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Original article

Extra-skeletal impact of vitamin D supplementation protocol in an adult population with cystic fibrosis

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SUMMARY

Background: Due to lack of vitamin D absorption in patients with cystic fibrosis (CF), vitamin D supplementation becomes necessary. Our aim was to study the association between serum vitamin D levels and key clinical factors, such as nutritional status, pulmonary function and pulmonary exacerbations (PEx) frequency, in an adult CF population.

Methods: Prospective analysis of a published vitamin D ($VitD_3$) supplementation protocol (N = 200 adult patients) over a follow-up period of 5 years. Data were collected from the medical files before (baseline) and after (follow-up) the implementation of the $VitD_3$ supplementation protocol, between 2009 and 2014. Serum samples to measure vitamin D were also collected at baseline and follow-up.

Results: A positive relationship between serum vitamin D and lung function was observed at baseline (R = 0.158, P = 0.027), but it disappeared at follow-up (P = 0.454). There was no association between serum vitamin D levels and body mass index. At follow-up, patients with significantly higher serum vitamin D levels were women, older in age, had CF-related diabetes or had a history of recurring PEx.

Conclusion: No direct link was observed between heightened serum vitamin D and lung function or BMI in an adult CF population. We suggest that better compliance to treatments and closer follow-up from health professionals could partially explain why such patients reached higher vitamin D serum levels.

1. Introduction

Cystic Fibrosis (CF) is a fatal autosomal recessive genetic disease that affects 1 in 3600 Canadians [1]. Caused by a mutation on the CF Transmembrane Regulator (CFTR) gene [2], CF is a multisystem disorder, affecting primarily the respiratory and the digestive systems [2]. The implementation of newborn screening, multidisciplinary care, novel treatments and transplantation has resulted in a rapid evolution in the demographics of the CF population. In fact, mean values of pulmonary function has increased by 16% from 1995 to 2015 and the life expectancy has now reached 52.1 years old in Canada [2]. Still to this day, the most common cause of death in CF remains respiratory insufficiency [2]. Risk factors associated to higher mortality in CF include, among many others, delF508 allele, CF-related diabetes (CFRD), presence of pancreatic insufficiency and sex [3]. As patients live longer, the number of complications in CF increases [4]. For instance, CFRD, the most common secondary CF complication, has been associated to a 6-fold increase in mortality rate, a poor nutritional status, a worse pulmonary function and higher risk of intestinal polyps [4,5].

Approximately 90% of patients with CF have a pancreatic impairment and are supplemented with pancreatic enzymes to enhance digestion and absorption of nutrients [2,6]. Abnormal or absent CFTR protein leads to pancreatic duct obstruction, autodigestion of the exocrine pancreas, inactive pancreatic enzymes and loss of bile salts [7]. Pancreatic exocrine insufficiency in CF contributes significantly to malabsorption and malnutrition, hence resulting in critically low body weight [2,6]. Pancreatic insufficiency impairs especially the absorption of lipids and fat-soluble vitamins (A, D, E and K) [6]. Up to 90% of patients with CF have vitamin D deficiency [8]. Vitamin D deficiency is implicated in the

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elevated prevalence of osteopenia and osteoporosis in CF, which is now affecting 38% and 23% of patients respectively [4]. In addition to its role in bone health, observational and epidemiological studies have identified potential important extra-skeletal vitamin D roles in the general population. Non-CF individuals with low vitamin D levels are at higher risk of developing cardiovascular diseases, malignancies, diabetes and autoimmune disease [9]. In CF, some but not all studies have associated lower levels of vitamin D to higher inflammation [10], higher rates of pulmonary exacerbation (PEx) [11], lower pulmonary function [12] and increased risk of diabetes [13,14]. It is speculated that vitamin D up-regulates antimicrobial peptides and down-regulates pro-inflammatory markers such as cytokines, chemokines and immunoglobulin G, which leads to a lower neutrophil influx [10]. The mechanisms of how vitamin D could impact those elements are still unknown.

