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Vitamin D Deficiency in Asthma and Chronic Obstructive Pulmonary Disease

A Chicken-or-Egg Story

Whereas, traditionally, vitamin D has been considered as a main regulator of calcium and phosphate homeostasis, it has become increasingly clear that vitamin D is also an important regulator of immunity and host defense against infections in various tissues, including the lung (1–3). Asthma and chronic obstructive pulmonary disease (COPD) are both characterized by chronic inflammation, and exacerbations of these diseases are associated with respiratory infections. Therefore, the growing interest in the role of vitamin D in asthma and COPD is well justified. Patients with (severe) asthma and COPD are characterized by low circulating levels of 25-hydroxyvitamin D (25[OH]D), the main circulating but inactive form of vitamin D (3–6). However, the most important question that remains to be answered is the chicken and egg question: does vitamin D deficiency contribute to the development of asthma and COPD and their exacerbations, or is it solely a consequence of the disease (reverse causality)?

In this issue of the *Journal*, Jolliffe and coworkers (pp. 371–382) shed light on this issue through the study of vitamin D metabolism in patients with asthma and COPD as compared with healthy control subjects (7). The metabolism of vitamin D is complex, with enzymes regulating the formation of the active form of vitamin D, 1,25-dihydroxyvitamin D ($1,25[OH]_2D$), and various enzymes being involved in its catabolism. Two cytochrome P450 (CYP) enzymes take center stage in the balance between 25(OH)D and $1,25(OH)_2D$: CYP24A1 catabolizes both 25(OH)D and $1,25(OH)_2D$, whereas CYP27B1 is crucial for the generation of $1,25(OH)_2D$ through its 1-hydroxylase activity (8). Whereas these enzymes were initially considered to be mainly expressed in the liver and kidney, also cells of the immune system, and, for example, airway epithelial cells express these enzymes where they may contribute to local vitamin D metabolism (8, 9). Importantly, mechanistic studies have indicated that inflammatory mediators may increase activity of CYP24A1 and CYP27B1, which may result in lower local 25(OH)D concentrations (10–12).

The authors used samples collected in three clinical trials in which patients with asthma or COPD, or healthy control subjects, received high-dose vitamin D_3 supplementation every two months (7). They used serum samples obtained at baseline, after 2 months, and after 12 months for a detailed analysis of vitamin D_3, 25(OH)D_3, and the vitamin D metabolites $1,25(OH)_2D_3$, $24R,25(OH)_2D_3$, and $4\beta,25(OH)_2D_3$. They assessed a panel of 19 SNPs in DNA extracted from whole blood that may help to explain differences in serum 25(OH)D levels. They combined this analysis with that of available gene expression in 14 data sets from seven different studies to assess expression of vitamin D pathway genes in tissue from the respiratory tract and blood from patients with asthma and COPD, and control subjects.

The authors present interesting and sometimes unexpected findings. First, they observed that vitamin D_3

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supplementation–induced increases in circulating 25(OH)D were lower in patients with asthma or COPD compared with control subjects. This would still be compatible with catabolism induced by inflammation. In line with this, they show that genetic variation in the vitamin D pathway as assessed by the SNP analysis is not a likely explanation for their findings. The first surprise comes in with the analyses of ratios of the vitamin D metabolites. They found that the $25(OH)D_3$-to-vitamin D_3 ratio was significantly lower at baseline and after supplementation, whereas $1,25(OH)_2D_3$-to-$25(OH)D_3$ ratios were higher in asthma and COPD. Gene profiling demonstrated reduced 25-hydroxylase CYP27A1 expression in lung tissue, indicating a potential inhibition of production of $25(OH)_2D_3$ in asthma and COPD. The second surprise is the absence of a difference in $24R,25(OH)_2D_3$-to-$25(OH)D_3$ and $4\beta,25(OH)_2D_3$-to-$25(OH)D_3$ ratios between groups. This suggests that catabolism of $25(OH)D_3$ leading to generation of these two metabolites does not contribute to lower levels of $25(OH)D_3$. In line with this, but in contrast with previous *in vitro* findings, gene expression in respiratory tract tissue did not support increased catabolism. The authors therefore conclude that not increased catabolism but potentially hampered production or, for example, sequestration in other depots such as adipose tissue may lower $25(OH)D_3$ levels in asthma and COPD. Collectively, these results do provide strong evidence for altered vitamin D_3 metabolism in asthma and COPD, and therefore point to reverse causality. Based on the combination of their data sets, the authors conclude that the interaction between vitamin D deficiency and airway inflammation may be bidirectional. When reviewing these results, it is important to keep in mind that circulating and not local lung metabolites were assessed, and that the rate of their clearance may differ.

The present study unfortunately does not provide an unequivocal answer to the chicken-and-egg question regarding vitamin D deficiency in asthma and COPD. Important new research questions need to be addressed before these findings can be properly put into clinical perspective. For instance, it remains to be determined whether higher supplementation dosages of cholecalciferol (vitamin D_3) or supplementation with 25-hydroxycholecalciferol (calcidiol; $25[OH]D_3$) may be required in patients with asthma or COPD to aim for certain $25(OH)D_3$ concentrations in contrast to in healthy individuals. Also, a crucial issue to be solved first is the finding of the optimal level of circulating $25(OH)D_3$ in these patients regarding inflammation, immunity, and host defense outcomes. Therefore, more information on local vitamin D metabolism and levels of vitamin D metabolites in lung tissue are needed. In addition, for instance, mechanistic studies on the impact of medication on vitamin D metabolism are required. Vitamin D supplementation trials demonstrate a reduction in the number of asthma and COPD exacerbations but especially in those with baseline levels of 25(OH)D below 25 nmol/L and based on *post hoc* analyses. Therefore, there is an urgent need to perform randomized controlled trials in predefined patients with vitamin D deficiency, such as the ongoing PRECOVID (Ongoing Prevention of Exacerbations in Patients with COPD and Vitamin D Deficiency) study in COPD (13). ■

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