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Original article

Effect of high dose vitamin D3 therapy on serum vitamin D3 levels in vitamin D insufficient adults with cystic fibrosis

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SUMMARY

Background: The effect of a high dose oral cholecalciferol repletion strategy in Vitamin D insufficient adults with CF is still unknown. Therefore, we assessed the effectiveness of our current approach, giving oral vitamin D3 supplementation at a dose of 10,000 IU from Monday to Friday for a total of 50,000 IU D3 weekly in vitamin D insufficient adult with CF.

Methods: We performed a retrospective chart review of all 59 adult CF patients between the ages of 17 and 64 years routinely followed at the CF Adult Program of Winnipeg Health Sciences Centre. Through consultation with the endocrinologist, our clinic vitamin D repletion protocol for treating CF adult patients who have serum 25-hydroxyvitamin D (25-OHD) < 30 ng/ml (<75 nmol/L) was to prescribe vitamin D3 10,000 IU orally from Monday to Friday (or the weekly equivalent of 50,000 IU) for 12 weeks in addition to their regular CF vitamin that supplied from 800 to 2000 IU vitamin D3 daily. Cholecalciferol was conveniently administered orally as either one capsule (oil-based) 10,000 IU or one tablet (powder-based) 10,000 IU. All patients were instructed to obtain follow-up serum 25-OHD levels post completion of treatment.

Results: Of the 59 adult patients at our CF Clinic, 35 patients (59%) had below optimal serum 25-OHD levels. Of the 35 patients identified, 10 patients with insufficient serum 25-OHD levels between 10 and 30 ng/ml (25–75 nmol/L) fulfilled the inclusion criteria. A significant increase in serum 25-OHD levels was observed ($P < 0.01$) from mean value of 21.6 ± 5.9 ng/ml (54.1 ± 14.8 nmol/L) at baseline to 31.7 ± 9.1 ng/ml (79.3 ± 22.8 nmol/L) ≥ 2 months post intervention. The current treatment approach was successful in treating Vitamin D insufficiency in 70% of the patients with low 25-OHD levels.

Conclusion: The results of this study demonstrate that a large number of adults attending Winnipeg Health Sciences Centre CF Clinic have serum 25-OHD levels below 30 ng/ml (75 nmol/L). This supports the need for dedicated and individualized approach to manage this condition. High dose therapy of vitamin D3, although a more aggressive treatment approach, may result in achieving optimal levels of serum 25-OHD in adults with CF.

Introduction

Cystic fibrosis

Cystic fibrosis (CF) is the most common life-threatening inherited progressive genetic disease. The prevalence rate in Canada is one in every 3600 people and an estimated 70,000 children and adults are affected worldwide [1,2]. CF is considered a multi-

Abbreviations: cystic fibrosis, CF; cystic fibrosis transmembrane conductance regulator, CFTR; serum 25-hydroxyvitamin D, 25-OHD; semi-automated liquid chromatography tandem mass spectrometry, LC-MS/MS; research electronic data capture, REDCap; forced expiratory volume in one second, FEV_1.

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system disease that primarily affects the lungs and digestive system. CF is caused by mutations in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene which codes for a chloride channel located in the plasma membrane of mucus-secreting epithelial cells. This protein is required to regulate the components of sweat, digestive fluids and mucus. The defective protein causes the body to produce unusually thick, sticky mucus that clogs the lungs leading to life-threatening lung infections and obstructs the pancreatic exocrine secretion, preventing normal digestion and absorption.

Vitamin D

Vitamin D either in the form of ergocalciferol or cholecalciferol is essential for optimal calcium absorption in the gastrointestinal tract. Calcium is vital for adequate bone development and strength in addition to several other physiologic roles. Potential benefits of vitamin D extend beyond bone health in CF [3–8]. Vitamin D is endogenously produced through synthesis from 7-dehydrocholesterol in the skin after exposure to UVB radiation with a wavelength of 290–320 nanometers, or exogenously from some dietary sources or as a supplement [9]. Brief casual exposure (approximately 15 minutes) of the face, arms and hands to direct sunshine can be equivalent to ingesting 200 IU of vitamin D and repeated total body exposure causing mild erythema is equivalent to ingesting 10,000 IU of vitamin D per day [10]. Many factors modify the intensity and duration of the action of sunlight including geographic location, time of the year, atmospheric conditions, amount of melanin present in the skin, length of exposure, blocking of effective rays by windows or the use of sunscreens. Seasonal influence is well-documented in northern countries like Canada due to lower sun exposure during winter. About 40% of Canadians during winter had vitamin D levels below 20 ng/ml (50 nmol/L) compared to 25% during summer [11]. Serum 25-OHD has approximately two month half-life; thus levels do not fluctuate acutely [12].

