Sunlight is an important determinant of vitamin D serum concentrations in cystic fibrosis

Article *in* European journal of clinical nutrition · January 2011

DOI: 10.1038/ejcn.2010.280 · Source: PubMed

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Sunlight is an important determinant of vitamin D serum concentrations in cystic fibrosis.

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Short title: Sunlight determines vitamin D concentration in CF

Non-standard abbreviations: 25 (OH) D : 25-OH cholecalciferol; CF: cystic fibrosis

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Reprints not available from the author

Neither author had a personal or financial conflict of interest.

Abstract

Background/Objectives:

The increase of bone disease in adult CF patients is partly attributed to inadequate serum concentrations of 25-OH cholecalciferol (25 (OH) D) blamed on fat malabsorption. Based on physiological, clinical and biochemical observations this pathogenesis is debatable. The objective was to ascertain the relative importance of different 25 (OH) D sources.

Subjects/Methods: Over four consecutive years, 474 annual 25 (OH) D serum concentrations from 141 CF patients of all ages were compared to values of healthy peers and weighed against annual UVB exposure.

Results: Ranked per month, 25 (OH) D concentrations depicted a curve strikingly parallel to the amount of UVB exposure in the preceding months. A significant difference exists between 25 (OH) D concentrations in the "Months with high UVB exposure" (May-October) and the "Months with low UVB exposure" (November-April) but not with healthy controls in the same period.

Conclusions: 25 (OH) D concentrations clearly respond to the amount of sunshine in preceding months. They are not clearly influenced by daily oral supplements of 800 IU of cholecalciferol. Sun exposure should be encouraged, and the recommended dosage of oral supplements increased.

Key Words: Cystic fibrosis, 25-OH cholecalciferol serum concentrations, sunshine, oral vitamin D supplements, children and adolescents, adults.

Introduction

Changes in the understanding and in the clinical management of cystic fibrosis (CF) have increased life expectancy from single digits in the 1970's to more than 35 years at present (CF foundation, 2006) . As a consequence, new clinical problems have emerged, such as the increased bone fracture rate in adolescents and adults. These bone fractures are the result of a multitude of contributing factors such as lack of physical exercise, elevated cytokine production caused by chronic inflammation, delayed pubertal maturation, corticosteroid therapy, vitamin D and calcium deficiency and a poor nutritional status (Aris et al., 2005). Remarkably, because of the fact that vitamin D is fat-soluble and most CF patients suffer from fat malabsorption, vitamin D deficiency is primarily blamed (Lark et al., 2001) (Aris et al., 2005). As a natural consequence, all nutritional guidelines insist on preventing this deficiency by means of a daily oral supplement (Borowitz et al., 2002) (Sinaasappel et al., 2002) (Aris et al.,2005). Data on serum concentrations of 25-OH cholecalciferol (25 (OH) D) in CF are, however, not unequivocal, since they have been reported as too low by some authors (Donovan et al., 1998) (Mortensen et al, 2000) (Rovner, 2007) , while others disagree (Chavasse et al, 2004) (Buntain et al, 2004). Moreover, the failure of oral supplement treatments is common and has been widely published (Donovan et al., 1998) (Boyle et al, 2005) (Green et al, 2008) (Green et al, 2010). Holding fat malabsorption solely responsible for vitamin D deficiency overlooks the importance of the dermal supply, which in healthy people determines up to 85% of 25 (OH) D concentrations in conditions of sunshine (Heaney et al., 2003). In less sunny regions, dermal vitamin D production is expected to be high during the sunnier months and low for the rest of the year (Rapuri et al, 2002) . Annual determination of 25 (OH) D concentrations, as is usually performed (Carr & Dinwiddie, 1996), will thus only provide information about a single limited and recent period of time. In an attempt to understand the relative importance of different 25 (OH) D sources, more specifically the influence of sunlight, a retrospective study was undertaken which looked at all available 25 (OH) D concentrations from the patients' annual follow-up visits, collected over four consecutive years. They were compared

to values of healthy controls of the same age group and similar geographical latitude (latitude 50° N). We hypothesize that sunlight will prove to be an important determinant of 25 (OH) D concentrations in cystic fibrosis patients.

