Original Communication

Serum 25-hydroxy Vitamin D Levels in Chronic Fatigue Syndrome: a Retrospective Survey

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Abstract: *Introduction:* Patients with chronic fatigue syndrome (CFS) may be at risk of osteoporosis due to their relative lack of physical activity and excessive time spent indoors, leading to reduced vitamin D synthesis. We hypothesized that serum 25-OH vitamin D levels are lower in CFS patients than in the general British population. *Subjects and methods:* We performed a retrospective survey of serum 25-OH vitamin D levels in 221 CFS patients. We compared this to a group of patients attending the hospital for other chronic conditions and to a large British longitudinal survey of 45-year old women, using a variety of appropriate statistical approaches. *Results:* 25-OH vitamin D levels are moderately to severely suboptimal in CFS patients, with a mean of 44.4 nmol/L (optimal levels >75 nmol/L). These levels are lower and the difference is statistically significant ($p<0.0004$) than those of the general British population from a recent national survey, but similar to those in patients with other chronic conditions. *Conclusions:* This data supports the recommendation made in recent NICE guidelines that all patients with moderate to severe CFS should be encouraged to obtain adequate sun exposure and eat foods high in vitamin D. Oral or intramuscular vitamin D supplementation should be considered for those whose levels remain suboptimal.

Key words: chronic fatigue syndrome, myalgic encephalomyelitis, osteoporosis, vitamin D, cholecalciferol

Introduction

Patients with chronic fatigue syndrome (CFS) may be at risk of osteoporosis due to relative lack of physical activity and sun exposure, the predominance of CFS in females (sometimes perimenopausal), and in some cases deficient diet.

Recent evidence suggests that the optimal serum 25-OH vitamin D concentration for multiple health outcomes should be upwards of 75 nmol/L [1,2]. This is significantly higher than that which is accepted in current

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practice (the reference range is given as 15–120 nmol/L from our hospital laboratory) and many physicians remain unaware of this discrepancy. Vitamin D deficiency is a cause of muscle weakness, malaise, and myalgia [3] and deficiency may possibly contribute to CFS symptoms. However, we have been unable to locate any research on 25-OH vitamin D levels in CFS.

We therefore determined initially to perform a retrospective survey of serum 25-OH vitamin D concentrations from patients in our CFS clinic and compare them to the optimum levels described above, to those of the general British population and to those of patients with other chronic diseases tested in routine practice during the same period at our hospital. We also investigated the relationship between 25-OH vitamin D levels and severity of CFS and myalgia obtainable from patient records. We hypothesized that 25-OH vitamin D levels would be lower than those of the general British population.

Subjects and Methods

Routine serum 25-OH vitamin D levels have been performed in our specialist CFS clinic for all patients since July 2005. We obtained these results from our laboratory database from July 2005 until July 2007. From case notes, we documented age, sex, duration of illness, and as far as possible, the approximate severity of fatigue and myalgia [using the Myalgic Encephalomyelitis Disability Score (MEDS) and Chalder Fatigue Scale], and the taking of supplements containing vitamin D, at the time of blood sampling. Our laboratory method is that after acetonitrile extraction from serum, 25-OH vitamin D is analyzed by a radioimmunoassay (Diasorin Ltd.) that detects the D2 and D3 forms equally.

For comparison, we also obtained 25-OH vitamin D levels from patients with a variety of chronic diseases (mostly rheumatological), which were taken routinely at our hospital over the same time period. For statistical comparison, we used a recently published large British population longitudinal survey of a cohort of 45-year-old women [4].

The chi-squared test was used to compare the CFS and General Population groups with respect to the proportions of people falling into four 25-OH vitamin D groups. For the CFS patients, univariate linear regression was used to investigate associations between 25-OH vitamin D levels and the continuous factors, age and severity of fatigue. The *t*-test was used to compare 25-OH vitamin D levels in CFS patients stratified according to sex, presence or absence of muscle pain, and whether receiving or not receiving vitamin D supplementation.

Results

A total of 324 patients had had 25-OH vitamin D levels checked, 221 with CFS and 103 with miscellaneous chronic conditions. Two hundred patients had no record of taking vitamin D at the time of sampling, and 21 were recorded as receiving supplementation. The sample was overwhelmingly Caucasian (95%), making analysis of the results by ethnic background not a useful exercise.

Table I illustrates demographic data and mean 25-OH vitamin D levels in patients with CFS and other chronic diseases. Since the groups are not from the same population they should not be compared statistically, but for both groups the mean serum 25-OH vitamin D level was very similar and significantly suboptimal [less than two thirds (50 nmol/L) of the optimal level]. Age and sex distribution was similar, although data regarding duration of illness in the chronic disease group was not collected.

For CFS patients, moderately suboptimal (<50 nmol/L) or severely suboptimal (<25 nmol/L) levels were present in 60.1% of CFS patients not receiving supplements. Only 6.8% of patients had optimal 25-OH vitamin D levels.

