Vitamin D supplementation in patients with cystic fibrosis: A systematic review and meta-analysis

Márk Félix Juhász[1], Orsolya Varannai[1,2], Dávid Németh[1], Zsolt Szakács[1], Szabolcs Kiss[1], Vera Izsák[1,2], Ágnes Martonosi[1,2], Péter Hegyi[1,3], Andrea Párniczky[1,2] **on behalf of the Hungarian Pancreatic Study Group**

[1]Institute for Translational Medicine, Medical School, University of Pécs, Pécs, Hungary; [2]Heim Pál Children's Hospital, Budapest, Hungary; [3]János Szentágothai Research Center, University of Pécs, Pécs, Hungary

Introduction

85-90% of cystic fibrosis (CF) patients develop pancreatic exocrine insufficiency (PEI). Loss of exocrine function will lead to fat malabsorption, failure to thrive, poor weight gain and the **deficiency of fat-soluble vitamins, including vitamin D**, which is crucial for **bone health** but might also influence **respiratory outcomes** through immunological pathways. Despite routine supplementation, most of these patients are deficient.

Our aim was to assess the effects of vitamin D supplementation on vitamin D levels, respiratory outcomes and the safety of vitamin D administration in CF.

Methods

This systematic review and meta-analysis was registered on PROSPERO, with the registration ID: CRD42020155847. We included **randomised controlled trials (RCTs) that compared vitamin D supplementation** (any dose, form and duration) **with placebo** (i.e. 'non-increased dose') in CF patients (regardless of age and comorbidities). We conducted a systematic search in 4 databases: Embase, MEDLINE, CENTRAL and Web of Science. No filters were applied and there were no restrictions based on language, country of origin, and date. Our **primary outcomes of interest were bone-disease related outcome measures and mortality**, but all reported outcomes (including respiratory and immunological) were collected. In meta-analysis, weighted mean differences (WMD) with 95% confidence intervals (CI) were calculated.

Outcome	Overall WMD (95% CI)	Number of studies	Heterogeneity: I^2 (p)
Bone alkaline phosphatase*	-0.31 (-0.86; 0.25)	2	0% (0.896)
Osteocalcin*	-0.16 (-0.72; 0.39)	2	0% (0.981)
Lumbar spine Z-score*	+0.32 (-0.24; 0.88)	2	0% (0.44)
se25OHD (ng/ml)	+10.48 (0.72; 20.24)	4	89.7% (0.0)
Serum calcium (mg/dl)	+0.05 (-0.08; 0.17)	2	0% (0.632)
Increase in serum PTH (pg/dl)	+0.4 (-11.73; 12.53)	3	37.3% (0.203)
Serum LL-37 (ng/ml)	+6.02 (-5.75; 17.79)	2	0% (0.981)
Serum albumin (g/dl)	-0.03 (-0.22; 0.17)	2	10% (0.292)

Table 1 – Meta-analysis results of outcomes that were reported on by at least two studies. WMD: weighted mean difference, CI: confidence interval, se25OHD: serum 25-hydroxyvitamin D, PTH: parathyroid hormone, LL-37: cathelicidin. '+' indicates result favoring intervention, '-' comparator. *Bone-related outcome effects are presented as standardized mean difference instead of WMD.

Results

8 RCTs were eligible for inclusion. The intervention group had significantly higher serum 25-hydroxyvitamin D (se25OHD) levels (WMD 10.48 ng/ml, CI 0.72-20.24 ng/ml). There were no significant differences found in the quantitative synthesis of clinical outcomes, including bone disease-related, respiratory and immunological outcomes. For most comparisons only 2 studies provided data. Only 2 studies of CF patients in exacerbation reported cases of mortality, with no significant differences between groups. 6 studies reported on adverse events also with no significant differences. All of the included studies had a mean se25OHD below the recommended 30 ng/ml at baseline, while all intervention groups reached this value by the end of the study.

Discussion

Vitamin D deficiency often results from fat malabsorption caused by PEI, high latitude, poor nutritional intake, reduced exposure to sunlight, impaired activation, and non-adherence to the prescribed vitamin D treatment. Based on our current findings, a higher vitamin D dose, while **increased serum levels, did not seem to positively influence clinical outcomes**. However, **studies were few, constrained to a low sample size and heterogenous** in their examined outcomes. Participants were generally receiving vitamin D doses similar to the recommended initial doses of the current guideline but failed to reach required se25OHD levels, indicating that **a higher initial dose might be necessary for these patients.**

Authors declare no conflicts of interest