Comparison of the association between circulating vitamin D₃ levels and clinical outcomes in patients with asthma and chronic obstructive pulmonary disease: a prospective observational study

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Summary

Vitamin D has an immune-modulating effect, related to the pathophysiology of asthma and chronic obstructive pulmonary disease (COPD). However, few studies have focused on the difference between patients with asthma and COPD in the association of circulating vitamin D levels with clinical outcomes. We sought to investigate the associations of circulating vitamin D levels with health-related quality of life (HR-QOL), severity, and exacerbations. Subjects included 152 asthma patients and 50 COPD patients. We measured plasma concentrations of 25-hydroxyvitamin D₃ [25(OH)D₃]. HR-QOL was assessed using the EuroQoL 5-Dimension (EQ-5D) and the 12-item Short Form Health Survey (SF-12) scales. Exacerbations were recorded during a one-year follow-up. Associations between plasma 25 (OH)D₃ concentrations and outcome variables were evaluated using linear regression. Plasma concentrations of 25(OH)D₃ were positively associated with the EQ-5D index value and the SF-12 physical component score in patients with asthma; however, such associations were not observed in patients with COPD. A significant association between severity and plasma concentrations of 25(OH)D₃ was found only in patients with COPD. The hazard ratios (95% confidence interval) of plasma 25(OH)D₃ concentrations (per 1 ng/mL decrease) for time to first exacerbation was 1.38 (1.10–1.75; \(p = 0.006\)) and 0.95 (0.87–1.03; \(p = 0.179\)) in patients with COPD and asthma, respectively. Lower concentrations of plasma 25(OH)D₃ contributed to lower HR-QOL in patients with asthma, and were associated with severity and risk of future exacerbations in patients with COPD.

Keywords: asthma; chronic obstructive pulmonary disease; QOL; vitamin D
**Introduction**

Vitamin D has been recognized as a bio-activator for maintaining skeletal health; recently it has been suggested to have the ability to modulate immune function.\(^1\) Vitamin D is produced by sunlight exposure, and is mainly present in its hydroxylated form, 25-hydroxyvitamin D [25(OH)D], in circulating blood. Vitamin D status, which can be evaluated by measuring the plasma/serum concentrations of 25(OH)D, is affected by geography and season.\(^2\) Vitamin D deficiency, defined as 25(OH)D levels less than 20 ng/mL, \(^3\) is now a global public health problem,\(^4,5\) and was reported to be associated with the pathology of several illnesses, including asthma and chronic obstructive pulmonary disease (COPD).\(^6,7\) Therefore, the evaluation of vitamin D status may be considered to be important for disease control.

Asthma and COPD have a common feature of airway inflammation; however, the inflammatory processes of these diseases are different. Although asthma is recognized as a heterogeneous disorder, its dominant phenotype can be explained by eosinophilic inflammation.\(^8\) COPD is generally characterized by chronic airflow limitation and neutrophilic inflammation, caused by cigarette smoke and oxidative stress; and systemic inflammation is also known to be associated with the pathophysiology COPD.\(^9\) Recent randomized trials attempted to demonstrate the beneficial effects of vitamin D supplementation as a potential therapy for asthma and COPD; however, whether vitamin D supplementation improves the clinical outcomes of these patients remains controversial.\(^10,11\) The differences in inflammation between asthma and COPD may contribute to different associations between vitamin D status and clinical outcomes; however, this hypothesis has not been validated.
In the treatment of asthma and COPD, severity and exacerbation are some of the important clinical outcomes, which are related to the quality of life (QOL). Patients with severe asthma and COPD have a higher risk for the occurrence of exacerbations, which can be life-threatening if not treated promptly. Therefore, with respect to treatment, it is highly relevant to control the symptoms and prevent progression to the severe stage, so as to contribute to improving QOL. Few studies have assessed the influence of vitamin D status on clinical manifestations in both asthma and COPD patients using the same index. Health-related QOL (HR-QOL) is a global multidimensional construct, useful to measure health properties of numerous illness using the same index. This study aimed to investigate the difference between Japanese patients with asthma and COPD in terms of the association of vitamin D status with HR-QOL and clinical manifestations, namely severity and exacerbation.