A recent Cochrane review concluded that more data are required to assess the effects of vitamin D supplementation on disease evolution in CF [15]. We recently published that a vitamin D supplementation ($VitD_3$) of 1600 IU/daily or 10 000 IU/weekly during summer and 3200 IU/daily or 20 000 UI/weekly during winter leads to an increase in the proportion of patients with sufficient levels (25(OH)D $\geq$ 75 nmol/L) from 31.0 to 74.5% in a period of 2–5 years [16]. Since the results of available studies differ, it is still not clear what is the clinical impact of vitamin D supplementation [15,17]. Using this prospective observational cohort, our objective was to observe the association between serum vitamin D (before and after the supplementation protocol) and key clinical factors including nutritional status, pulmonary function and PEx frequency. This allowed us to identify conditions associated with a better response to a vitamin D supplementation protocol in an adult CF population.

2. Methods

2.1. Subjects

This is a prospective analysis of a published vitamin D supplementation protocol, which includes 200 adult patients ($\geq$18 years old) with a follow-up period of approximately 5 years [16]. Patients were recruited at the CF Clinic if they had a plasma 25(OH)D value available before the introduction of the VitD3 supplementation protocol (November 2009) and one value after (latest value measured between November 2011 and June 2014). Inclusion and exclusion criteria have been previously described [16]. The principal exclusion factor was the absence of a 25(OH)D plasma concentration before the protocol implementation. This study is based on an intention-to-treat protocol for vitamin D deficiency at the CF clinic of the Centre Hospitalier de l'Université de Montréal (CHUM).

2.2. Clinical data

Age, sex, genotype status, presence of exocrine pancreatic insufficiency, CFRD status and the number of PEx events were collected from the medical files at baseline and at follow-up. Pancreatic insufficiency was defined by current pancreatic enzyme replacement therapy. Pulmonary function was measured by spirometry using predicted forced expiratory volume in 1 s (% FEV_1) (Medgraphic 1870, St. Paul, MN, USA). Body mass index (BMI) was calculated by dividing the body weight in kilograms (measured with an electronic scale; Tanita Corporation Arlington heights, IL, USA) by height (measured with a wall stadiometer) in square meters. The number of PEx events was recorded 1 year prior to the date of the vitamin D measurement at baseline and 1 year after to the date of the vitamin D measurement at follow-up. PEx was defined as a deterioration of the usual symptoms of CF, such as cough, chest pain, fever and decreased lung function, and which required intravenous antibiotics treatment at home or during hospitalisation.

2.3. Blood parameters

Levels of 25(OH)D were measured using a high-performance liquid chromatography coupled with tandem mass spectrometry (TQ Detector, Waters, Milford, MA, USA).

2.4. Statistical methods

Values are expressed as mean ± standard deviation for each group. SPSS statistical software for Mac (Version 24, SPSS Inc, Chicago, IL) was used to compare transversally using Mann–Whitney U-test and Chi^2 test as well as prospectively using Wilcoxon signed rank test and Mc Nemar's Test the following clinical variables: men and women, non-CFRD and CFRD patients, patients who experienced no PEx and patients who did. Statistical significance was present when probability value (P) was $\leq$0.05.

3. Results

A total of 200 adults with CF, of which 55.3% were men, were included in the analysis. The average age at baseline was 29.4 years, 85.4% had pancreatic insufficiency, 22.7% had CFRD and 51.5% were homozygote for the delF508 mutation. The mean BMI, FEV_1 and vitamin D levels at baseline were 22.5 ± 3.3 kg/m^2, 71.0 ± 20.4% and 64.7 ± 25.6 nmol/L, respectively. The average time between baseline and follow-up was 5.0 ± 0.9 years. At follow-up, the mean age and serum vitamin D level were 34.4 ± 8.3 years and 92.3 ± 28.4 nmol/L, respectively. At follow-up, there was an increase in mean BMI of 0.7 kg/m^2 and a decline in the mean FEV_1 of 5.9%, an average of 1.18% per year. Interestingly, patients that were able to reach vitamin D values $\geq$ 50 nmol/L at follow-up were significantly older (34.8 ± 8.4 years) than those who maintained < 50 nmol/L (28.9 ± 4.7 years).