Materials and methods

In a retrospective study design, a total of 474 values of 25 (OH) D serum concentrations from 141 CF patients was gathered. The values had been measured at the systematic annual follow-up visits between October 2001 and December 2005. For each patient the annual follow-up visit had taken place around the same time of the year. The group included all CF patients above the age of one year that were followed at the CF centre of the Ghent University Hospital (latitude 50°N), without any selection. The group therefore contains every degree of disease severity. No transplanted patients were included. The median age was 15.6 years, ranging from 1 to 42 years; 56% of the patients were male. Based on faecal elastase 1 measurement, (Borowitz et al., 2004) 91 % of the patients (n=128) had pancreatic insufficiency (<15µg/g) and were being treated with pancreatic enzyme replacement, in accordance with guidelines (Sinaasappel et al., 2002). Patients with faecal elastase 1 concentrations above 400 µg/g were regarded as pancreatic sufficient (7%). Faecal elastase 1 concentrations between 15 and 400 µg/g were considered equivocal and not taken into consideration (3%). Although a daily vitamin D supplement was prescribed to all patients regardless of exocrine pancreatic status, just only 93% reported taking it regularly (median dose: 800 IU cholecalciferol per day). The 25 (OH) D serum concentrations of 160 local (latitude 50° N) healthy individuals, with a median age of 20 years (age range: 10 y – 45 y), served as controls for the comparison with the values of CF patients measured during the "Months with low UVB exposure", from October to December.

Analysis

Venous blood samples were obtained. 25 (OH) D serum concentrations were determined after extraction by RIA (DiaSorin, Stillwater, Minnesota, USA). This assay shows 100% cross-reactivity between 25-OH- D2 and 25-OH- D3. In order to ascertain the importance of sunlight, 25 (OH) D serum concentrations were checked against the varying intensity of UV-B light from the sun over the four year period. This information was retrieved from records at the Royal

Meteorological Institute at the University Observatory Armand Pien, which is located within a 50 km distance from the place of residence of all patients in the study. Based on these records of varying intensity of UVB light, one year can be divided into two distinct periods: a period with less UVB exposure between November and April and a period with higher UVB exposure from May to October.

Statistical methods

SPSS 12.0 (Chicago, Illinois USA) was used in the statistical processing of the study data. Since the data did not show a normal distribution, non-parametric tests were chosen. The correlation between 25 (OH) D serum concentrations and the varying intensity of UVB light was examined using the Spearman correlation coefficient. For the comparison between two groups, the Mann-Whitney U test was used. The study was approved by the Medical Ethics board of the University Hospital at Ghent.

Results

Seasonal variations.

The 474 values of 25 (OH) D serum concentrations from the annual follow-up visits (over the four years) were pooled and plotted per month (figure 1). These values depicted an S-shaped curve which was convex from May to October ("Months with high UVB exposure") and concave in the subsequent period from November to April ("Months with low UVB exposure"). The lowest values were seen in February.

The median 25 (OH) D serum concentrations during the" Months with high UVB exposure" were significantly higher than those in the "Months with low UVB exposure" (table 1).

There is an important fraction of the CF population with 25 (OH) D concentrations below 20 ng/ml (table 2). However there is an important influence of the varying exposure to UVB light from the sun over the different years.

The 25 (OH) D serum concentrations were compared to reference values from healthy peers. No significant difference was found in comparison to local controls during the "Months with low UVB exposure": CF patients: 18.0 ng/ml (IQR: 10.2 –24.5 ng/ml); control group: 17.2 ng/ml (IQR: 12.7-19.3 ng/ml); p = 0.60. During the "Months with high UVB exposure", 25 (OH) D serumconcentrations were not statistically inferior to values from a reported group of comparable age and geographical location (Guillemant et al., 2001).