Materials and Methods

Subjects

This study included 152 patients with asthma and 50 patients with COPD from a previously published observational study. Subjects were recruited from the Shizuoka General Hospital between February and December 2015, with the following inclusion criteria: 1) patients aged 20 years or older and 2) patients without exacerbations in the previous 8 weeks. The present study was approved by the Shizuoka General Hospital Ethics Committee (approval number: SGH 15-01-55) and written informed consent was obtained from each subject before participation. All patients with asthma and COPD fulfilled the
diagnosis according to the Global Initiative for Asthma guidelines\textsuperscript{13)} and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) report,\textsuperscript{14)} respectively.

**Study design and clinical variables**

All subjects underwent blood sampling, lung function tests, measurement of fractional exhaled nitric oxide (FeNO), and assessment of HR-QOL in a cross-sectional manner. On the same day, we performed the Asthma Control Test (ACT; higher scores indicate better control) and Asthma Control Questionnaire (ACQ; lower scores indicate better control) to assess asthma control level in patients with asthma, and the COPD Assessment Test (CAT; lower scores indicate better control) to assess COPD control level in patients with COPD. Severe asthma was defined according to the European Respiratory Society/American Thoracic Society guidelines\textsuperscript{15)} as uncontrolled asthma despite treatment with high-dose inhaled corticosteroid (≥ 1000 μg/day fluticasone equivalent dose), plus a long-acting β2-agonist or another controller or treatment with continuous systemic oral corticosteroids or omalizumab. Severe COPD was defined according to the GOLD stage, namely GOLD stage 3 [forced expiratory volume in 1 second (FE\textsubscript{1}), 30–40% of the predicted value] and GOLD stage 4 (FE\textsubscript{1} < 30%).\textsuperscript{14)} We recorded the occurrence of exacerbations, defined as worsening symptoms requiring hospitalization or treatment with oral corticosteroids and/or antibiotics, during the one-year follow-up period.

**HR-QOL**

HR-QOL was assessed using the Japanese version of the EuroQoL 5-Dimension (EQ-5D) 5-level questionnaire and the Japanese version of 12-item Short Form Health
Survey (SF-12). The EQ-5D consists of the visual analog scale (VAS) applied to the 5 dimensions of health, including mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. We calculated the EQ-5D index value for the 5 dimensions of health according to the conversion criteria, which were validated in Japan. We also summarized the result of the SF-12 as three component scores: physical component score (PCS), mental component score (MCS), and role-social component score (RCS). Higher scores of EQ-5D and SF-12 indicate better HR-QOL. EQ-5D index value 1.0 and EQ-5D VAS 100 represent the best health state. SF-12 scores over 50 mean a better than average health state.

Measurements of plasma 25(OH)D₃ concentrations

We measured plasma concentrations of 25(OH)D₃ using an LC-MS/MS system consisting of a Waters ACQUITY UPLC coupled to a Waters TQD (Waters, Milford, MA, USA) mass spectrometer. Analytical samples were prepared with supported liquid extraction (SLE) from 50 μL of plasma mixed with d6-25(OH)D₃ (Toronto Research Chemicals, North York, Ontario, Canada) and 50% isopropanol aqueous solution. The diluted plasma samples were applied to an Isolute SLE+ cartridge (Biotage Japan, Tokyo, Japan) and eluted with heptane. The eluates were evaporated to dryness at 40 °C under a stream of nitrogen, and diluted with 50 μL of the mobile phase. Cadenza CD-C18 (75 × 2 mm, 3 μm, Intakt, Kyoto, Japan) was used at 40 °C for chromatographic separation. The mobile phase consisted of water containing 2 mmol/L ammonium acetate and 0.1% formic acid/methanol containing 0.1% formic acid (10:90, v/v). The MS/MS was performed in electrospray ionization positive ion mode, collision energy at 25 eV and monitoring the transitions m/z 401.35 to 159.1 for 25(OH)D₃ and 407.35 to 159.1 for d6-25(OH)D₃. Calibration curves were fitted using a
weighted \((1/x^2)\) linear regression over the concentration range of 5–100 ng/mL.