We first categorized our study population by CFRD status and compared clinical factors at baseline and follow-up. Data for 198 patients was available for this analysis: 114 patients were stable non-CFRD, 45 patients were stable CFRD and 39 patients became diabetic (transitioned) during the vitamin D supplementation protocol (they were non-CFRD at baseline and became CFRD at follow-up) (Fig. 1). Gender, age and BMI were similar between the 3 groups at baseline and at follow-up. At baseline, serum vitamin D levels were similar between non-CFRD, CFRD and the patients who transitioned (P = 0.437). However, at follow-up, serum vitamin D levels were statistically lower in the non-CFRD group compared to CFRD and patients who transitioned (87.5 ± 27.7 vs 100.9 ± 30.0 nmol/L and 97.4 ± 26.6 respectively, P = 0.023). Nonetheless, it is important to note that all groups reached average vitamin D levels >75 nmol/L at follow-up (Fig. 1).

Next, we performed an analysis based on the number of pulmonary exacerbations events 1 year prior to the date of the first serum vitamin D measurement (baseline) and 1 year after the follow-up vitamin D value. A total of 187 patients had at least one PEx treated at home and 155 patients treated at the hospital. Age, BMI and YKL-40 were similar between groups. Baseline serum vitamin D levels were similar between PEx and No-PEx groups and increased significantly at the follow-up, regardless if the PEx was at home or at the hospital. At follow-up, serum vitamin D levels reached >75 nmol/L for PEx treated at home and at the hospital. The only significant difference was observed only at follow-up, where serum vitamin D values were higher in patients with PEx treated at the hospital compared to those who had no PEx at the hospital (P = 0.023, Fig. 2B).