Figure 1 and Table II show the comparison between the CFS and population groups. From Figure 1, Winter/Spring (W/Sp) levels are lower than Summer/Autumn (Su/Aut) within both groups as expected, due to the reduction in daylight hours in W/Sp. Patients with CFS appear to have lower 25-OH vitamin D levels than the population sample both in Winter/Spring and Summer/Autumn. The relative deficiencies appear more marked in Summer/Autumn. Table II shows that the differences are statistically significant both in W/Sp and Su/Aut. These differences are largely driven by the lowest and highest groups for W/Sp and by the highest and second lowest groups for Su/Aut. In order to make the groups more comparable, the CFS group was restricted to women within 5 years of age 45 (40–50). The comparisons with the population group still attained statistical significance [n=26, p=0.04 for W/Sp, n=31, p=0.003 for Su/Aut].

We also used linear regression to investigate the univariable associations between 25-OH vitamin D level and various factors using the CFS group (Table III). The only factor of high significance is, as expected, vitamin D supplementation. However, it is of note that patients supplemented with vitamin D (typically 10–20 mcg/day or 400–800 IU/day) do not reach optimal levels, probably due to insufficient dosage (it has been documented that for every 100 IU of vitamin D ingested daily the blood level of 25(OH)D increases by 1 ng/mL [5]).

Table 1: Comparison of serum 25-OH vitamin D levels between CFS patients and those with other chronic diseases

	CFS group	Chronic disease
Number of patients	221	103
Mean age (years)	47	52
Mean duration of CFS (years)	13	
Sex ratio (F/M) (%)	84 : 16	86 : 14
Serum 25-OH vitamin D level		
Mean Median (range) (nmol/L)	44.4 43 (7–116)	45.5 43 (12–108)
>75 nmol/L (%)	6.8	11.6
51–75 nmol/L (%)	32.1	28.2
26–50 nmol/L (%)	41.2	39.8
0–25 nmol/L (%)	19.9	20.4

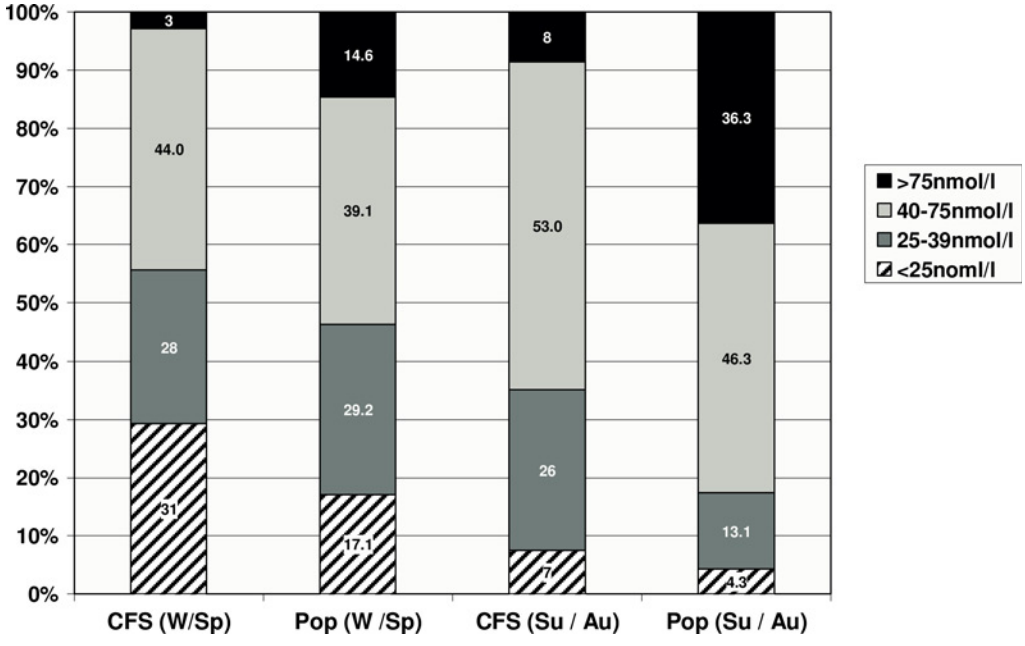

Figure 1: Serum 25-OH vitamin D levels in CFS patients not receiving supplements (n=200) compared to a 45-year-old white female British population sample ('Pop'). (W/Sp = Winter/Spring; Su/Au = Summer/Autumn)

Discussion

Interestingly, the comparison of our CFS group with a broadly similar population sample seems to demonstrate a more marked reduction in 25-OH vitamin D levels in Summer/Autumn than in Winter/Spring. This seems counterintuitive since levels are generally lower in Winter/Spring. One possible explanation is that patients with CFS do not obtain the extra sunlight exposure in summer/autumn because they remain indoors for a proportionally large amount of time.