**Statistical analysis**

Categorical variables are presented as numbers and percentages, and continuous variables are expressed as medians and interquartile ranges (IQR). The relationships between plasma concentrations of \(25(\text{OH})\text{D}_3\) and clinical variables were assessed using linear regression with \(25(\text{OH})\text{D}_3\) concentrations as the dependent variable. We evaluated the association of plasma concentrations of \(25(\text{OH})\text{D}_3\) with the time to first exacerbation using Cox proportional hazards regression models, and the hazard ratio and its 95% confidence interval were estimated. In multivariate analysis, covariates were selected by the forward and backward stepwise selection procedure based on the Akaike Information Criterion. We performed all analyses using R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria). P-values less than 0.05 were considered statistically significant.

**Results**

**Concentration of \(25(\text{OH})\text{D}_3\) in patients with asthma and COPD**

Demographic and clinical characteristics of patients with asthma \((n = 152)\) and COPD \((n = 50)\) were previously described.\(^{12}\) The median age was 66 (IQR, 50–74) and 75 years (IQR, 71–79), and the number of male patients was 71 (46.7%) and 45 (90.0%) in patients with asthma and COPD, respectively. The median concentration of \(25(\text{OH})\text{D}_3\) in all patients was 13.4 ng/mL (IQR, 10.6–16.5). There was no significant difference in \(25(\text{OH})\text{D}_3\) concentration between patients with asthma (median, 13.6; IQR, 10.6–16.9) and COPD...
The proportion of patients with plasma 25(OH)D₃ concentration < 20 ng/mL was 89.5% and 94.0% in patients with asthma and COPD, respectively.

**Association of 25(OH)D₃ concentration with HR-QOL and clinical variables**

COPD patients had lower EQ-5D index value, VAS, and SF-12 PCS, and slightly higher SF-12 MCS, than patients with asthma (Fig. 2). ACT, ACQ, and CAT scores were weakly to moderately correlated with EQ-5D index, VAS, and SF-12 PCS (Supplementary Table 1). The association of plasma 25(OH)D₃ concentration with HR-QOL and clinical variables was evaluated using linear regression (Table 1). We obtained significantly positive coefficients for index value and VAS in EQ-5D, PCS and MCS in SF-12, and ACT in patients with asthma, suggesting that higher concentrations of 25(OH)D₃ were associated with higher HR-QOL and proper control of asthma. On the other hand, no significant associations of 25(OH)D₃ plasma concentration with HR-QOL or CAT were found in patients with COPD.

**Association of 25(OH)D₃ concentration with the severity of asthma and COPD**

The number of patients with severe asthma and severe COPD was 25 (16.4%) and 17 (34.0%), respectively. Patients with severe COPD had significantly lower plasma concentrations of 25(OH)D₃ than those with non-severe COPD; however, no significant difference was found in 25(OH)D₃ concentration between patients with severe and non-severe asthma (Table 1).
Association of 25(OH)D₃ concentration with exacerbations of asthma and COPD

During a one-year follow-up, exacerbations were observed in 15.1% of patients with asthma and 26.0% of patients with COPD. There was a significant association between the decrease of 25(OH)D₃ plasma concentrations and future exacerbations during the follow-up in patients with COPD (Table 2). This association was still significant after lung function was added as a covariate in the multivariate model (Table 2). In patients with asthma, we observed no significant association of 25(OH)D₃ concentration with exacerbations (Table 2).

Discussion

The present study demonstrated relevant differences in the association of vitamin D status with HR-QOL and clinical manifestations between patients with asthma and COPD. First, the association between 25(OH)D₃ plasma concentration and HR-QOL was assessed using the same indices, namely EQ-5D and SF-12, for the two diseases. Lower HR-QOL scores were related to lower concentrations of plasma 25(OH)D₃ in patients with asthma, but not COPD. Second, we showed that lower concentrations of plasma 25(OH)D₃ contributed to the severity and the risk for future exacerbations in patients with COPD, but not asthma.