Vitamin D deficiency in CF

Reported possible causes of low vitamin D in CF include decreased gastrointestinal absorption, reduced 25-hydroxylation of vitamin D, reduced sun exposure, increased use of sunscreens, seasonal influence, geographical location, reduced vitamin D binding protein, and reduced vitamin D receptors [13–17]. Vitamin D deficiency in CF has been associated with low bone mineral density, failure to achieve expected peak bone mass in young adults, osteoporosis in adults and may impact other comorbidities common in CF [18–21].

Assessment and treatment of vitamin D deficiency in CF

The Institute of Medicine (IOM) historically defined vitamin D deficiency as a level less than 20 ng/ml (50 nmol/L) and insufficiency as a serum 25-OHD 0f 21–29 ng/ml [9,13,22–26]. With the optimal level of serum 25-OHD still remains somewhat controversial and the subject of debate, our study used the current target values defined by our treatment centre [22,27–29]. Pre and post treatment serum 25-OHD levels were classified as deficient if $<$ 10 ng/ml ($<$25 nmol/L), insufficient if 10–30 ng/ml (25–75 nmol/L), optimal status if 30–100 ng/ml (75–250 nmol/L) and potential adverse effects if $>$100 ng/ml ($>$250 nmol/L).

The current CF Foundation guidelines recommend that all individuals with CF maintain a serum 25-OHD goal of $\geq$30 ng/ml ($\geq$75 nmol/L) [30]. It is part of the guidelines that all adults with CF receive a starting dose of 800–2000 IU daily and increase to 1600–6000 IU daily to a maximum of 10,000 IU daily.

Despite current treatment guidelines, achieving optimal vitamin D levels remains a challenge for both patients and CF care providers. Aggressive yet safe and effective treatment options for repletion should be made available to prevent potential adverse long-term consequences.

The effect of a high dose oral cholecalciferol repletion strategy in Vitamin D insufficient adults with CF is still unknown. Therefore, we assessed the effectiveness of our current approach, giving oral vitamin D3 supplementation at a dose of 10,000 IU from Monday to Friday for a total of 50,000 IU D3 weekly in vitamin D insufficient adults with CF.

Materials and methods

A retrospective chart review of 59 adult CF patients between the ages of 17 and 64 years was completed. We reviewed charts and nutrition profiles for all patients seen from March 2012 through December 2014. The 59 patients represented all of the adults with CF routinely followed at the CF Adult Program of Winnipeg Health Sciences Centre at the time of the study. Winnipeg CF Clinic is located at latitude 49.8994° N, 97.1392° W. All patients had been diagnosed with CF on the basis of sweat chloride testing, genotyping or both. Pancreatic status was determined by faecal elastase measurements. Patients with pancreatic insufficiency are prescribed acceptable brand-name enzymes with doses between 1000 and 2500 lipase units/kg/meal. Adults with CF who had previously undergone lung transplantation ($n = 4$) or who were documented to have Cystic Fibrosis Liver Disease characterized by persistently abnormal liver enzymes, and/or radiological abnormalities such as hepatomegaly, cirrhosis with or without portal hypertension or abnormal liver histology ($n = 1$), or had weekly dosing of Vitamin D3 below 50,000 IU ($n = 10$) or had weekly dosing of over 50, 000 IU of vitamin D3 per week ($n = 3$) or who did not have repeat vitamin D testing ($n = 7$) were excluded. This study was approved by the University of Manitoba Bannatyne Campus Health Research Ethics Board.

Vitamin D supplementation protocol

Beginning in September 2010 following consultation with an endocrinologist, our clinic vitamin D repletion protocol was to prescribe vitamin D3 10,000 IU orally from Monday to Friday (or the weekly equivalent of 50,000 IU) for 12 weeks in addition to their regular CF vitamin that supplied 800–2000 IU vitamin D3 daily. Cholecalciferol was conveniently administered orally as either one capsule (oil-based) 10,000 IU or one tablet (powder-based) 10,000 IU. All baseline serum 25-OHD results were monitored by the CF dietitian. Oral supplement adherence was encouraged during clinic visits and follow-up phone calls with detailed discussion on potential risks of low vitamin D levels on bone health and lung function. In addition, patients are provided specific instruction to catch up with missed doses to achieve the weekly equivalent of 50,000 IU as needed. All of our patients were instructed to obtain follow-up serum 25-OHD levels immediately post completion of treatment. Patients who continued to have serum 25-OHD levels less than 30 ng/ml (75 nmol/L) upon re-evaluation received the recommended second course of vitamin D3 10,000 IU orally from Monday to Friday (or the weekly equivalent of 50,000 IU) for 12 weeks or longer at the discretion of the CF dietitian and treating physician. Repeat 25-OHD concentrations were measured at least two months after the intervention.

