Vitamin D, lung functions, and chronic obstructive pulmonary disease: *Quod non erat demonstrandum*

Sir,

Apropos the article, “Should Vitamin D be routinely checked for all chronic obstructive pulmonary disease (COPD) patients,”[1] we would like to raise certain relevant points.

1. The population recruited in this study seems to be a “heterogeneous” one as the following questions beg to be answered:
   - Were COPD patients with exacerbation also included?
   - Were included patients admitted for respiratory or only nonrespiratory causes?
   - The exclusion criteria as mentioned by the authors included “hemodynamically unstable patients” but were the patients critically ill? Low 25(OH) Vitamin D is known to be associated with various disease processes apart from COPD, e.g., sepsis[2]
   - As 82% of COPD cases had neutrophilic leukocytosis, it might imply that patients with active infection were also included in the study?
   - Were cases and controls on Vitamin D? And if yes for what duration? – as it can potentially confound the results.

2. Various factors have an influence on lung volume and lung capacities (e.g., forced vital capacity [FVC] = 5.048 – 0.014 × age + 0.054 × ht + 0.006 × wt) of which stature and ethnicity are two of the important factors. Studies have shown that tall stature is associated with higher lung volumes than say weight.[3] In this study,[1] body mass index has been matched between cases and controls, but height and ethnicity were not compared between two groups. Without “matching” these factors, e.g., height, weight, etc., the comparison between the two groups [Group I and Group II] might have been inappropriate [Figure 1]

3. The difference in forced expiratory volume in 1 s (FEV1) between the first and third quartiles of Vitamin D level in the two groups was 1.08 l or 47% (of FEV1 in the first quartile). In a similar study by Black and Scragg, the mean difference between highest (25-hydroxyvitamin D ≥85.7 nmol/L) and lowest quintile Vitamin D (≤40.4 nmol/L) was 126 ml for FEV1 and 172 ml for FVC.[4] Clearly, the results of the present study are quantitatively different from that of aforementioned study and other studies in literature, and the degree of variation of lung volume is higher by a factor of around 9–10 raising concerns of overestimation of effect of Vitamin D on lung function in the present study.

We conducted a short systematic review using the MEDLINE database using keywords such as “COPD,” “Vitamin D,” and “lung function” including clinical studies to look at the present evidence on the effect of Vitamin D on lung function [Table 1].

The results showed that serum Vitamin D levels had no bearing on the lung function, except a single trial,[5] which showed that Vitamin D intake decreased COPD exacerbation and improved FEV1 in the patients with severe and very severe COPD. However, it was a very small study with some methodological peculiarities, making it difficult to generalize the result.

In conclusion, we would like to reiterate that though the last word has not been said about the role of Vitamin D in COPD, the available evidence do imply a very weak “effect,” if at all, of Vitamin D on lung functions in COPD.

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**Figure 1:** We consider x and y, where x and y are two patients with the same age (20 years), gender, ethnicity, and body mass index (but with different weights and heights); their predicted forced vital capacity using the abovementioned formula is as shown in the figure. Hence, a difference of 153 ml is expected between X and Y even if their body mass index is the same.
Table 1: Brief systematic review of clinical studies on effect of vitamin D in COPD

