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Jean de Schepper

► **To cite this version:**

Eddy Robberecht, Sara Vandewalle, Charline Wehlou, Jean Marc Kaufman, Jean de Schepper. Sunlight is an important determinant of vitamin D serum concentrations in cystic fibrosis. *European Journal of Clinical Nutrition*, 2011, 10.1038/ejcn.2010.280 . hal-00609400

**HAL Id: hal-00609400**

**<https://hal.science/hal-00609400>**

Submitted on 19 Jul 2011

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

Eddy Robberecht MD, PhD<sup>a</sup>, Sara Vandewalle MD <sup>a</sup>, Charline Wehlou MD <sup>a</sup>, Jean-Marc Kaufman MD, PhD<sup>b</sup>, Jean De Schepper MD, PhD<sup>b,c</sup>.

ER, SV: both authors contributed to the same extent

<sup>a</sup> CF Centre Ghent University Hospital

<sup>b</sup> Department of Endocrinology Ghent University Hospital

<sup>c</sup> CF Centre Brussels University Hospital

Short title: Sunlight determines vitamin D concentration in CF

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

Address correspondence to E. Robberecht, CF Centre, Ghent University Hospital, 5K6  
De Pintelaan 185 B-9000 Ghent, Belgium. Telephone number : 00329/332.39.66. Email:  
[eddy.robberrecht@Uzgent.be](mailto:eddy.robberrecht@Uzgent.be)

Reprints not available from the author

Neither author had a personal or financial conflict of interest.

2 **Abstract**

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4 **Background/Objectives:**

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

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

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

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

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

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## 28 **Introduction**

29 Changes in the understanding and in the clinical management of cystic fibrosis (CF) have  
30 increased life expectancy from single digits in the 1970's to more than 35 years at present (CF  
31 foundation, 2006) . As a consequence, new clinical problems have emerged, such as the increased  
32 bone fracture rate in adolescents and adults. These bone fractures are the result of a multitude of  
33 contributing factors such as lack of physical exercise, elevated cytokine production caused by  
34 chronic inflammation, delayed pubertal maturation, corticosteroid therapy, vitamin D and calcium  
35 deficiency and a poor nutritional status (Aris et al., 2005). Remarkably, because of the fact that  
36 vitamin D is fat-soluble and most CF patients suffer from fat malabsorption, vitamin D deficiency  
37 is primarily blamed (Lark et al., 2001) (Aris et al., 2005). As a natural consequence, all nutritional  
38 guidelines insist on preventing this deficiency by means of a daily oral supplement (Borowitz et  
39 al., 2002) (Sinaasappel et al., 2002) (Aris et al.,2005). Data on serum concentrations of 25-OH  
40 cholecalciferol (25 (OH) D) in CF are, however, not unequivocal, since they have been reported  
41 as too low by some authors (Donovan et al., 1998) (Mortensen et al, 2000) (Rovner, 2007) , while  
42 others disagree (Chavasse et al, 2004) (Buntain et al, 2004). Moreover, the failure of oral  
43 supplement treatments is common and has been widely published (Donovan et al., 1998) (Boyle  
44 et al, 2005) (Green et al, 2008) (Green et al, 2010). Holding fat malabsorption solely responsible  
45 for vitamin D deficiency overlooks the importance of the dermal supply, which in healthy people  
46 determines up to 85% of 25 (OH) D concentrations in conditions of sunshine (Heaney et al.,  
47 2003). In less sunny regions, dermal vitamin D production is expected to be high during the  
48 sunnier months and low for the rest of the year (Rapuri et al, 2002) . Annual determination of 25  
49 (OH) D concentrations, as is usually performed (Carr & Dinwiddie, 1996), will thus only provide  
50 information about a single limited and recent period of time. In an attempt to understand the  
51 relative importance of different 25 (OH) D sources, more specifically the influence of sunlight, a  
52 retrospective study was undertaken which looked at all available 25 (OH) D concentrations from  
53 the patients' annual follow-up visits, collected over four consecutive years. They were compared