Measurement of serum vitamin D

Serum 25-OHD concentrations were measured by a semi-automated liquid chromatography tandem mass spectrometry (LC-MS/MS) analysis. This methodology is able to separately quantify 25OH vitamin D2 and 25OH vitamin D3 and accuracy of methodology is verified on an ongoing basis through participation in DEQAS [31].

At our treatment centre, analysis of 25-OHD by LC-MS/MS began March 2012. At this time routine CF vitamins contained 800–2000 IU vitamin D3 per day. Beginning January 2015, all CF patients in our clinic had access to a new and improved CF vitamin formulation that provided considerable amounts of vitamin D3 (6000 IU daily). Patients were excluded from the analysis if serum 25-OHD levels were obtained before March 1, 2012; if no follow-up level was available or if follow-up levels occurred after December 31, 2014 when a new and improved CF vitamin formulation was available.

Seasonal variation

The specific date when the serum 25-OHD levels were measured was collected to identify any seasonal variation. Seasons were defined as follows: winter – from December 22nd to March 21st; spring – from March 22nd to June 21st; summer – from June 22nd to September 21st; and fall – from September 22nd to December 21st.

Statistical analysis

Data collected were entered and managed using Research Electronic Data Capture (REDCap) electronic data capture tools hosted at the University of Manitoba. REDCap is a secure, web-based application designed to support data capture for research studies [32]. Descriptive statistics for continuous variables were given as means and SDs. Paired t tests were performed to evaluate before and after intervention differences. Categorical variables were compared by using chi-square test. Statistical significance was set at $P < 0.05$. Statistical analysis was performed with SAS software (version 9.1; SAS Institute Inc., Cary, NC).

Results

Baseline serum 25-OHD levels were measured in 59 patients. Ninety percent had pancreatic insufficiency. At baseline, 35 patients (59%) had below optimal serum 25-OHD during the study period, three patients were vitamin D deficient with serum 25-OHD levels of <10 ng/ml (<25 nmol/L) and 32 patients were vitamin D insufficient with serum 25-OHD levels between 10 and 30 ng/ml (25–75 nmol/L). Fifteen adults with CF who had previously undergone lung transplantation or who were known to have cirrhotic liver disease or had weekly dosing of Vitamin D3 below or over 50,000 IU were excluded. Overall descriptive characteristics of the 20 adults who fulfilled the inclusion criteria are summarized in Table 1. Mean serum 25-OHD levels in 20 adult CF patients was 18.1 ± 7.1 ng/ml (45.25 ± 17.7 nmol/L) and median was 20 ng/ml (50 nmol/L).

With the use of analysis of variance (ANOVA) to compare multiple groups, significant difference between groups were observed ($P < 0.05$) on baseline serum 25-OHD of the remaining 20 patients: mean values were highest in the summer 23.3 ng/ml (58.3 nmol/L), and winter 12.6 ng/ml (31.4 nmol/L), spring 20.9 ng/ml (52.2 nmol/L), and fall 22.1 ng/ml (55.3 nmol/L) were lower.

Of the 20 patients who were identified, 7 patients did not have repeat vitamin D testing because of failure to return to clinic and 3 patients did not receive the prescribed vitamin D_3 supplementation due to pharmaceutical errors. Post-intervention serum 25-OHD levels were available in 10 of the 20 potential patients. Of the 10 patients who fulfilled the inclusion criteria, 5 patients received powder-based tablet and the other half received the oil-based capsule. Using Pearson's Chi-Squared test, there were no significant difference detected between powder-based and oil-based users. The mean age, BMI, and initial FEV_1 were 25.1 years, 21.9 kg/m^2, 58.4% predicted, respectively (Table 2).