Relation to sunshine hours

The comparison between the variation in 25 (OH) D serum concentrations in the CF group over the four years and the amount of UVB exposure in the preceding months showed a remarkably manifest correlation. It was clear that median 25(OH) D serum concentrations ran parallel to the

amount of UVB exposure in the two or three preceding months ($p < 0.001$). It was also evident that in a year with more UVB exposure during the summer -such as 2003- 25(OH) D serum concentrations were higher than those recorded in a year with a summer with less UVB exposure (figure 2).

Discussion

The past decade a great amount of studies are published concerning vitamin D in CF. These publications mainly discuss the 25 (OH) D serum concentrations in CF patients. As the incidence of spontaneous bone fractures rises along with patient longevity, there is also a growing interest in the role of vitamin D in CF. The results presented in the different studies however are not unequivocal. The main source of confusion is disagreement on reference values to determine which values are too low. In most studies 25 (OH) D serum concentrations are considered normal when above 20 ng/ml (Malabanan et al, 1998), while more recently values above 30 ng/ml at any time of the year are recommended (Aris et al, 2005) (Green et al, 2008). It is not entirely clear on what basis those recommendations are made, while at the same time, in most surveys, these levels are not met by large groups of healthy people. Depending on geographical location, age and season, between 22 % and 97 % of 25 (OH) D serum concentrations in healthy controls are below 20 ng/ml (Cashman, 2007) (Andersen et al, 2005). It is therefore to be expected that at least as many people with CF will also have 25(OH) D serum concentrations under the recommended values. Just as it occurs in healthy people, the percentages of 25(OH) D serum concentrations below 20 ng/ml observed in CF patients can vary considerably from one study to another due to disparity in disease severity, age, geographical location and season (Buntain et al, 2004) (Boyle et al, 2005) (Gronowitz et al, 2004) (Rovner et al, 2007). In the present study the difference between the percentages of 25 (OH) D serum concentrations below 20 ng/ml in the four successive years amounted to 58 % exclusively because of sunshine variations. Since vitamin D insufficiency (i.e.: 25(OH) D serum concentrations below the theoretically recommended 30 ng/ml (Rovner et al, 2007)) is widespread even in healthy controls, preference was given to a comparison of actual serum concentrations in order to determine whether 25(OH) D serum concentrations in patients with CF are significantly different from those in healthy people. We find no statistical difference in 25(OH) D serum levels between people with CF and healthy controls. This seems to confirm results from other studies (Buntain et al, 2004). These findings have important implications for

clinical practice as they allow comparison of 25(OH) D serum concentrations from CF patients with values from healthy controls, always taking into account the season of the year. It should be kept in mind that these conclusions are based on data from CF patients who were systematically taking a daily oral vitamin D supplement and from a healthy control population taking none. We found a significant difference in 25 (OH) D concentrations when we compared "Months with high UVB exposure" to "Months with low UVB exposure". We found those differences as well in the patient group as in the healthy controls. The total amount of UV light during the period May-October at our location is approximately 5889 J/cm² (estimated amount of UVB light 589J /cm²) and the total amount of UV light during the period November-April is approximately 1761 J/cm² (estimated amount of UVB light 176 J/cm²). The curve of 25(OH) D serum concentrations and that of varying intensity of UVB light from the sun run a parallel course with a time-lag of approximately two months, as was also described in healthy people (Need et al, 1993). A maximum is reached in late summer and a minimum at the end of the winter. Higher 25 (OH) D serum concentrations in September correlate with higher 25 (OH) D serum concentrations in March of the subsequent year. This is explained by the storage of 25-OH cholecalciferol from dermal sun exposure during the months with high UVB exposure and consumption during the months with less UVB exposure, resulting in a progressive depletion of stocks (Rapuri et al, 2002) (Guillemant et al, 2001). It is generally accepted that the skin is the major source of vitamin D, probably more than 85% of 25 (OH) D is obtained through exposure to sunlight (Heaney et al, 2003). Exposure of 6% of the body surface to one minimal erythemal dose of sunlight is equivalent to the oral administration of 600 to 1000 IU of vitamin D. This means that in conditions of sunshine, mild sun exposure of hands, arms, face or back, 2 to 3 times per week, would comply with vitamin D recommendations (Holick, 1996) (Hollick, 1999). This is certainly feasible in sunny climates, whereas in regions with less sunny climates, it is only possible during some months of the year, and oral supplements thus remain imperative.