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

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## 80 **Materials and methods**

81 In a retrospective study design, a total of 474 values of 25 (OH) D serum concentrations from 141  
82 CF patients was gathered. The values had been measured at the systematic annual follow-up visits  
83 between October 2001 and December 2005. For each patient the annual follow-up visit had taken  
84 place around the same time of the year. The group included all CF patients above the age of one  
85 year that were followed at the CF centre of the Ghent University Hospital (latitude 50°N),  
86 without any selection. The group therefore contains every degree of disease severity. No  
87 transplanted patients were included. The median age was 15.6 years, ranging from 1 to 42 years;  
88 56% of the patients were male. Based on faecal elastase 1 measurement, (Borowitz et al., 2004)  
89 91 % of the patients (n=128) had pancreatic insufficiency (<15µg/g) and were being treated with  
90 pancreatic enzyme replacement, in accordance with guidelines (Sinaasappel et al., 2002). Patients  
91 with faecal elastase 1 concentrations above 400 µg/g were regarded as pancreatic sufficient (7%).  
92 Faecal elastase 1 concentrations between 15 and 400 µg/g were considered equivocal and not  
93 taken into consideration (3%). Although a daily vitamin D supplement was prescribed to all  
94 patients regardless of exocrine pancreatic status, just only 93% reported taking it regularly  
95 (median dose: 800 IU cholecalciferol per day). The 25 (OH) D serum concentrations of 160 local  
96 (latitude 50° N) healthy individuals, with a median age of 20 years (age range: 10 y – 45 y),  
97 served as controls for the comparison with the values of CF patients measured during the “Months  
98 with low UVB exposure”, from October to December.

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## 100 **Analysis**

101 Venous blood samples were obtained. 25 (OH) D serum concentrations were determined after  
102 extraction by RIA (DiaSorin, Stillwater, Minnesota, USA). This assay shows 100% cross-  
103 reactivity between 25-OH- D2 and 25-OH- D3. In order to ascertain the importance of sunlight,  
104 25 (OH) D serum concentrations were checked against the varying intensity of UV-B light from  
105 the sun over the four year period. This information was retrieved from records at the Royal

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

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112 Statistical methods

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

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132 **Results**

133 *Seasonal variations.*

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

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

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

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

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154 *Relation to sunshine hours*

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



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

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**184 Discussion**

185 The past decade a great amount of studies are published concerning vitamin D in CF. These  
186 publications mainly discuss the 25 (OH) D serum concentrations in CF patients. As the incidence  
187 of spontaneous bone fractures rises along with patient longevity, there is also a growing interest in  
188 the role of vitamin D in CF. The results presented in the different studies however are not  
189 unequivocal. The main source of confusion is disagreement on reference values to determine  
190 which values are too low. In most studies 25 (OH) D serum concentrations are considered normal  
191 when above 20 ng/ml (Malabanan et al, 1998), while more recently values above 30 ng/ml at any  
192 time of the year are recommended (Aris et al, 2005) (Green et al, 2008). It is not entirely clear on  
193 what basis those recommendations are made, while at the same time, in most surveys, these levels  
194 are not met by large groups of healthy people. Depending on geographical location, age and  
195 season, between 22 % and 97 % of 25 (OH) D serum concentrations in healthy controls are below  
196 20 ng/ml (Cashman, 2007) (Andersen et al, 2005). It is therefore to be expected that at least as  
197 many people with CF will also have 25(OH) D serum concentrations under the recommended  
198 values. Just as it occurs in healthy people, the percentages of 25(OH) D serum concentrations  
199 below 20 ng/ml observed in CF patients can vary considerably from one study to another due to  
200 disparity in disease severity, age, geographical location and season (Buntain et al, 2004) (Boyle et  
201 al, 2005) (Gronowitz et al, 2004) (Rovner et al, 2007). In the present study the difference between  
202 the percentages of 25 (OH) D serum concentrations below 20 ng/ml in the four successive years  
203 amounted to 58 % exclusively because of sunshine variations. Since vitamin D insufficiency (i.e.:  
204 25(OH) D serum concentrations below the theoretically recommended 30 ng/ml (Rovner et al,  
205 2007)) is widespread even in healthy controls, preference was given to a comparison of actual  
206 serum concentrations in order to determine whether 25(OH) D serum concentrations in patients  
207 with CF are significantly different from those in healthy people. We find no statistical difference  
208 in 25(OH) D serum levels between people with CF and healthy controls. This seems to confirm  
209 results from other studies (Buntain et al, 2004). These findings have important implications for

