Journal of Clinical & Translational Endocrinology 24 (2021) 100255

Contents lists available at ScienceDirect

Journal of Clinical & Translational Endocrinology

journal homepage: www.elsevier.com/locate/jcte

Vitamin D supplementation is associated with serum uric acid concentration in patients with prediabetes and hyperuricemia

Hataikarn Nimitphong [a], Sunee Saetung [a], La-or Chailurkit [a], Suwannee Chanprasertyothin [b], Boonsong Ongphiphadhanakul [a,*]

[a] Department of Medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand
[b] Office of Research, Academic Affairs and Innovations, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Thailand

ARTICLE INFO

Keywords:
Vitamin D
Uric acid
Diabetes
Hyperuricaemia

ABSTRACT

Aims: Vitamin D deficiency is associated with a number of noncommunicable conditions. We conducted a randomised controlled trial to determine the effect of vitamin D supplementation on serum uric acid concentration in patients with prediabetes, in whom hyperuricaemia is common.
Methods: Seventy-one volunteers (35–80 years), with impaired fasting glucose and/or impaired glucose tolerance were randomised to three groups, vitamin D_3, vitamin D_2 and control, and followed for 12 months.
Results: After 12 weeks, vitamin D supplementation was associated with a reduction in serum uric acid concentration in participants with baseline uric acid concentration > 6 mg/dL, but no significant change was observed in controls. We then assessed the dose–response relationship between vitamin D supplementation and the change in serum uric acid concentration and found that the change in serum total 25-hydroxyvitamin D did not correlate with the change in serum uric acid that occurred during vitamin D supplementation. The factors associated with larger reductions in serum uric acid were a higher baseline serum uric acid and a larger increase in serum 1,25-dihydroxyvitamin D.
Conclusions: Vitamin D supplementation lowers serum uric acid in prediabetic patients with hyperuricaemia, and supplementation might be considered to help alleviate hyperuricaemia in these patients.

Introduction

Hyperuricaemia and gout are common clinical problems in adults in many populations [1,2]. It can be either asymptomatic or symptomatic. The available therapies for symptomatic hyperuricaemia include allopurinol, which is effective, but not without potentially serious adverse effects. Lifestyle modification and particularly dietary measures have been advocated to lower serum urate concentration [3], but these typically have only limited success. Therefore, more effective or adjunct measures are required. Vitamin D deficiency is increasingly common, even in geographical areas where sunlight is abundant [4]. It has been associated with a number of medical conditions, including noncommunicable diseases. In a recent cross-sectional study, we applied mediation analysis to demonstrate that serum 25-hydroxyvitamin D [25(OH)D] and urate concentrations are likely to be reciprocally related [5]. With regard to vitamin D supplementation, vitamin D_2 and D_3 are commonly used. It has been demonstrated that vitamin D3 increases circulating 25(OH)D levels more effectively than vitamin D_2 [6]. Supplementation with vitamin D_2 rather than vitamin D_3 would therefore require higher doses to achieve comparable serum 25(OH)D levels. For example, weekly administration of 20,000 U D_2 for 12 weeks resulted in comparable 25(OH)D concentrations as compared to weekly 15,000 U D3 supplementation [7].

We hypothesized that vitamin D supplementation might represent another means of alleviating hyperuricaemia. Therefore, in the present study, we used a randomised controlled trial to determine the effect of vitamin D_2 or D_3 supplementation on serum uric acid concentration in patients with prediabetes, in whom hyperuricaemia is common.

Material and methods

Study design

We conducted an open-label, randomised controlled study at

* Corresponding author.
E-mail address: boonsong.ong@mahidol.ac.th (B. Ongphiphadhanakul).

https://doi.org/10.1016/j.jcte.2021.100255
Received 12 October 2020; Received in revised form 17 February 2021; Accepted 29 March 2021
Available online 2 April 2021

Ramathibodi Hospital, Mahidol University, Bangkok, Thailand. This study was approved by the Institutional Review Board, Faculty of Medicine Ramathibodi Hospital, Mahidol University and all the participants provided their written informed consent prior to their inclusion. All methods were performed in accordance with relevant guidelines and regulation. The clinical trial number is TCTR20200219002 (Thai Clinical Trials Registry, date of registration 19/02/2020).