The data obtained in the present study suggest that the current practice of supplementing CF patients can result in 25 (OH) D serum concentrations similar to those found in healthy controls. However, if concentrations constantly above 30 ng/ml are to be reached, as recommended, (Aris et al, 2005) current guidelines seem inadequate, and a supplementation with higher doses of vitamin D would be required. This brings us to the problem that in CF patients it proves extremely difficult to correct low 25 (OH) D serum concentrations with the aid of oral supplements (Boyle et al, 2005) (Green et al, 2008) (Green et al, 2010). High doses of oral vitamin D supplements e.g. 50000 IU of ergocalciferol daily for 28 days was effective in correcting vitamin D insufficiency in 50 % of the subjects. However, almost half of the successfully treated patients were unable to maintain normal 25-OHD levels more than 6 months after completion of the therapy (Green et al,2010). A recent study of Khazai et al. 2009 , compared three treatment modes to correct low 25(OH) concentrations e.g. 50000 IU of ergocalciferol or of cholecalciferol weekly or treatment with UV light five times a week. Serum was collected for 25(OH)D at baseline and at 12 weeks. Treatment with ergocalciferol and cholecalciferol raised 25 (OH)D significantly, treatment with UV did not raise 25(OH)D significantly, however only 55% of subjects were adherent with UV therapy. However in other studies different methods of UV B exposure have been proved to be effective in increasing 25 (OH) D serum concentrations (Gronowitz et al, 2005) (Chandra et al,2007).
Treatment with high doses of vitamin D may have at least a temporary result, further investigations to determine a possible role of treatment with UVB therapy are needed

Conclusion:

This study shows the prominent role of sunlight exposure in determining the levels of 25 (OH) D serum concentrations in CF patients. Concentration values reflect the previous amount of UVB exposure with a time-lag of approximately two months. Comparison of 25(OH) D serum concentrations in both groups (CF patients and healthy controls) showed no significant difference,

on condition that the period of the year be taken into account. As a consequence of the general recommendation that 25 (OH) D serum concentrations should stay above 30 ng/ml, a large percentage of controls and CF patients are labeled as vitamin D insufficient, especially during the months with less UVB exposure. Currently recommended daily oral supplements of 400-1000 IU are unable to correct this and therefore a higher oral vitamin D dose (1000-2000 IU cholecalciferol) should systematically be administered. A number of publications suggest that phototherapy could be a promising alternative still awaiting the development of adequate methods of application. In the meantime,prudent sunlight exposure, the natural form of phototherapy, should be encouraged during the months with a high UVB exposure.

Acknowledgments

The authors' contributions are as follows: ER, SV participated in all stages of the research project. ER, CW and SV conceived the study and the collection of data. JMK and JDS provided data on control patients. ER, CW and SV carried out the data analysis and ER and SV wrote the manuscript. All authors read and approved the final manuscript. We would like to thank Nele Iserentant and Santiago Grau for linguistic help in the drawing of the manuscript.

