoglobin A_{1c} levels in patients with type 2 diabetes and stage 1–5 chronic kidney disease. *Int J Endocrinol* 2014;2014:142468.

- 8 Levin A, Bakris GL, Molitch M, et al: Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: results of the study to evaluate early kidney disease. *Kidney Int* 2007;71:31–38.
- 9 Chen W, Roncal-Jimenez C, Lanaspa M, et al: Uric acid suppresses 1 alpha hydroxylase in vitro and in vivo. *Metabolism* 2014;63:150–160.
- 10 Vanholder R, Patel S, Hsu CH: Effect of uric acid on plasma levels of 1,25(OH)₂D in renal failure. *J Am Soc Nephrol* 1993;4:1035–1038.
- 11 Hayashino Y, Okamura S, Tsujii S, et al: Association of serum uric acid levels with the risk of development or progression of albuminuria among Japanese patients with type 2 diabetes: a prospective cohort study (Diabetes Distress and Care Registry at Tenri [DDCRT 10]). *Acta Diabetol* 2016;53:599–607.
- 12 Kitada M, Kanasaki K, Koya D: Clinical therapeutic strategies for early stage of diabetic kidney disease. *World J Diabetes* 2014;5:342–356.
- 13 Bonakdaran S, Varasteh AR: Correlation between serum 25 hydroxy vitamin D₃ and laboratory risk markers of cardiovascular diseases in type 2 diabetic patients. *Saudi Med J* 2009;30:509–514.
- 14 Nasri H, Behradmanesh S, Maghsoudi AR, et al: Efficacy of supplementary vitamin D on improvement of glycemic parameters in patients with type 2 diabetes mellitus; a randomized double blind clinical trial. *J Renal Inj Prev* 2013;3:31–34.
- 15 Leung PS: The potential protective action of vitamin D in hepatic insulin resistance and pancreatic islet dysfunction in type 2 diabetes mellitus. *Nutrients* 2016;8:E147.
- 16 Calvo-Romero JM, Ramiro-Lozano JM: Metabolic effects of supplementation with vitamin D in type 2 diabetic patients with vitamin D deficiency. *Diabetes Metab Syndr* 2015;10:72–74.
- 17 Holick MF: Vitamin D deficiency. *N Engl J Med* 2007;357:266–281.
- 18 Levey AS, Stevens LA, Schmid CH, et al: A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;150:604–612.
- 19 Yilmaz H, Kaya M, Sahin M, et al: Is vitamin D status a predictor of glycaemic regulation and cardiac complication in type 2 diabetes mellitus patients? *Diabetes Metab Syndr* 2012;6:28–31.
- 20 Isaia G, Giorgino R, Adami S: High prevalence of hypovitaminosis D in a female type 2 diabetic population. *Diabetes Care* 2001;24:1496.
- 21 Kostoglou-Athanassiou I, Athanassiou P, Gkoutouvas A, et al: Vitamin D and glycaemic control in diabetes mellitus type 2. *Ther Adv Endocrinol Metab* 2013;4:122–128.
- 22 Pilz S, van den Hurk K, Nijpels G, et al: Vitamin D status, incident diabetes and prospective changes in glucose metabolism in older subjects: the Hoorn study. *Nutr Metab Cardiovasc Dis* 2012;22:883–889.
- 23 Zoppini G, Galletti A, Targher G, et al: Glycated haemoglobin is inversely related to serum vitamin D levels in type 2 diabetic patients. *PLoS One* 2013;8:e82733.
- 24 Soric MM, Renner ET, Smith SR: Effect of daily vitamin D supplementation on HbA_{1c} in patients with uncontrolled type 2 diabetes mellitus: a pilot study. *J Diabetes* 2012;4:104–105.
- 25 Hossein-nezhad A, Holick MF: Vitamin D for health: a global perspective. *Mayo Clin Proc* 2013;88:720–755.
- 26 Joergensen C, Gall MA, Schmedes A, et al: Vitamin D levels and mortality in type 2 diabetes. *Diabetes Care* 2010;33:2238–2243.
- 27 Shehab D, Al-Jarallah K, Abdella N, et al: Prospective evaluation of the effect of short-term oral vitamin D supplementation on peripheral neuropathy in type 2 diabetes mellitus. *Med Princ Pract* 2015;24:250–256.
- 28 Takahashi S, Yamamoto T, Moriwaki Y, et al: Decreased serum concentrations of 1,25(OH)₂-vitamin D₃ in patients with gout. *Metabolism* 1998;47:336–338.
- 29 Peng H, Li H, Li C, et al: Association between vitamin D insufficiency and elevated serum uric acid among middle-aged and elderly Chinese Han women. *PLoS One* 2013;8:e61159.
- 30 Hui JY, Choi JW, Mount DB, et al: The independent association between parathyroid hormone levels and hyperuricemia: a national population study. *Arthritis Res Ther* 2012;14:R56.