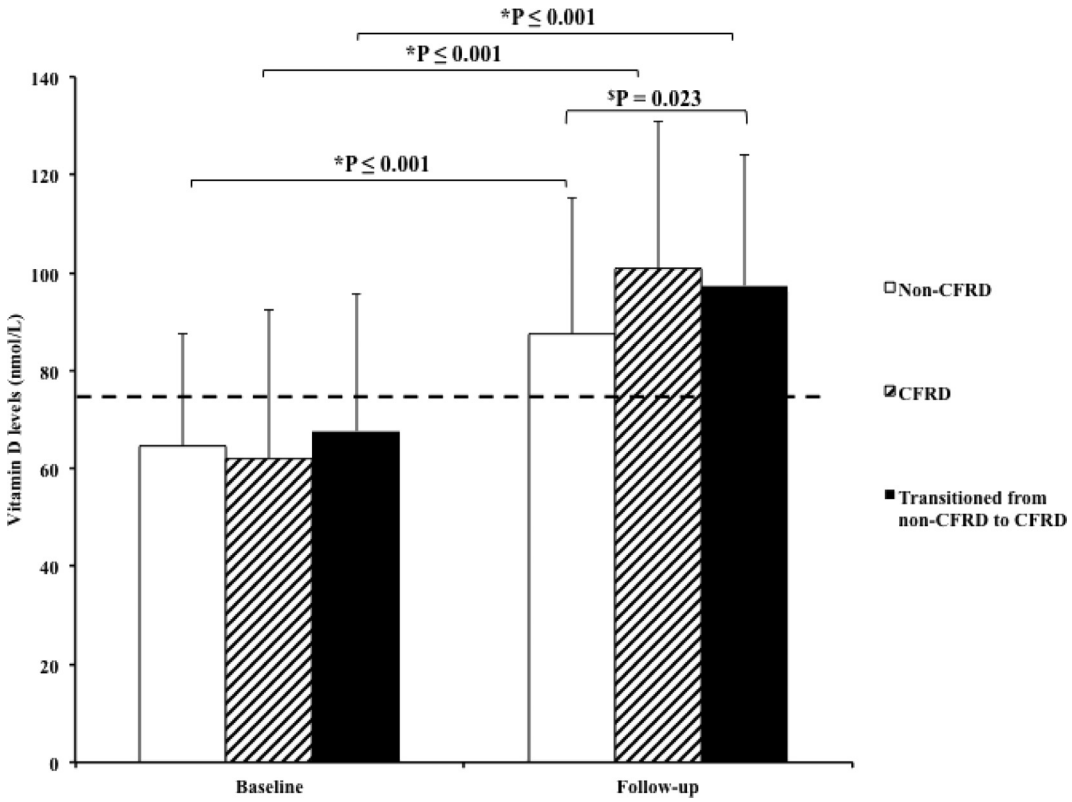

Fig. 1. Serum vitamin D levels at baseline and follow-up of CF patients with CFRD, without CFRD and who became CFRD during the vitamin D supplementation protocol (n = 198). Dotted line represents the recommended serum vitamin D levels. CFRD, cystic fibrosis-related diabetes; Mean and SD are shown (±); P value was determined by $Krustal-Wallis Related Sample Test; *Wilcoxon signed rank test.

We then examined serum vitamin D levels of men and women at baseline and at follow-up. Serum vitamin D levels were consistently higher in women compared to men, at baseline and follow-up (Fig. 3). However, the difference in vitamin D values between men and women is higher at baseline than at follow-up (Δvitamin D of 12.2 nmol/L at baseline versus 7.9 nmol/L at follow-up).

Finally, we assessed whether an association exists between serum vitamin D level and clinical parameters (BMI, FEV_1 and PEx

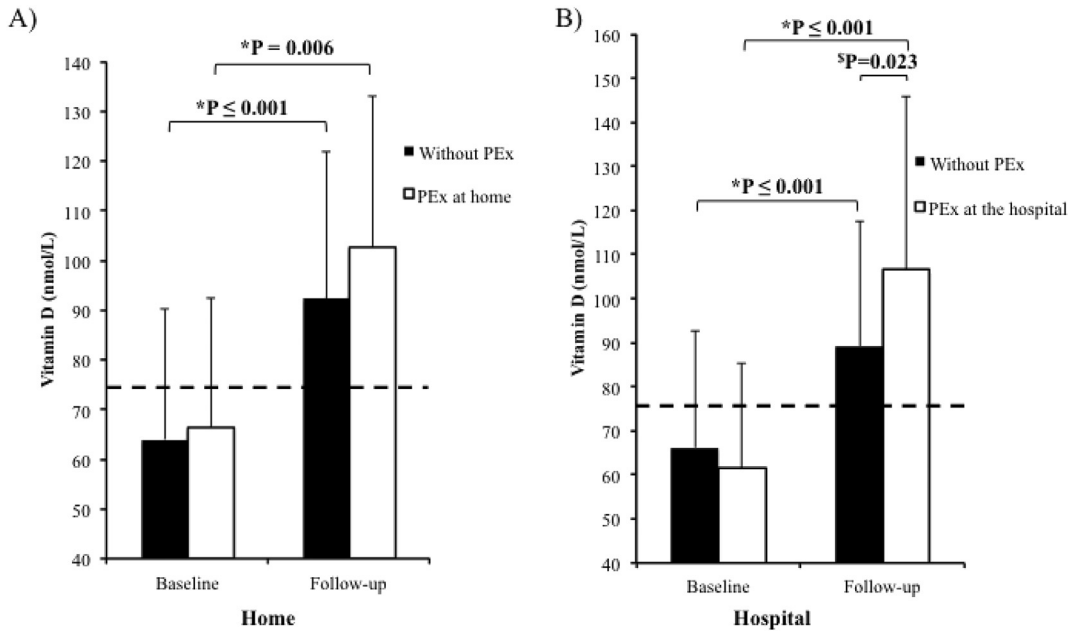

Fig. 2. Vitamin D levels of CF patients with and without pulmonary exacerbations (PEx) treated A) at home (n = 187) and B) at the hospital (n = 155) at baseline and follow-up. Dotted line represents the recommended serum vitamin D levels. PEx, pulmonary exacerbations; Mean and SD are shown (±); P value was determined by Mann–Whitney U-test; *Wilcoxon signed rank test.