313 **Conflict of interest**

314 None of the authors had a personal or financial conflict of interest.

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Table 1: Median 25 (OH) D concentrations versus UVB exposure

	N	Median 25 (OH) D concentrations (ng/ml) "Months with high UVB exposure" [a]	n	Median 25 (OH) D concentrations (ng/ml) "Months with low UVB exposure "[b]	p-value
2005	70	27.9 (IQR: 19.3– 35.0)	59	17.0 (IQR: 11.8– 26.4)	< 0.001
2004	72	28.5 (IQR: 21.7– 35.0)	56	22.5 (IQR: 14.7– 28.9)	<0.001
2003	71	28.5 (IQR: 18.6– 35.1)	56	18.6 (IQR: 11.2– 23.4)	<0.001
2002	59	21.7 (IQR: 14.0– 27.5)	40	11.0 (IQR: 8.0– 19.6)	<0.001

[a] " Months with high UVB exposure" : May to October; [b] "Months with low UVB exposure": November to April

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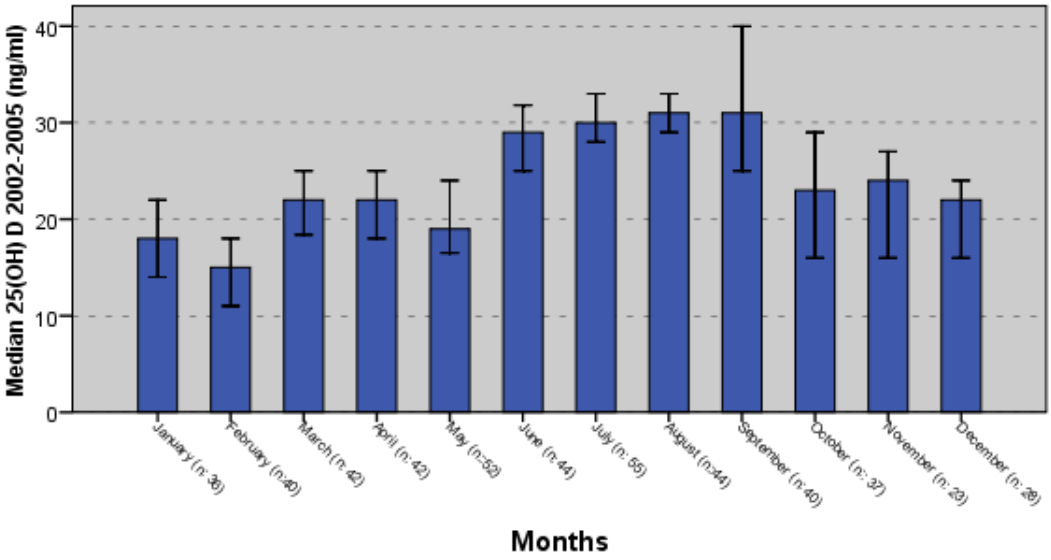
Table 2: Percentage of 25 (OH) D concentrations < 20 ng/ml in 2002, 2003, 2004 and 2005 .

	% 25 (OH) D < 20 ng/ml "Months with high UVB exposure"	% 25 (OH) D < 20 ng/ml "Months with low UVB exposure"
2002	38,9	77,5
2003	24,6	51,4
2004	19	46,2
2005	19	64,3

Figure 1: Median 25 (OH) D serum concentrations in the period 2002-2005 per month in cystic fibrosis patients. Median 25 (OH) D serum concentrations per month depicted an S-shaped curve convex from May to October (Months with high UVB exposure) and concave in the subsequent period from November to April (Months with low UVB exposure). The minimum value is found in February.

Figure 2: Median 25 (OH) D serum concentration and UVB exposure per month through the period 2002-2005 in cystic fibrosis patients. Figure 2 showed the median 25 (OH) D serum concentrations (bar) and the mean
UVB exposure per month (dotted line) for the four successive years 2002 through 2005. It was clear that median 25 (OH) D concentrations run parallel to the amount of sunshine in the two or three preceding months ($p < 0.001$). (Jan: January)



Error bars: 95% CI