To our knowledge, this is the first report demonstrating a positive relationship between vitamin D status and HR-QOL scores in patients with asthma. The decrease of 25(OH)D₃ plasma concentration was strikingly linked with lower EQ-5D index value, VAS score, and SF-12 PCS. Furthermore, we evaluated the relationship between vitamin D status and asthma control scores. A significant association with 25(OH)D₃ levels was found only for the ACT score, and not for the ACQ score of asthma patients. This difference can be postulated to be
caused by the difference in the duration of asthma symptoms reflected by the ACT and ACQ scores: the ACT consists of questionnaires evaluating the control status of asthma symptoms during the past four weeks, while the ACQ evaluates them during the past week. Although there is no previous evidence indicating the relationship between ACQ and vitamin D levels, a positive correlation between vitamin D levels and ACT was reported in asthmatic adults and children with moderate to severe asthma.\textsuperscript{16,17} We found that the ACT and ACQ scores correlated with the EQ-5D index value, VAS, and PCS, in agreement with previous studies.\textsuperscript{18,19} The difference in the association between ACT and ACQ may help explain the role of vitamin D in disease control and HR-QOL in patients with asthma. Vitamin D deficiency has been associated with an increase in pro-inflammatory cytokines, the reduction of regulatory T cells, and airway remodeling in asthma.\textsuperscript{20} In this study, most patients with asthma had deficient concentrations of 25(OH)D$_3$, suggesting that vitamin D deficiency contributed to an increase in chronic inflammation, and influenced the subsequent increase in respiratory symptoms. Further studies, which can uncover the mechanisms of action of vitamin D, may help assess the use of vitamin D supplementation in asthma, since the goal of asthma treatment is improving the patients’ QOL.

The HR-QOL scores in COPD patients, who are characterized by lower scores in EQ-5D and in the PCS of SF-12 compared with asthma patients, were not significantly associated with plasma concentrations of 25(OH)D$_3$. Patients with COPD generally have higher smoking status and lower lung function, and these factors were found to be associated with HR-QOL scores.\textsuperscript{21} These results suggested that the influence of vitamin D status on HR-QOL score was relatively limited compared to the clinical features of COPD. Our results support the findings of previous cross-sectional studies which did not find associations.
between vitamin D status and general and COPD-specific HR-QOL scores, including EQ-5D scores and the St. George’s Respiratory Questionnaire, in COPD patients.\textsuperscript{22–24)}

By contrast, it is interesting to observe that in COPD patients, lower concentrations of plasma $25(\text{OH})\text{D}_3$ contributed to lower lung function, corresponding to increased COPD severity, in agreement with previous studies.\textsuperscript{25–28)} Moreover, the multivariate model indicated that the decrease of plasma $25(\text{OH})\text{D}_3$ level was independently associated with future exacerbations after lung function was added as a covariate. Exacerbations of COPD are commonly caused by respiratory tract infections associated with viruses or bacteria.\textsuperscript{29)} A large cohort study evaluated the association of vitamin D status and self-reported respiratory tract infections in subjects aged over 12 years.\textsuperscript{30)} Decreased vitamin D levels were associated with a higher risk for respiratory tract infections, and this risk was greater in patients with COPD.\textsuperscript{30)} In addition, a meta-analysis demonstrated the efficacy of vitamin D supplementation in the prevention of respiratory tract infections, and this benefit was particularly evident in subjects with vitamin D deficiency.\textsuperscript{31)} It has been reported that vitamin D deficiency was associated with hospitalization for COPD exacerbations in the previous year.\textsuperscript{32)} In contrast, no association was found between vitamin D levels and subsequent exacerbations of COPD over one year; however, only approximately one-third of study subjects had vitamin D insufficiency.\textsuperscript{33)} A recent study suggested that only in patients with vitamin D deficiency supplementation has a protective effect against COPD exacerbations.\textsuperscript{34)} Our results can complement these previous studies, because vitamin D insufficiency was predominant among the patients in the present study.