Study population

Healthy volunteers aged 35–80 years were recruited by advertising for type 2 diabetes screening. A 75-g oral glucose tolerance test was conducted in the morning after an 8-h overnight fast to identify patients with impaired fasting glucose and/or impaired glucose tolerance, according to the diagnostic criteria by the American Diabetes Association. The participants were randomised to three groups: a vitamin D_3 (cholecalciferol) group, a vitamin D_2 (ergocalciferol) group, and a control (no vitamin D treatment) group. We aimed to raise the total 25(OH)D concentration to comparable levels using either vitamin D_2 or D_3 supplementation; therefore, different weekly doses of vitamin D_2 (20,000 IU) or vitamin D_3 (15,000 IU) were administered [7]. Seventy one participants were included and randomly assigned (1:2:2) to receive vitamin D_3 (15,000 IU weekly, n = 20), vitamin D_2 (20,000 IU weekly, n = 40), or control (no vitamin D, n = 41) for 12 weeks. Compliance was assessed by tablet counting at the end of the study and is reported as the percentage of the tablets missing taken. All the participants in the vitamin D_2 and vitamin D_3 groups demonstrated over 90% compliance.

Measurement of serum 25(OH)D and 1,25(OH)$_2$D concentrations

Serum 25(OH)D_2 and 25(OH)D_3 concentrations were analysed by LC-MS/MS using an Agilent 1200 Infinity liquid chromatograph (Agilent Technologies, Waldbronn, Germany) coupled to a QTRAP 5500 tandem mass spectrometer (AB SCIEX, Foster City, CA, USA) and a MassChrom 25-OH-Vitamin D_3/D_2 diagnostics kit (Chromsystems, Munich, Germany). The sum of the serum 25(OH)D_2 and 25(OH)D_3 concentrations was used to assess overall vitamin D status. The inter- and intra-assay coefficients of variation (CVs) for the serum total 25(OH)D concentration were 6.3% and 5.0%, respectively [9]. Serum 1,25(OH)$_2$D was measured by a chemiluminescent immunoassay using a LIAISON® XL analyser (DiaSorin Inc., Stillwater, MN, USA). This assay had inter- and intra-assay CVs of 6.6% and 5.5%, respectively [8].

Uric acid measurement

Serum uric acid concentration was determined applying the uricase method (Siemens Healthcare Diagnostics Inc., Newark DE, USA). The assay range was 0–20 mg/dl, with reference ranges of 2.6–6.0 and 3.5–7.2 mg/dl for women and men, respectively. The intra- and inter-assay CVs were 1.4% and 1.4% for a uric acid concentration of 5.1 mg/dl and 1.2% and 1.3% for a uric acid concentration of 9.0 mg/dl, respectively.

Statistical analyses

Data are expressed as mean ± SE, unless stated otherwise. Comparison of clinical characteristics between vitamin D supplementation group (received vitamin D_2 or vitamin D_3) and control were performed by independent-Samples *T* Test. The changes in serum uric acid during vitamin D supplementation were assessed using paired Student's *t*-test. Multivariate linear regression was applied to evaluate the influence of independent variables on the changes in serum uric acid concentration. A p value < 0.05 was considered to represent statistical significance. Statistical analysis was conducted using the Statistical Package for the Social Sciences (v13.0, SPSS, Chicago, IL, USA).

Results

Table 1 presents the clinical characteristics of the study population. There were no significant differences in the age, baseline uric acid concentration or 25(OH)D concentration between the vitamin D supplementation group (received vitamin D_2 or vitamin D_3) and controls. However, the vitamin D supplementation group comprised more women. With regard to safety, none of the participants had hypervitaminosis D and hypercalcemia.