Figure 1 shows the distribution of 10 patients with their corresponding s-25OHD levels before and after supplementation. The major observation of this study was the significant increase in serum 25-OHD levels ($P < 0.01$) post intervention, from 21.6 ± 5.9 ng/ml (54.1 ± 14.8 nmol/L) to 31.7 ± 9.1 ng/ml (79.3 ± 22.8 nmol/L). Predictably, we observed the highest serum 25-OHD level post intervention from the only patient included in the study who had pancreatic sufficiency 51.2 ng/ml (128 nmol/L). Figure 1 also shows 7 out of 10 patients (70%) achieved serum 25-OHD levels >30 ng/ml (>75 nmol/L). There is no adverse events observed and reported during the study period.

Table 1
Cohort characteristics of the adult patients with cystic fibrosis at baseline.

Characteristics	Total
Number of patients	20
Baseline 25-OHD (nmol/L), mean ± SD	45.25 ± 17.7
Age (years), mean ± SD	25.6 ± 8.7
Female gender, N (% of group)	50%
BMI (kg/m2), mean ± SD	22.13 ± 2.4
Pancreatic insufficient, N (% of group)	9 (90%)
Pre FEV1 actual (L/sec), mean ± SD	2.3 ± 1.1
Pre FEV1% predicted, mean ± SD	58.1 ± 19.3
Exacerbation during 25-OHD treatment, N (% of group)	4 (40%)

25-OHD: 25-hydroxyvitamin D; Mean and Standard deviations are shown (±); N: total number; BMI: body mass index; FEV1: forced expiratory volume in one second.

Discussion

The results of our study are consistent with the numerous reports confirming that the majority of adults with CF require vitamin D repletion therapy. Similarly, multiple large CF clinics have documented low levels of 25-OHD from around the world [33–35]. This supports the need for aggressive yet safe and effective treatment options for vitamin D repletion to prevent potential adverse long-term consequences. To our understanding, our study contributed a novel approach on vitamin D3 treatment strategy for vitamin D insufficiency in adult patients with CF. The studies available are not directly comparable due to differences in supplementation protocol, outcome reporting and participant characteristics. The current clinic approach was successful in treating Vitamin D insufficiency in approximately 70% of the patients with low 25-OHD levels.

Table 2
Clinical characteristics of the selected adult patients with cystic fibrosis.

Characteristics	Total
Number of patients	10
Baseline 25-OHD (nmol/L), mean ± SD	54.1 ± 14.8
Age (years), mean ± SD	25.1 ± 9.1
Female gender, N (% of group)	7 (70%)
BMI (kg/m2), mean ± SD	21.98 ± 2.6
Pancreatic insufficient, N (% of group)	9 (90%)
Pre FEV1 actual (L/sec), mean ± SD	2.31 ± 1.1
Pre FEV1% predicted, mean ± SD	58.4 ± 21.9
Exacerbation during 25-OHD treatment, N (% of group)	4 (40%)

25-OHD: 25-hydroxyvitamin D; Mean and Standard deviations are shown (±); N: total number; BMI: body mass index; FEV1: forced expiratory volume in one second.