Asthma can be controlled with inhaled corticosteroids in most patients; however, approximately 5–10\% of patients with asthma, classified as severe asthma, have inadequate
control despite optimal pharmacological treatment. We found no significant association of plasma concentrations of 25(OH)D₃ with severe asthma. The pathophysiology of severe asthma is not fully understood, because of the heterogeneity of this phenotype. Several mechanisms and comorbidities, such as eosinophilic and neutrophilic disorders, allergies, and obesity are considered to be related to inflammation in severe asthma. We also showed that vitamin D status was not a sufficiently predictive marker of future asthma exacerbations, although a few studies have demonstrated the independent association of vitamin D levels and exacerbations in adults patients with asthma. As with severe asthma, several factors are associated with asthma exacerbations. In the present study, it is notable that serum total IgE levels showed a positive association trend with 25(OH)D₃ levels, as observed in a previous study. A higher level of IgE is considered to contribute to severity, and this fact could explain the non-significant results of this study. The effects of vitamin D on the inflammatory mechanisms associated with severe asthma or asthma exacerbations are still incompletely clarified, and our findings suggest the need for further study.

This study has several limitations. First, we measured plasma concentrations of 25(OH)D₃ in a cross-sectional manner. Vitamin D status is known to vary with season, but we could not exclude this influence in the present study. Second, the number of patients with COPD was relatively small compared with that of asthma patients.

In conclusion, plasma levels of vitamin D, a modulator of immune function, showed different association patterns between asthma and COPD in Japanese patients. Lower concentrations of plasma 25(OH)D₃ contributed to lower HR-QOL in patients with asthma, while were associated with severity and the risk of future exacerbations in patients with COPD. Our observations suggest that vitamin D status affects different immune responses or
symptoms in patients with asthma and COPD. Supplementation of vitamin D may have a
different effect on clinical outcomes in asthma and COPD.

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Conflict of Interest

T. Shirai reports personal fees from AstraZeneca Japan outside the submitted work. The other authors have nothing to disclose.

Supplementary Materials

The online version of this article contains supplementary materials.
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Fig 1. Plasma concentrations of 25(OH)D\textsubscript{3} in patients with asthma and COPD.
Fig 2. HR-QOL scores in patients with asthma and COPD.

EQ-5D scores represented as index value and visual analog scale (VAS). SF-12 scores represented as physical component score (PCS), mental component score (MCS), and role-social component score (RCS).
Table 1. Univariate linear regression analysis of factors associated with plasma concentrations of 25(OH)D₃