210 clinical practice as they allow comparison of 25(OH) D serum concentrations from CF patients  
211 with values from healthy controls, always taking into account the season of the year. It should be  
212 kept in mind that these conclusions are based on data from CF patients who were systematically  
213 taking a daily oral vitamin D supplement and from a healthy control population taking none. We  
214 found a significant difference in 25 (OH) D concentrations when we compared “Months with high  
215 UVB exposure” to “Months with low UVB exposure”. We found those differences as well in the  
216 patient group as in the healthy controls. The total amount of UV light during the period May-  
217 October at our location is approximately 5889 J/cm<sup>2</sup> (estimated amount of UVB light 589J /cm<sup>2</sup>)  
218 and the total amount of UV light during the period November-April is approximately 1761 J/cm<sup>2</sup>  
219 (estimated amount of UVB light 176 J/cm<sup>2</sup>). The curve of 25(OH) D serum concentrations and  
220 that of varying intensity of UVB light from the sun run a parallel course with a time-lag of  
221 approximately two months, as was also described in healthy people (Need et al, 1993). A  
222 maximum is reached in late summer and a minimum at the end of the winter. Higher 25 (OH) D  
223 serum concentrations in September correlate with higher 25 (OH) D serum concentrations in  
224 March of the subsequent year. This is explained by the storage of 25-OH cholecalciferol from  
225 dermal sun exposure during the months with high UVB exposure and consumption during the  
226 months with less UVB exposure, resulting in a progressive depletion of stocks (Rapuri et al, 2002)  
227 (Guillemant et al, 2001). It is generally accepted that the skin is the major source of vitamin D,  
228 probably more than 85% of 25 (OH) D is obtained through exposure to sunlight (Heaney et al,  
229 2003). Exposure of 6% of the body surface to one minimal erythemal dose of sunlight is  
230 equivalent to the oral administration of 600 to 1000 IU of vitamin D. This means that in  
231 conditions of sunshine, mild sun exposure of hands, arms, face or back, 2 to 3 times per week,  
232 would comply with vitamin D recommendations (Holick, 1996) (Hollick, 1999). This is certainly  
233 feasible in sunny climates, whereas in regions with less sunny climates, it is only possible during  
234 some months of the year, and oral supplements thus remain imperative.

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

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256 Conclusion:

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

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

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**287 Acknowledgments**

288 The authors' contributions are as follows: ER, SV participated in all stages of the research project.

289 ER, CW and SV conceived the study and the collection of data. JMK and JDS provided data on

290 control patients. ER, CW and SV carried out the data analysis and ER and SV wrote the

291 manuscript. All authors read and approved the final manuscript. We would like to thank Nele

292 Iserentant and Santiago Grau for linguistic help in the drawing of the manuscript.

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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)<br>“Months with high UVB exposure” <sup>a</sup> | n  | Median 25 (OH) D concentrations (ng/ml)<br>“Months with low UVB exposure” <sup>b</sup> | 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  |

<sup>a</sup> “Months with high UVB exposure” : May to October; <sup>b</sup> “Months with low UVB exposure”:

November to April

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

|      | % 25 (OH) D < 20 ng/ml<br>“Months with high UVB<br>exposure” | % 25 (OH) D < 20 ng/ml<br>“Months with low UVB<br>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)