After 12 weeks of vitamin D supplementation, 25(OH)D levels significantly increased to 38.6 ± 1.3 ng/mL ($p < 0.001$) in vitamin D supplementation group whereas there was no change in 25(OHD levels in control group (24.9 ± 1.2 ng/mL, $p = 0.27$). As presented in Table 2A, there were no significant changes in the serum uric acid concentration in the vitamin D or control groups. However, in participants with baseline serum uric acid concentration > 6 mg/dL, serum uric acid decreased significantly ($p < 0.05$), whereas there was no change in controls ($p = 0.49$) (Table 2B). A multivariate analysis of the changes in serum uric acid, the form of vitamin D supplementation, and other relevant variables revealed that there were no relationships between the change in serum uric acid concentration and age, sex, BMI, supplementation with vitamin D_2 or D_3, and other baseline parameters, including the uric acid, 25(OH)D, and fasting plasma glucose (FPG) concentrations. However, higher HbA1c level at baseline correlated with the reduction in serum uric acid (Table 3).

To assess the dose–response relationship between vitamin D supplementation and the change in serum uric acid concentration, we applied regression analysis and found that the change in serum 25(OH)D did not correlate significantly with the change in serum uric acid during the period of vitamin D supplementation. The only factor that was found to be associated with the change was baseline serum uric acid concentration (Table 4).

However, the change in serum 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] concentration negatively correlated with the change in serum uric acid concentration during vitamin D supplementation. Furthermore, the statistical significance of this relationship persisted after controlling for age, body mass, baseline uric acid concentration, the type of vitamin D supplementation, and the change in 25(OH)D concentration (Table 5).

Discussion

In the present randomised controlled trial, we have shown that vitamin D supplementation is associated with a reduction in serum uric acid concentration in patients with prediabetes and hyperuricaemia. The present finding is consistent with that of our previous study, in which we applied mediation analysis to prove that circulating uric acid and 25(OH)D concentrations may be reciprocally related [5]. Moreover, changes in the concentrations of both serum 1,25$(OH)_2$D and uric acid were demonstrated during vitamin D supplementation. Taken together, these results suggest that vitamin D may reduce serum uric acid concentration.

Table 1
Clinical characteristics of the study population.

	Controls (n = 29)	Vitamin D (n = 42)	*p* value
Age	57.1 ± 2.0	61.5 ± 1.3	0.07
Female	65.5%	85.7%	<0.05
BMI (kg/m^2)	29.4 ± 1.15	27.5 ± 0.6	0.14
Uric acid (mg/dL)	6.2 ± 0.2	5.8 ± 0.3	0.24
25(OH)D (ng/mL)	25.6 ± 1.1	26.7 ± 0.9	0.42
FPG (mg/dL)	105.1 ± 1.6	103.2 ± 1.6	0.43
HbA1c (%)	6.03 ± 0.05	5.98 ± 0.05	0.47

BMI, body mass index; 25(OH)D, 25-hydroxyvitamin D; FPG, fasting plasma glucose; HbA1a, hemoglobin A1C. Data are expressed as mean (SE). SD, standard error.

Table 2A
Changes in serum uric acid concentration during the study period in all participants (n = 71).

	Uric acid (mg/dL)		p value
	Baseline	12 weeks	
Vitamin D (n = 42)	5.8 ±0.2	5.6 ±0.3	0.15
Control (n = 29)	6.2 ±0.2	6.3 ±0.2	0.90

Table 2B
Changes in serum uric acid concentration during the study period in participants with baseline concentration > 6 mg/dL (n = 36).

	Uric acid (mg/dL)		p value
	Baseline	12 weeks	
Vitamin D (n = 19)	7.4 ±0.2	6.8 ±0.3	<0.05
Control (n = 17)	7.1 ±0.2	6.9 ±0.3	0.49

Table 3
Multivariate analysis of the relationships between the change in uric acid concentration, the form of vitamin D used, and other variables.