Limitations include the retrospective nature of the study and the inevitable inaccuracies resulting from case note audit, such as incomplete retrieval of all notes requested and an incomplete data set. For myalgia in particular, we were only able to analyze one-third of the sample, and what audit data was available was retrieved from the first consultation, which may not have reflected the situation at the time of blood sampling, which in some cases was performed some years later. Similar problems applied to the MEDS score, which was only available for two-thirds of the sample. In addition, MEDS is only an

Table II: Comparison of proportions of patients with different ranges of serum 25-OH vitamin D (from Figure 1)

	Serum 25-OH vitamin D level (nmol/L)				
	<25	<40	<75	>=75	P-value*
CFS (W/Sp) n=106	31 (29.2 %)	28 (26.4 %)	44 (41.5 %)	3 (2.8 %)	<0.0004
Pop (W/Sp) n=1437	246 (17.1 %)	419 (29.2 %)	562 (39.1 %)	210 (14.6 %)	
CFS (Su/Aut) n=94	7 (7.4 %)	26 (27.7 %)	53 (56.4 %)	8 (8.5 %)	<0.0001
Pop (Su/Aut) n=2275	98 (4 .3 %)	298 (13.1 %)	1053 (46.3 %)	826 (36.3 %)	

* Chi^2-test

Table III: Regression coefficients from univariable analyses of serum 25-OH vitamin D level against age, sex, severity of fatigue (using MEDS), myalgia [using Chalder Fatigue myalgia subscale (0–6)], and vitamin D supplementation

Factor	Category / units	Number of observations	Regression coefficient (95 % CI)	P-value*
Age[1]	Years	200	0.217 (95 % CI: -0.007 to 0.440)	0.06
Severity of Fatigue[1] [n=142]	0 (no fatigue) – 100 (most severe)	142	0.177 (95 % CI: -0.036 to 0.389)	0.10
Sex[1]	Male	35	1	
	Female	165	2.3 (-4.7 – 9.3)	0.52
Muscle pain[1] [n=72]	High (>3/6)	45	1	
	Low (=<3/6)	27	6.3 (-3.1 – 15.6)	0.19
Vitamin D supplementation	Not supplemented	200	1	
	Supplemented (>10 mcg/day)	21	17.2 (8.4 – 26.0)	0.0002

[1] excluding any patient receiving vitamin D supplementation.
* Wald test

indirect measure of fatigue severity and may not accurately correlate with sun exposure. We were unable to accurately estimate dietary and supplemental vitamin D intake. Our CFS patients may not be comparable to those in other secondary care CFS services (for instance, many are on self-imposed exclusion diets), to patients presenting with newly diagnosed CFS, or to those remaining in primary care. Our comparison with the British population is only an approximation. Overall, our preliminary data must be interpreted with caution and can only be regarded as hypothesis-generating at this stage. Further work to verify our findings should include a case-control study.

This survey represents to our knowledge the first attempt to systematically quantify serum 25-OH vitamin D levels in CFS. In our sample of over 200 CFS patients, 25-OH vitamin D levels are moderately to severely suboptimal, and probably more so than the general British population, but probably no more so than other patients with other disabling chronic conditions of similar duration and severity. We could not demonstrate a strong relationship between serum 25-OH vitamin D levels and severity of myalgia or fatigue.

Blood testing for serum 25-OH vitamin D levels should be considered for all patients presenting with symptoms of CFS and supplementation considered for

those with suboptimal levels, with the aim of raising levels to >75 nmol/L.

In view of the risk of osteoporosis in this patient group, particular attention should be paid to vitamin D intake, as advised by NICE guidelines [6], in all patients with moderate to severe CFS. They should be advised to eat foods high in vitamin D (e.g., oily fish) and obtain adequate sun exposure.

Basic vitamin D supplementation should be in the form of a combined calcium and vitamin D supplement providing 20 mcg/800 IU cholecalciferol (vitamin D3) per day. In our experience, higher doses are often required to achieve optimal levels in CFS, using extra vitamin D capsules (usually containing 10 mcg/400 IU cholecalciferol). Vitamin D injections (100,000 units every 4 months) may be considered for those with severely suboptimal levels or those whose levels do not improve on repeat testing.

Interest in the multiple effects of vitamin D has increased recently. In addition to its beneficial effects on bone strength, vitamin D is immunomodulatory [7], may help prevent upper respiratory tract infections [8], and has been shown to improve muscle strength and reduce falls in the elderly [9]. It is possible that vitamin D may have clinical benefits for CFS sufferers. We are currently collecting prospective observational data regarding the effects of vitamin D supplementation on fatigue, myalgia, and muscle strength in CFS, with a view to a pilot randomized, controlled intervention trial.

Non-standard abbreviations

25-OH:	25-hydroxy-
CDC:	Centers for Disease Control and Prevention
CFS:	Chronic Fatigue Syndrome
MEDS:	Myalgic Encephalomyelitis Disability Score
NICE:	National Institute of Clinical Excellence
Su/Aut:	Summer/Autumn
W/Sp:	Winter/Spring

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Conflict of interests

None

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