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ORIGINAL STUDY

Serum 25-Hydroxyvitamin D Level Does Not Affect the Aggressiveness and Prognosis of Papillary Thyroid Cancer

Hwa Young Ahn,[1] Yun Jae Chung,[1] Kwang-Yeol Park,[2] and Bo Youn Cho[1]

Background: Vitamin D deficiency has been known to be associated with the aggressiveness and prognosis of several cancers. This study evaluated the effect of preoperative serum vitamin D levels on the aggressiveness and prognosis of papillary thyroid cancer (PTC).
Methods: In total, 820 patients with PTC were enrolled. 25-hydroxyvitamin D levels were measured in blood samples before surgery. Clinical, pathologic, and recurrence data were accessed to examine the prognostic effects of vitamin D. Patients were categorized into four quartiles by preoperative serum vitamin D levels.
Results: Of the enrolled patients, 795 (97%) had insufficient vitamin D levels (<30 ng/mL). Vitamin D levels showed positive correlations with age and body mass index (BMI), and negative correlations with serum thyrotropin levels and antithyroid peroxidase antibody titers. The association between vitamin D quartile and the risks of extrathyroidal invasion, lymph node metastasis, advanced cancer stages (III or IV), and risk of recurrence were not significant after adjusting for age, sex, BMI, preoperative ionized calcium, and parathyroid hormone. Additionally, serum vitamin D was not associated with recurrent or persistent PTC.
Conclusion: Serum vitamin D levels are not associated with either disease aggressiveness or poor outcomes among patients with PTC and vitamin D insufficiency.

Introduction

Vitamin D has been known to be essential for bone mineralization by regulating calcium and phosphate metabolism (1). In addition to skeletal action, vitamin D levels have also been associated with several malignancies, including breast, colon, and prostate cancer (2). Previous epidemiological studies have reported an association between low serum vitamin D and increased risk of colorectal (3), breast (4), and prostate (5) cancer. Additionally, low vitamin D levels have been associated with high mortality and low disease-free survival rates in patients with colorectal cancer, breast cancer, and lymphoma (6). However, a small pilot study found no association between vitamin D levels and occurrence of thyroid cancer (7). Recently, Kim *et al.* reported that low serum vitamin D is associated with poor clinicopathological findings in female patients with papillary thyroid cancer (PTC) (8).

Calcitriol (1,25-OH Vitamin D_3) is a potent activated form of vitamin D and is converted from 25-hydroxyvitamin D_3 by cytochrome P450 enzyme CYP27B1 in the kidney (9). The action of vitamin D is mediated by the vitamin D receptor (VDR), a ligand-regulated nuclear hormone receptor. In previous studies, *VDR* expression has been reported in normal thyroid tissue as well as thyroid cancer tissue (10,11). *VDR* expression was shown to be higher in differentiated thyroid cancer tissue than normal thyroid tissue, but decreased expression was observed in cases of local or distant metastasis (11), suggesting the possibility of a local impact of calcitriol on thyroid cancer at an early stage. Another enzyme, CYP24A1, catabolizes calcitriol into the inactive 1α, $24,25(OH)_3D$ and $24,25(OH)_2D$, and it was found to be increased in PTC (12). Furthermore, overexpression of *CYP24A1* showed a strong correlation with the presence of the $BRAF^{V600E}$ mutation (12). These molecular findings suggest that vitamin D might have antitumor activities in thyroid cancer cells.

25-hydroxyvitamin D_3 is the circulating form of vitamin D and is usually measured in the blood to monitor vitamin D levels in human subjects. Deficiency of vitamin D is defined as serum $25(OH)D_3$ of <20 ng/mL, and vitamin D insufficiency is defined as a level of 21–29 ng/mL (13). Vitamin D insufficiency is very common in Korea, and vitamin D deficiency was found in 47.3% of males and 64.5% of females in the 2008 Korea National Health and Nutrition Examination Survey (KNHANES) (14). In addition, PTC has recently become a very common cancer in Korea. Therefore, this study evaluated the associations of preoperative serum

Departments of [1]Internal Medicine and [2]Neurology, Chung-Ang University Hospital, Chung-Ang University College of Medicine, Seoul, Korea.