	Standardised coefficient	P value
Age (year)	−0.11	0.42
Female	−0.34	0.09
BMI (kg/m^2)	0.24	0.16
Baseline uric acid (mg/dL)	−0.42	<0.05
Baseline 25(OH)D (ng/mL)	0.02	0.92
Baseline FPG (mg/dL)	0.12	0.42
Baseline HbA1c (%)	−0.35	<0.05
Form of vitamin D (D_3 versus D_2)	−0.24	0.36

BMI, body mass index; 25(OH)D, 25-hydroxyvitamin D; FPG, fasting plasma glucose; HbA1c, hemoglobin A1C.

Table 4
Multivariate analysis of the relationship between the change in uric acid concentration, the change in 25(OH)D levels, and other variables.

	Standardized coefficient	P value
Age (year)	−0.08	0.53
Female	−0.24	0.07
BMI (kg/m^2)	−0.08	0.53
Baseline uric acid (mg/dL)	−0.41	< 0.01
HbA1c (%)	−0.17	0.16
The change in 25(OH)D (ng/mL)	−0.04	0.76

BMI, body mass index; HbA1c, hemoglobin A1C; 25(OH)D, 25-hydroxyvitamin D.

Table 5
Multivariate analysis of the relationship between changes in uric acid concentration, the change in $1,25(OH)_2D$ levels, and other variables.

	Standardized coefficient	P value
Age (year)	−0.04	0.74
Female	−0.20	0.10
BMI (kg/m^2)	−0.06	0.61
Baseline uric acid (mg/dL)	−0.35	< 0.01
HbA1C (%)	−0.18	0.10
The change in $1,25(OH)_2D$ (pg/mL)	−0.33	<0.01

BMI, body mass index; HbA1c, hemoglobin A1C; $1,25(OH)_2D$, 1,25-dihydroxyvitamin D.

Previous studies conducted in the general population and in patients with type 2 diabetes have revealed an inverse relationship between serum uric acid concentration and vitamin D status [10,11]. However, it is not clear whether there is a causal relationship due to the cross-sectional nature of most of the previous studies. To our knowledge, there have been no studies to date of the serum uric acid response to vitamin D supplementation. However, a possible causal link between uric acid and vitamin D metabolism may be indicated by the finding that the use of allopurinol to reduce serum uric acid concentration is associated with a reduction in $1,25(OH)_2D$ concentration. It has also been shown that uric acid suppresses 1α hydroxylase activity, both *in vivo* and *in vitro* [12].

The underlying mechanism of this potential urate-reducing effect of vitamin D is unclear. Vitamin D affects many physiological functions through its action on a number of target genes [13]. It is therefore conceivable that it will affect uric acid production, disposal or both. Genome-wide association studies have identified a number of genes that influence circulating uric acid concentration, including the *ABCG2* gene, which encodes a high-capacity urate transporter gene in the intestinal epithelium and on the luminal surface of renal proximal tubular epithelial cells [14]. The other genes that have been reported to be associated with circulating uric acid concentration are principally renal urate transporters, such as *SLC2A9*, *SLC17A3* and *SLC22A12*. Although it is conceivable that vitamin D will affect the expression of these uric acid-regulating genes, there have been no studies to support or refute such a possibility. It is also likely that the reduction in uric acid that occurs during vitamin D supplementation may be mediated through a decrease in parathyroid hormone (PTH) concentration. It is known that serum PTH is associated with uric acid concentration [15,16], and this relationship is likely to be causal, because the administration of teriparatide to patients with osteoporosis can induce hyperuricaemia.