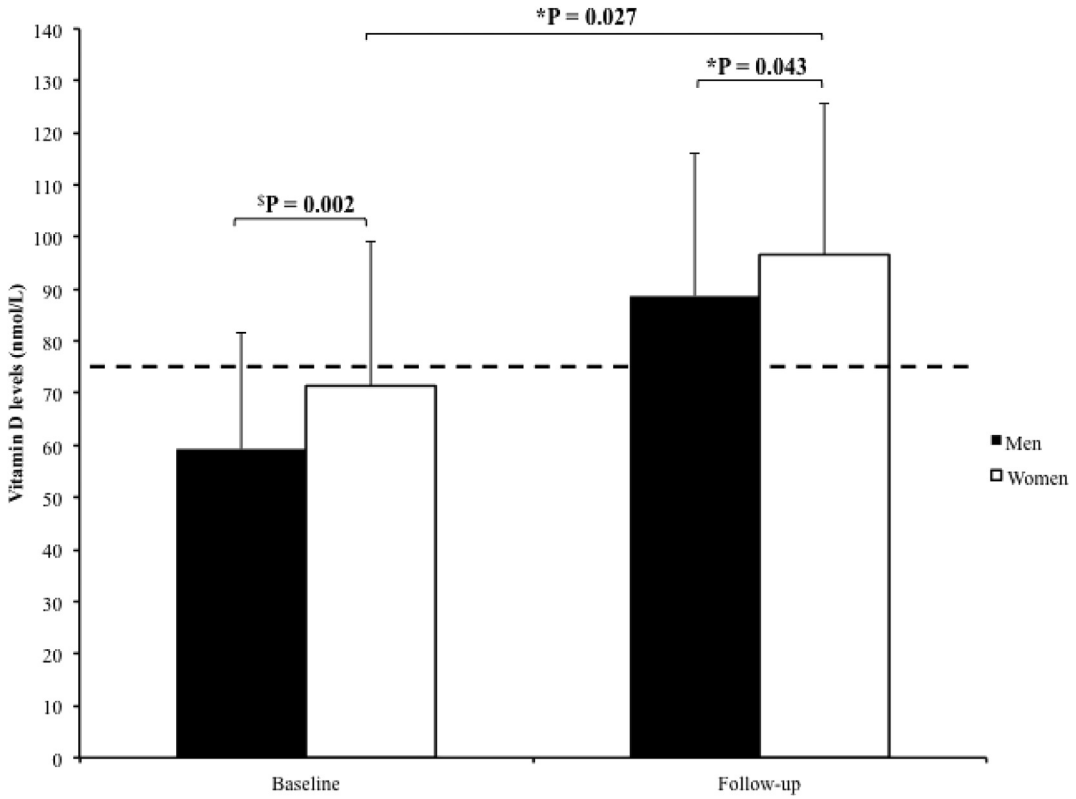

Fig. 3. Vitamin D levels of CF patients according to sex before and after a Vitamin D supplementation protocol (n = 200). Mean and SD are shown (±); P value was determined by Mann–Whitney U-test; *Wilcoxon signed rank test.

events) at baseline, when vitamin D values were low, and at follow-up, when vitamin D values were above the recommended level. As expected, a positive association was found between FEV_1 and serum vitamin D at baseline (R = 0.158, P = 0.027) which disappeared at follow-up (R = −0.053, P = 0.454) (Fig. 4). There was also a positive association between the frequency of PEx treated at home and serum vitamin D levels at baseline (R = 0.143, P = 0.045) but it also disappeared at follow-up (R = −0.079, P = 0.264). We did not observe an association between serum vitamin D level and BMI or other types of PEx frequency neither at baseline or at follow-up (Table 1).