| Study name, Author, place of the study, year | Type of the study, sample size, and methods | Results | Conclusion |
|---------------------------------------------|---------------------------------------------|---------|------------|
| Effect of Monthly, High-Dose, Long-Term Vitamin D on Lung Function: A Randomized Controlled Trial, Sluyter JD et al., New Zealand, 2017 | Randomized clinical trial Population (n=442): 50-84 years old patients Intervention (n=223): Vitamin D3 Comparator (n=216): Placebo Outcome: FEV1, time: 1.1 years | There were no significant lung function improvements between the two groups | Vitamin D supplementation benefited only smokers, especially with Vitamin D deficiency or asthma or COPD |
| Effects of daily Vitamin D supplementation on respiratory muscle strength and physical performance in Vitamin D-deficient COPD patients: A pilot trial Rachida Rafiq et al., The Netherlands, 2017 | Randomized clinical trial Participants (n=50): Vitamin D-deficient COPD patients (age: 40-70 years) Intervention: Vitamin D3 (n=24) Comparator: Placebo (n=26) Time: 6 months Outcome: Respiratory muscle strength | Primary outcome did not differ between the groups after 6 months | Vitamin D supplementation did not affect (respiratory) muscle strength or physical performance in Vitamin D-deficient COPD patients |
| Effects of Vitamin D Intake on FEV1, and COPD Exacerbation: A Randomized Clinical Trial Study, Abolfazl Zendede et al., Iran, 2014 | Randomized clinical trial Participants (n=88): Patients with severe and very severe COPD Intervention: Oral Vitamin D Comparator: Placebo Outcome: FEV1, and the number of COPD exacerbations | FEV1 (before intervention) cases: (34.6±8.5), control: (34.4±9.2) and FEV1 (after intervention) cases: (51.6±9.4), control: (31.9±7.6) (P=0.001) | Vitamin D intake decreased COPD exacerbation and improved FEV1, in the patients with severe and very severe COPD |
| Serum Mg and not Vitamin D is associated with better QoL in COPD: A cross-sectional study, Sarah Hashim Ali Hussein et al., Denmark, 2015 | Cross-sectional study Population (n=143): Stable COPD patients Serum Vitamin D, Mg, and Ca in COPD patients and their associations with both (FEV1) and QoL | FEV1 was not correlated with serum Vitamin D, Mg, or Ca in COPD | Serum levels of Vitamin D, Mg, and Ca were not related to FEV1. Only serum Mg was associated with QoL in COPD |
| ViDiCO: A multicentre, double-blind, randomised controlled trial, Adrian R Martineau et al., UK, 2015 | Randomized clinical trial Population (n=240): Patients with COPD Intervention: Vitamin D3 Comparator: Placebo Coprimary outcomes: Time to first moderate or severe exacerbation and first upper respiratory infection | Vitamin D3 compared with placebo did not affect time to first moderate or severe exacerbation or time to first upper respiratory infection (adjusted hazard ratio: 0.95, 95% CI: 0.69-1.31, P=0.75) | Vitamin D3 supplementation protected against moderate or severe exacerbation, but not upper respiratory infection, in patients with COPD with baseline 25-hydroxyvitamin D levels of less than 50 nmol/L |
| Supplemental Vitamin D and physical performance in COPD: A pilot randomized trial, Sonja M Bjerk et al., USA, 2013 | Randomized clinical trial Population (n=36): COPD patients Intervention: Vitamin D Comparator: Placebo Primary outcome: 6 weeks change in SPPB score | There was no difference in improvements in either SPPB scores (95% CI: –0.8–1.5; P=0.56) or SGRQ scores (95% CI: −2.3–6.9; P=0.32) | Vitamin D supplementation had no discernible effect on a simple measure of physical performance |
| Serum Vitamin D in Patients with Chronic Obstructive Lung Disease Does Not Correlate with Mortality - Results from a 10-Year Prospective Cohort Study, Dennis Back Holmgaard et al., Denmark, 2013 | Prospective cohort Population (n=462): Patients with moderate to very severe COPD Outcome measure: Mortality in a 10-year follow-up period | No association between baseline serum levels of 25-OHD and mortality rate could be demonstrated | Serum level of 25-OHD does not seem to be associated with mortality rate |
| High doses of Vitamin D to reduce exacerbation in COPD: A randomised trial, An Lehouck et al., Belgium, 2012 | Randomized clinical trial Population (n=182): Patients with moderate-to-very severe COPD and a history of recent exacerbations Intervention: Vitamin D Comparator: Placebo Primary outcome: Time to first exacerbation | The median time to first exacerbation did not significantly differ between the groups | High-dose Vitamin D supplementation in patients with COPD did not reduce the incidence of exacerbations but may reduce exacerbations in patients with severe deficiency |
| Vitamin D levels and risk of AECOPD: A prospective cohort study, Ken M. Kanisak et al., Minnesota, 2012 | Prospective cohort study Population (n=973): Patients with COPD | Baseline 25(OH)D levels had no relationship to time to first AECOPD or AECOPD rates | Among patients with COPD at high risk of AECOPD, baseline blood 25(OH) D levels are not related to the risk of subsequent AECOPDs |

Mg: Magnesium, Ca: Calcium, SPPB: Short Physical Performance Battery, COPD: Chronic obstructive pulmonary disease, FEV1: Forced expiratory volume 1 s, ViDiCO: Vitamin D3 supplementation in patients with COPD, QoL: Quality of life, CI: Confidence interval, AECOPD: Acute exacerbations of COPD
SIR,

A tuberculid is a cutaneous immunologic reaction to the presence of tuberculosis, which is often occult. Currently, only three entities are regarded as true tuberculids: (1) papulonecrotic tuberculid, (2) lichen scrofulosorum (LS), and (3) erythema induratum.

LS is a rare tuberculid, first recognized by Hebra in 1868, that occurs mostly in children and young adults. The eruption consists of tiny, perifollicular, lichenoid papules arranged in groups. The papules have a flat top or there might be a minute horny spine or fine scale on their surface. The size of an individual papule rarely exceeds 2–3 mm.

A 30-year-old female came with complaints of skin rashes over the trunk and loin regions for the past 2 years. There was no history of fever, cough, or any other systemic symptoms. Past and family history did not reveal any significant illness. Physical examination found a nontender, firm, and matted bilateral enlargement of the supraclavicular nodes, measuring < 1 cm.

Cutaneous examination revealed multiple, grouped, erythematous, 2–3 mm, lichenoid follicular and extrafollicular papules over both anterior and posterior aspects of the trunk and loin [Figure 1].

Laboratory investigations found normal complete blood cell count, renal and hepatic functions, urinalysis, and chest radiograph. Erythrocyte sedimentation rate was 52 mm in the 1st h and the Mantoux test was reactive, with an induration of 17 mm. Fine-needle aspiration cytology from an enlarged cervical lymph node showed granulomatous infiltrate comprising epithelioid cells, Langhans giant cells, and few lymphocytes, consistent with tuberculous lymphadenitis. Stain and culture for acid-fast bacilli were negative. Skin biopsy showed perifollicular tuberculoid granulomatous inflammation comprising lymphocyte and epithelioid cells. Another similar focus was present in the mid-dermis around a vessel. Tubercle bacilli could not be detected on acid-fast staining, and a culture for Mycobacterium tuberculosis was sterile. A standard 6-month regimen of antituberculous therapy (ATT) was instituted and the patient is currently on follow-up.

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