Uric acid has been associated with a number of metabolic disorders. For example, the serum uric acid concentration is frequently higher in patients with type 2 diabetes and non-alcoholic fatty liver disease [17], in which, together with fructose, it might play a pathogenic role [18]. Hyperuricaemia is also associated with the metabolic syndrome, and this association strengthens as the number of adverse metabolic factors present increases [19]. In addition, mean serum uric acid is a strong predictor of the development of prediabetes [20], and hyperuricaemia is associated with a number of adverse effects in patients with diabetes, such as atrial fibrillation [21]. Moreover, hyperuricaemia contributes to a more rapid progression of diabetic nephropathy [22]. A causal role of uric acid in macrovascular disease has also been suggested in a study that used a Mendelian randomisation approach [23]. With regard to ethnicity, there are ethnic differences in serum uric acid levels as well as the degree of relationship between uric acid and metabolic syndrome with non-Hispanic white females exhibited the lowest degrees of correlation between levels of uric acid and components of the metabolic syndrome [24]. Data with regard to the serum uric acid and its relationship to metabolic syndrome are relatively few. At least a study has examined serum uric acid in specific Asian ethnic groups and found that there are higher concentrations of serum uric acid in Chinese compared with Indians and Malays unexplained by the metabolic syndrome and other demographic variables [25]. Our findings are supportive of the role of vitamin D supplementation in reducing serum uric acid in Asians with higher fasting plasma glucose which may be at risk of developing metabolic syndrome.

Therapeutic agents for hyperuricaemia, although effective, can have adverse events that are sometime serious, such as the agranulocytosis and toxic epidermal necrolysis that can develop after allopurinol use. Our results suggest that vitamin D supplementation is considered for prediabetic patients with mild hyperuricaemia. However, the benefits of ameliorating hyperuricaemia as a strategy to reduce the risks of macrovascular disease and non-alcoholic fatty liver disease, although possible, on the basis of the aforementioned studies, remain to be determined.

There are a number of limitations in the study. The number of participants was small, the duration of intervention is relatively short, and subjects in the present study were prediabetes. Generalization to other population may be limited. Further studies with larger sample sizes,

longer-term follow-up period as well as in other study populations besides prediabetes are warranted. Moreover, as demonstrated in the present study, it is of note that serum $1,25(OH)_2D$ levels were related to the change in serum uric acid levels after supplementation. Response in uric acid levels after the administration of active analog of vitamin D should be explored

Conclusion

Vitamin D supplementation is associated with lower serum uric acid in prediabetic patients with hyperuricaemia, and supplementation might be considered to help alleviate hyperuricaemia in these patients.

CRediT authorship contribution statement

Hataikarn Nimitphong: Conceptualization, Methodology. **Sunee Saetung:** Methodology. **La-or Chailurkit:** Methodology. **Suwannee Chanprasertyothin:** Methodology. **Boonsong Ongphiphadhanakul:** Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

This study was supported by the National Science and Technology Development Agency of Thailand.