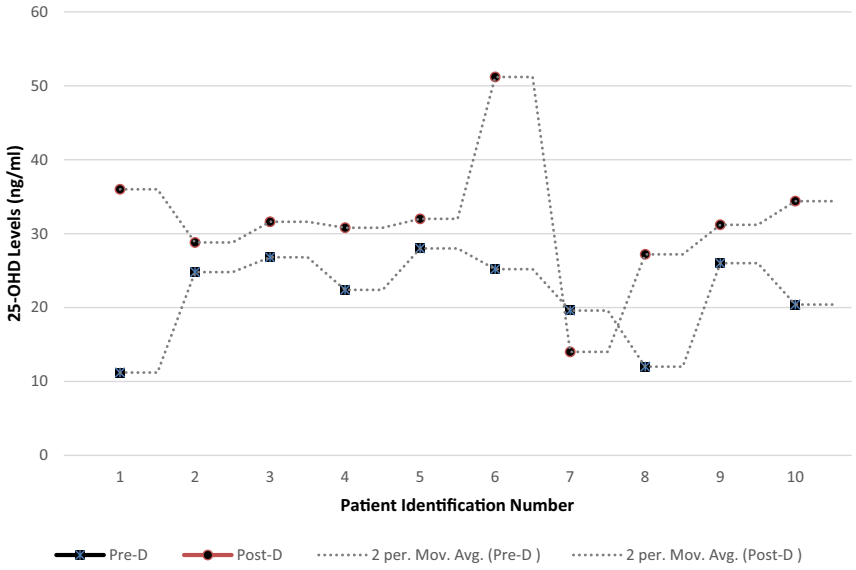

Fig. 1. Serum 25-OHD levels in adult patients with cystic fibrosis pre and post intervention. All baseline serum 25-OHD values (pre-D) were taken prior to vitamin D3 oral supplementation protocol. All patients were instructed to obtain follow-up serum 25-OHD levels (post-D) immediately post completion of supplementation. Repeat 25-OHD concentrations were measured at least two months after the intervention. Vitamin D3 supplementation protocol was 10,000 IU orally from Monday to Friday (or the weekly equivalent of 50,000 IU) for 12 weeks or longer at the discretion of the CF dietitian and treating physician, in addition to the routine CF vitamins that contained 800–2000 IU vitamin D3 per day. Paired t tests were performed to evaluate before and after intervention differences. Statistical significance was set at $P < 0.05$. Figure 1 shows significant increase in serum 25-OHD levels ($P < 0.01$) post intervention, from 21.6 ± 5.9 ng/ml to 31.7 ± 9.1 ng/ml. Each patient is represented in the figure as a pre-intervention point and a post-intervention point connected by a line. 25-OHD: 25-hydroxyvitamin D; Pre-D: pre serum 25-hyroxyvitamin D level; Post-D: post serum 25-hyroxyvitamin D level; N: total number of patients = 10.

Some patients did not have repeat vitamin D testing due to failure to return to clinic or dispensing errors. These findings not only reinforce the need for better attention to serum 25-OHD status but the awareness that close monitoring is necessary to safeguard and promote full adherence to the CF care plan.

Seasonal variation was included in an attempt to account for sun exposure but our medical records did not include information on sun exposure, sunscreen use or phototherapy use which could potentially confound the results. In addition, our study has no record on medication adherence. CF patients may be non-adherent especially if they take several different medications with multiple doses per day and refill prescriptions frequently.

Last, it is still not clear if vitamin D may exhibit differential absorption when solubilized in oil, lactose powders, cellulose powders or ethanol. Holick et al. suggested that the vehicle has an impact on the bioavailability of vitamin D supplements [36]. In order to make recommendations for vitamin D intake for the CF population, Grossman and Tangpricha suggested considering how the different vehicles may influence the bioavailability of vitamin D [37]. Our patients received either oil based capsule or powdered form caplets. While the work of Hermes and colleagues suggest that the powder vehicle was better in increasing serum vitamin D3 concentrations, our study did not see any significant difference between the two forms of oral cholecalciferol used [38]. The full extent to which the vehicle impacts the bioavailability of vitamin D still needs to be established. Currently, the CF Foundation is not able to make a recommendation for or against the use of an oil-based vs. a powder-based formulation of vitamin D3 in CF [30].

This study has limitations. Our study was a retrospective study and not a randomized controlled trial which limits the conclusions that can be drawn from the results observed. It cannot be stated absolutely that the observed changes were not due to regression toward the mean or if the changes observed would be different from the controlled groups. We can only assume that the effects observed were due to the vitamin D supplementation based on what is known in CF pathophysiology. Planned prospective controlled trial is needed to determine the acceptable dosage and duration of vitamin D3 supplementation required to achieve s-25OHD levels >30 ng/ml (75 nmol/L) in the adult CF population. Also, no data on sunscreen use nor sun exposure were collected which could play a significant role. Seasonal variation is well-documented and can possibly confound our results.

While vitamin D intoxication can occur, it is not observed until s-25OHD levels reach 150 ng/ml (375 nmol/L) or more [13]. There is no reported adverse events in this study. Since it is impossible to prove by observational studies and statistical analysis that our protocol has no harmful effect, we can only conclude that high dose of 10,000 IU D3 orally from Monday to Friday for 12 weeks or more is safe because there was no adverse effects reported and observed.

In conclusion, the findings of this study have shown that high dosing of cholecalciferol appears to increase serum 25-OHD to >30 ng/ml (>75 nmol/L) for most of our patients. This conclusion is similar to the Cochrane review that 25-OHD levels are significantly higher in patients receiving vitamin D supplementation [39]. There were no adverse events observed in our study. Due to the limited sample size and short duration of this study, further research is needed in order to determine if this strategy will be beneficial for most adult CF patients.

The most effective and safe therapeutic option to achieve optimal levels is still unclear. A randomized controlled clinical trial is needed to determine the dosage, duration and type of vehicle substance that would best achieve serum 25-OHD concentrations above the target >30 ng/ml (75 nmol/L) in the adult CF population.

Author contributions

All authors equally contributed to this work and approved the final manuscript.

Conflict-of-interest

The authors declare that they have no conflict of interest and nothing to disclose.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnesp.2017.12.001.

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