4. Discussion

Considering the important physiological roles of vitamin D, the objective of this prospective analysis was to study associations between plasma vitamin D and clinical markers before and following a successful vitamin D supplementation protocol in our CF population. Our main observation is that the positive relationship that existed between vitamin D and lung function at baseline disappears after the implementation of the vitamin D supplementation protocol. We also observed that sex, CFRD status and frequency of PEx are not associated to vitamin D levels in CF. Finally,

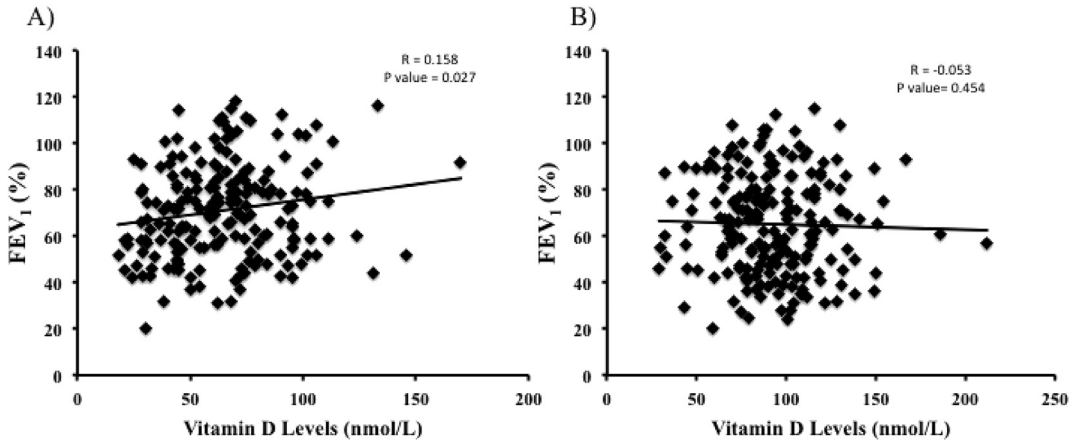

Fig. 4. Association between Vitamin D levels and FEV1 (%) A) before and B) after vitamin D supplementation. FEV1, Forced expiratory volume in one second.

Table 1
Association between vitamin D and clinical parameters before and after protocol.

	Vitamin D (nmol/L)			
	Before supplementation		After supplementation	
	R	p value	R	p value
BMI (kg/m^2)	0.760	0.296	0.042	0.556
FEV1, %	0.158	0.027	−0.053	0.454
PEx treated at home, events	0.143	0.045	−0.079	0.264
Pex treated at the hospital, events	−0.750	0.297	0.128	0.070
Total Pex, events	0.036	0.614	0.068	0.336

Abbreviations: BMI: body mass index; FEV1: forced expiratory volume in one second; PEx: pulmonary exacerbations; Mean and SD are shown (±); P value was determined by Spearman Correlation Test.

there is no correlation between vitamin D and BMI confirming the recent observation that vitamin D doesn't have a significant effect on nutritional status in CF [15]. Overall, these results do not support a direct clinical role of vitamin D supplementation in adult patients with CF.

CF is a disease that implies lifelong complex treatments requiring up to 3 h of physical and medical therapy each day [18]. Adherence to therapeutic plans in CF is estimated between 30 and 70% [19]. Therapies without immediate perceived benefits are usually associated with less compliance, such as vitamin supplementation which adherence is estimated to be close to 50% [18–20]. Raising awareness on how to take vitamins and about health problems associated with low vitamin D levels improved adherence in an interventional study on CF in the United States [20]. Patients with CFRD and who have PEx treated at the hospital are both clinical conditions for which we observed higher vitamin D levels, but only at the follow-up visit where serum vitamin D levels are above the recommended values. Those higher vitamin D levels at follow-up could be explained by a closer monitoring by the medical staff including more frequent appointments with the multi-disciplinary healthcare team, therefore increasing opportunities to address and correct lower vitamin D levels. In line with this observation, we previously published that older CF patients who tend to have more interactions with CF-team also tend to have generally higher vitamin D levels [16]. Our observations need to be validated in other CF clinics where patients have above the recommended serum values of vitamin D.

