Letters to the editor

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Ben Ponvilawan, Nipith Charoenngam

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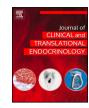
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## Vitamin D and Uric Acid: Is Parathyroid Hormone the Missing Link?

**Article type**: Letter to the editor

Authors: Ben Ponvilawan, MD<sup>1</sup>, Nipith Charoenngam, MD<sup>2,3</sup>

<sup>1</sup> Department of Pharmacology, Faculty of Medicine Siriraj Hospital, Mahidol University,

Bangkok, Thailand

<sup>2</sup> Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok,

Thailand

<sup>3</sup>Section Endocrinology, Diabetes, Nutrition and Weight Management, Department of Medicine,

Boston University School of Medicine, Boston, MA, United States

\*Corresponding author; Nipith Charoenngam, MD

Address: 85 E Newton St, Boston, MA 02118

E-mail: nipithcharoenngam@gmail.com

Running Head: PTH, vitamin D and serum uric acid level

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Dear Editor,

With interest, we read the article of Nimitphong et al. (1), which revealed the potential uric-lowering effect of vitamin D supplementation in patients with prediabetes and hyperuricemia. The result of this study supports the causal association between vitamin D deficiency and insufficiency and elevated serum uric acid that has been shown in previous observational studies (2) independent of the fact that the association might also be confounded by presence of comorbid obesity and metabolic syndrome.

We would like to highlight that the uric acid-lowering effect of vitamin D supplementation is likely mediated by the decrease in serum parathyroid hormone (PTH) level. Circulating 25(OH)D gets metabolized by the enzyme 1α-hydroxylase in the kidney into 1,25dihydroxyvitamin D [1,25(OH)<sub>2</sub>D], which inhibits PTH synthesis directly by the activation of vitamin D receptor in the parathyroid glands and indirectly by stimulating intestinal calcium absorption causing a transient increase in serum ionized calcium level (3). The authors did mention that vitamin D might affect the expression of uric acid-regulating genes. In fact, it is known that PTH could directly downregulate the ATP-binding cassette transporter G2 (ABCG2) transporter, causing a reduction in urinary uric acid excretion (4). Moreover, it has been shown that patients with primary hyperparathyroidism had increased levels of serum uric acid and that those patients who received parathyroidectomy also had decreased serum uric acid levels postoperatively (5-7). All of these, along with the evidence that teriparatide [PTH(1-34)] could induce hyperuricemia, would therefore support the causal association of hyperparathyroidism with decreased renal clearance of uric acid and hyperuricemia. Therefore, it would be of great interest to further investigate if the decrease in uric acid level after vitamin D supplementation is secondary to increased urinary uric acid excretion and if this change is dependent on the decrease in serum PTH level.

As mentioned by the authors, uric acid is shown to suppress the expression of the CYP27B1 gene which encodes the enzyme  $1\alpha$ -hydroxylase in the kidney *in vitro* and *in vivo*, leading to decreased conversion of 25(OH)D into 1,25-dihydroxyvitamin D (8). It should therefore worth noting that vitamin D, PTH and uric acid forms a cycle of positive feedback, as shown in the **Figure**.

Finally, we propose that elevation of serum uric acid may be a marker of vitamin D deficiency and/or hyperparathyroidism and that screening and treating vitamin D deficiency may be warranted in patients with hyperuricemia. Further study should be conducted to determine the clinical utility of this measure.

**Conflicts of interest:** The authors declare that they have no conflicts of interest.

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**Figure legend** Schematic representation of the interplay of vitamin D, parathyroid hormone and uric acid. Uric acid inhibits the expression of the CYP27B1 gene, which encodes the enzyme  $1\alpha$ -

hydroxylase that converts 25-hydroxyvitamin D into 1,25-dihydroxyvitamin D at the renal proximal tubule. 1,25-dihydroxyvitamin D inhibits parathyroid hormone secretion at the parathyroid glands directly and indirectly by stimulating intestinal calcium absorption leading to a transient increase in serum ionized calcium. Parathyroid hormone inhibits the ATP-binding cassette transporter G2 transporter, which, in turn, results in decreased urinary uric acid excretion and hyperuricemia.

Abbreviations: 1α-OHase: 1α-hydroxylase; 25-OHase: 25-hydroxylase; 1,25(OH)<sub>2</sub>D: 1,25-dihydroxyvitamin D; 25(OH)D: 25-hydroxyvitamin D; ABCG2: ATP-binding cassette transporter G2 transporter; PTH: parathyroid hormone