References

[1] Kuo C-F, Grainge MJ, Zhang W, Doherty M. Global epidemiology of gout: prevalence, incidence and risk factors. Nat Rev Rheumatol 2015;11(11):649–62.
[2] Zhu Y, Pandya B JandChoi H K. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008, Arthritis Rheum 2011;63(10):3136-41.
[3] Choi HK. A prescription for lifestyle change in patients with hyperuricemia and gout. Curr Opin Rheumatol 2010;22(2):165–72.
[4] Correia A, Azevedo MdS, Gondim F, Bandeira F. Ethnic aspects of vitamin D deficiency. Arq Bras Endocrinol Metabol 2014;58(5):540–4.
[5] Thakkinstian A, Anothaisintawee T, Chailurkit L, Ratanachaiwong W, Yamwong S, Sritara P, et al. Potential causal associations between vitamin D and uric acid: Bidirectional mediation analysis. Sci Rep 2015;5(1). https://doi.org/10.1038/srep14528.
[6] 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.
[7] Chailurkit L, Nimitphong H, Saetung S, Ongphiphadhanakul B. Urinary metabolic profiles after vitamin D2 versus vitamin D3 supplementation in prediabetes. J Clin Transl Endocrinol 2019;16:100194. https://doi.org/10.1016/j.jcte.2019.100194.
[8] Nimitphong H, Samittarucksa R, Saetung S, et al. The Effect of Vitamin D Supplementation on Metabolic Phenotypes in Thais with Prediabetes. J Med Assoc Thai 2015;98(12):1169–78.
[9] Zittermann A, Ernst JB, Becker T, Dreier J, Knabbe C, Gummert JF, et al. Measurement of circulating 1,25-Dihydroxyvitamin D: comparison of an automated method with a liquid chromatography tandem mass spectrometry method. Int J Anal Chem 2016;2016:1–6.
[10] Peng H, Li H, Li C, Chao X, Zhang Q, Zhang Y, et al. Association between vitamin D insufficiency and elevated serum uric acid among middle-aged and elderly Chinese Han women. PLoS One 2013;8(4):e61159. https://doi.org/10.1371/journal.pone.0061159.
[11] Yilmaz H, Kaya M, Sahin M, Delibasi T. Is vitamin D status a predictor glycaemic regulation and cardiac complication in type 2 diabetes mellitus patients? Diabetes Metab Syndr 2012;6(1):28–31.
[12] Chen W, Roncal-Jimenez C, Lanaspa M, Gerard S, Chonchol M, Johnson RJ, et al. Uric acid suppresses 1 alpha hydroxylase in vitro and in vivo. Metabolism 2014;63(1):150–60.
[13] Holick MF. Noncalcemic actions of 1,25-dihydroxyvitamin D3 and clinical applications. Bone 1995;17(2):S107–11.
[14] Huls M, Brown CDA, Windass AS, Sayer R, van den Heuvel JJMW, Heemskerk S, et al. The breast cancer resistance protein transporter ABCG2 is expressed in the human kidney proximal tubule apical membrane. Kidney Int 2008;73(2):220–5.
[15] Hui JY, Choi JWJ, Mount DB, Zhu Y, Zhang Y, Choi HK. The independent association between parathyroid hormone levels and hyperuricemia: a national population study. Arthritis Res Ther 2012;14(2):R56. https://doi.org/10.1186/ar3769.
[16] Chin K Y, Nirwana S IandNgah W Z. Significant association between parathyroid hormone and uric acid level in men, Clin Interv Aging 2015;101377-80.
[17] Fan N, Zhang L, Xia Z, Peng L, Wang Y, Peng Y. Sex-specific association between serum uric acid and nonalcoholic fatty liver disease in type 2 Diabetic Patients. J Diabetes Res 2016;2016:1–6.
[18] Moore J, Gunn P, Fielding B, Gunn PJ, Fielding BA. The role of dietary sugars and de novo lipogenesis in non-alcoholic fatty liver disease. Nutrients 2014;6(12):5679–703.
[19] Khichar S, Choudhary S, Singh VB, Tater P, Arvinda RV, Ujjawal V. Serum uric acid level as a determinant of the metabolic syndrome: A case control study. Diabetes Metab Syndr 2017;11(1):19–23.
[20] Zhang Q, Bao X, Meng G, et al. The predictive value of mean serum uric acid levels for developing prediabetes. Diabetes Res Clin Pract 2016:11879–89.
[21] Mantovani A, Rigolon R, Pichiri I, Pernigo M, Bergamini C, Zoppini G, et al. Hyperuricemia is associated with an increased prevalence of atrial fibrillation in hospitalized patients with type 2 diabetes. J Endocrinol Invest 2016;39(2):159–67.
[22] Bartáková V, Kuricová K, Pácal L, Nová Z, Dvořáková V, Švrčková M, et al. Hyperuricemia contributes to the faster progression of diabetic kidney disease in type 2 diabetes mellitus. J Diabetes Complicat 2016;30(7):1300–7.
[23] Yan D, Wang J, Jiang F, Zhang R, Wang T, Wang S, et al. A causal relationship between uric acid and diabetic macrovascular disease in Chinese type 2 diabetes patients: A Mendelian randomization analysis. Int J Cardiol 2016;214:194–9.
[24] DeBoer MD, Dong L, Gurka MJ. Racial/ethnic and sex differences in the relationship between uric acid and metabolic syndrome in adolescents: an analysis of National Health and Nutrition Survey 1999–2006. Metabolism 2012;61(4):554–61.
[25] Hawkins R. Serum Uric Acid Concentrations in Chinese, Indians, and Malays. Am J Clin Pathol 2012;138:A327–A327.