| Factors                         | Asthma  | COPD   |
|--------------------------------|---------|--------|
|                                | β(95% CI) | p value | β(95% CI) | p value |
| HR-QOL                         |         |        |         |        |
| EQ-5D index value (per 0.1)    | 0.93 (0.36, 1.49) | 0.002 | 0.33 (–0.46, 1.13) | 0.418 |
| EQ-5D VAS (per 10)             | 0.91 (0.39, 1.44) | <0.001 | 0.24 (–0.53, 1.01) | 0.546 |
| SF-12 PCS (per 10)             | 0.96 (0.36, 1.56) | 0.002 | 0.04 (–0.75, 0.82) | 0.928 |
| SF-12 MCS (per 10)             | 0.85 (0.03, 1.67) | 0.044 | –0.48 (–1.92, 0.96) | 0.515 |
| SF-12 RCS (per 10)             | –0.22 (–1.45, 1.01) | 0.726 | 0.34 (–1.81, 2.48) | 0.758 |
| Control score                  |         |        |         |        |
| ACT (per 1)                    | 0.39 (0.03, 0.75) | 0.037 | NA |
| ACQ (per 1)                    | –0.54 (–1.53, 0.45) | 0.286 | NA |
| CAT (per 1)                    | NA | –0.12 (–0.32, 0.08) | 0.258 |
| Clinical variables             |         |        |         |        |
| Age (per 10 years)             | 0.31 (–0.16, 0.78) | 0.197 | 0.05 (–1.90, 2.01) | 0.958 |
| Sex, male                      | 2.60 (1.21, 3.99) | <0.001 | –1.25 (–5.24, 2.73) | 0.540 |
| BMI (per 1 kg/m²)              | –0.08 (–0.22, 0.07) | 0.307 | 0.34 (0.01, 0.66) | 0.048 |
| Pack-years (per 10)            | 0.17 (–0.18, 0.52) | 0.344 | –0.08 (–0.44, 0.28) | 0.676 |
| FeNO (per 10 ppb)              | 0.14 (–0.04, 0.33) | 0.132 | 0.03 (–0.77, 0.83) | 0.943 |
| Total IgE (per 2-fold)         | 0.32 (–0.01, 0.64) | 0.061 | 0.37 (–0.20, 0.93) | 0.212 |
| Lung function                  |         |        |         |        |
| %FEV₁ (per 10%)                | –0.01 (–0.35, 0.32) | 0.932 | 0.46 (–0.03, 0.95) | 0.072 |
| FEV₁/FVC (per 10%)             | –0.37 (–0.99, 0.24) | 0.237 | 1.02 (0.11, 1.93) | 0.033 |
| Peripheral blood cells         |         |        |         |        |
| Eosinophils (per 100 /μL)      | 0.06 (–0.15, 0.27) | 0.590 | –0.09 (–0.48, 0.31) | 0.669 |
| Neutrophils (per 100 /μL)      | –0.02 (–0.07, 0.03) | 0.477 | –0.03 (–0.11, 0.06) | 0.530 |
| Severity                       |         |        |         |        |
| Severe asthma                  | –0.57 (–2.53, 1.38) | 0.568 | NA |
| Severe COPD                    | NA | –2.75 (–5.16, –0.34) | 0.030 |

ACT, Asthma Control Test; ACQ, Asthma Control Questionnaire; BMI, body mass index; CAT, COPD Assessment Test; CI, confidence interval; COPD, chronic obstructive pulmonary disease; EQ-5D, EuroQol 5-Dimension; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; HR-QOL, health-related QOL; IgE, immunoglobulin E; MCS, mental component score; NA, not applicable; PCS, physical component score; RCS, role-social component score; SF-12, 12-item Short Form Health Survey; VAS, visual analog scale. Regression coefficients (β) represent the difference in plasma concentrations of 25(OH)D₃ per indicated unit increase.
Table 2. Univariate and multivariate Cox proportional hazards regression models for exacerbations in patients with asthma and COPD.

| Variables | HR (95% CI) | p value |
|-----------|-------------|---------|
| Patients with asthma       |             |         |
| **Univariate model**       |             |         |
| Plasma 25(OH)D₃ concentrations (per 1 ng/mL decrease) | 0.93 (0.83, 1.01) | 0.088  |
| **Multivariate model**     |             |         |
| Plasma 25(OH)D₃ concentrations (per 1 ng/mL decrease) | 0.95 (0.87, 1.03) | 0.179  |
| BMI (per 1 kg/m² increase) | 1.09 (1.02, 1.17) | 0.013  |
| FeNO (per 10 ppb increase) | 1.14 (1.05, 1.25) | 0.003  |
| %FEV₁ (per 10% decrease)   | 1.04 (1.02, 1.06) | <0.001 |
| Patients with COPD         |             |         |
| **Univariate model**       |             |         |
| Plasma 25(OH)D₃ concentrations (per 1 ng/mL decrease) | 1.38 (1.08, 1.68) | 0.007  |
| **Multivariate model**     |             |         |
| Plasma 25(OH)D₃ concentrations (per 1 ng/mL decrease) | 1.38 (1.10, 1.75) | 0.006  |
| %FEV₁ (per 10% decrease)   | 1.05 (1.02, 1.08) | 0.002  |

BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; HR, hazard ratio; 25(OH)D₃, 25-hydroxyvitaminD₃.