CFRD is presently the most frequent non-respiratory comorbidity in CF and its pathophysiology is still not fully understood [21]. Though initial data in long-standing treated CFRD patients suggested a positive relationship between vitamin D insufficiency and CFRD [14], more recent data using more classical diagnosis criteria in newly diagnosed untreated CFRD have not confirmed this association [16]. In the present study, we observed that after implementation of the supplementation protocol, patients with CFRD reached a higher mean vitamin D level than CF patients without CFRD (Fig. 1). Our observation thus does not support a direct causal relationship between vitamin D level and CFRD. We propose that the higher serum vitamin D level in patients with CFRD might be related to more frequent contact with multidisciplinary healthcare team, in addition to being followed by an endocrinologist.

Non-CF individuals with vitamin D deficiency are more susceptible to infection, suggesting that vitamin D is an important regulator of the immune system [9]. For instance, data from the large US National Health and Nutrition Examination Survey indicated that subjects with low level of vitamin D (<75 nmol/L) had a higher risk of respiratory tract infection [22]. More recently, a non-CF specific systematic review of the non-skeletal impacts of vitamin D supplementation concluded that three out of seven meta-analysis showed beneficial effects of vitamin D supplementation on respiratory tract infections [9]. In patients with CF, a retrospective longitudinal study by McCauley and colleagues showed a higher rate of PEx in adolescents with CF with vitamin D deficiency (<52 nmol/L) compared to patients who were sufficient (≥78 nmol/L) or insufficient (52–78 nom/L) [11]. This association was not observed in younger children aged from 6 to 14 years old. In our study, before the initiation of the vitamin supplementation protocol, vitamin D levels were similar between patients with or without PEx regardless of whether they were treated at home or at the hospital. The only significant difference was observed at follow-up where patients that had a PEx treated at the hospital had higher levels than the patients who had no-PEx. Once again, we believe that there is no causal relationship between vitamin D levels and PEx and that one plausible explanation for our observation is that patients who experienced PEx at the hospital are more likely to be closely monitored for their clinical evolution.

Preserving pulmonary function is the most important objective in CF. Following data reporting cross sectional association between lower FEV_1 and lower vitamin D levels [12], a recent small interventional study (16 patients) reported that vitamin D supplementation may contribute to reduced inflammation and improved lung function in patients with CF [17]. We also observed an association between baseline vitamin D levels and FEV_1, however this correlation disappeared after patients reached vitamin D optimal levels with the supplementation protocol. Similarly to our study, McCauley and his colleagues did not detect differences in pulmonary function between vitamin D status subgroups [11]. We suggest that the observed relationship at baseline would be non-causal; vitamin D would not have a direct link with lung function in CF.

The present study has some limitations. First, this is an observational and not a randomized trial increasing the risk of bias. Second, we did not observe any direct clinical impact of a vitamin D supplementation protocol but it is possible that a longer follow-up period is required to observe such effect. Finally, the study sample was a homogenous French-Canadian population with relatively good nutritional and pulmonary status and it remains possible that vitamin D supplementation could have a more significant impact on sicker patients, for instance patients awaiting a lung transplant.

5. Conclusion

Our study suggests that vitamin D appears to have no direct clinical benefit (lung function, CFRD risk, frequency of PEx and BMI) in an adult CF population. After the implementation of a vitamin D supplementation protocol, patients with significantly higher vitamin D levels were women, older in age, had CFRD or have been frequently hospitalized for PEx. We suggest that better compliance to treatments and closer follow-up from health professionals could partially explain why such patients reach higher vitamin D levels. Reaching recommended vitamin D levels with appropriate supplementation remains essential for bone health in order to reduce the risk of osteoporosis and osteopenia [4,23]. Cystic Fibrosis Foundation stated that optimal serum vitamin D is between 75 and 125 nmol/L to promote bone health [24]. It would be interesting to evaluate if vitamin D has a beneficial effect on secondary complications such as osteoporosis for instance, but follow-up period of more than 5 years would be necessary.

Conflict of interest

None declared.

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