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Effects of vitamin D on patients with fibromyalgia syndrome: A randomized placebo-controlled trial

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ABSTRACT

The role of calcifediol in the perception of chronic pain is a widely discussed subject. Low serum levels of calcifediol are especially common in patients with severe pain and fibromyalgia syndrome (FMS). We lack evidence of the role of vitamin D supplementation in these patients. To our knowledge, no randomized controlled trial has been published on the subject. Thirty women with FMS according to the 1990 and 2010 American College of Rheumatology criteria, with serum calcifediol levels <32 ng/mL (80 nmol/L), were randomized to treatment group (TG) or control group (CG). The goal was to achieve serum calcifediol levels between 32 and 48 ng/mL for 20 weeks via oral supplementation with cholecalciferol. The CG received placebo medication. Re-evaluation was performed in both groups after a further 24 weeks without cholecalciferol supplementation. The main hypothesis was that high levels of serum calcifediol should result in a reduction of pain (visual analog scale score). Additional variables were evaluated using the Short Form Health Survey 36, the Hospital Anxiety and Depression Scale, the Fibromyalgia Impact Questionnaire, and the Somatization subscale of Symptom Checklist-90-Revised. A marked reduction in pain was noted over the treatment period in TG: a 2 (groups) × 4 (time points) variance analysis showed a significant group effect in visual analog scale scores. This also was correlated with scores on the physical role functioning scale of the Short Form Health Survey 36. Optimization of calcifediol levels in FMS had a positive effect on the perception of pain. This economical therapy with a low side effect profile may well be considered in patients with FMS. However, further studies with larger patient numbers are needed to prove the hypothesis.

1. Introduction

Individuals suffering from fibromyalgia syndrome (FMS) experience chronic extensive pain, as well as other comorbidities such as fatigue, sleep disorders, morning stiffness, poor concentration, and occasionally mild to severe mental symptoms such as anxiety and/or depressive disorders [9]. In many cases these conditions impair the patient's quality of life to a significant extent, culminating in loss of employment and/or withdrawal from social life. The condition cannot be cured in many patients, but the symptoms can be alleviated by various means, such as physical therapy, cognitive behavioral therapy, temporary drug therapy (mainly co-analgesic drugs such as amitriptyline, duloxetine, or pregabalin), and multimodal therapy approaches [8,16,20,25].

The role of vitamin D and the pathophysiology of FMS are diversely reported in the published literature. Recent case control studies report no difference in serum vitamin D levels (serum calcifediol levels) of healthy persons and patients with FMS [7,22], but a community-based study [18] and a case control study [14] reported an association between chronic widespread pain and low serum calcifediol levels. Aside from pain, the level of calcifediol may influence FMS-related symptoms such as anxiety or depression [2]. In a cohort study comprising 30 FMS patients with deficient levels of serum calcifediol, substitution of vitamin D led to clinical improvement of the symptoms [17]. In a further cohort study, 42 of 61 treated women with FMS and a vitamin D deficiency demonstrated improvement at a serum calcifediol level ⩾30 ng/mL [1]. To our knowledge, there is no randomized controlled trial on the subject.

Another randomized controlled trial revealed no significant effects of cholecalciferol (vitamin D2) in respect to the perception of pain in 50 patients suffering from widespread musculoskeletal

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pain and vitamin D deficiency, who received supplements of 50,000 IU per week over a period of 3 months. However, the authors of the study did not explicitly exclude patients with additional degenerative changes in the spine.

The aims of the present study were to establish the role of vitamin D in patients with FMS, and to determine whether serum calcifediol levels within the normal range could improve symptoms, particularly reduce pain, in patients with initially low calcifediol levels (vitamin D deficiency). We wished to determine whether elevated calcifediol levels in these patients would alleviate pain and cause a general improvement in concomitant disorders. The impact of vitamin D substitution on health-related quality of life as well as accompanying functional and vegetative symptoms were evaluated, especially with regard to depression, anxiety, concentration, somatization, and bowel function. Oral substitution of vitamin D might prove to be an extremely cost-effective alternative or adjunct to expensive pharmacological treatment, as well as physical, behavioral, and multimodal therapies. In accordance with Heaney [13], the optimum calcifediol level in our study was assumed to be 80 to 120 nmol/L, which equals 32 to 48 ng/mL.

2. Materials and methods

Subjects were recruited from the general Austrian population via newspaper advertisements, the outpatient and inpatient pain departments of the Orthopedic Hospital Speising, and local FMS support groups. Twenty-seven women and 3 men who fulfilled the 1990 [27] as well as the 2010 [26] American College of Rheumatology criteria for FMS, with serum calcifediol levels below 80 nmol/L (32 ng/mL), were included in the study. Test persons with notable degenerative changes in the spine, such as spondylolisthesis (Meyerding II or more) or herniated vertebral disks with a motor deficit, as well as those who had undergone spinal surgery or traumatic injury (eg, fracture of a vertebral body), or who had rheumatic diseases, infection, or cancer, were excluded. The following people also were excluded from the study: patients in the process of retirement because of FMS; those intending to undergo surgery during the period of intervention; patients who were unable to participate in the intervention program for physical or mental reasons or due to language difficulties; patients with clinically significant cardiovascular, renal, hepatic, gastrointestinal, or non-FMS–associated psychiatric disorders; or subjects with clinically significant hypocalcemia or hypercalcemia. Moreover, patients with cholelithiasis or nephrolithiasis, pulmonary tuberculosis, or severe arteriosclerosis in their medical history, or patients on cardiac glycosides, as well as pregnant or breastfeeding women, were excluded. In women of reproductive age, pregnancy was ruled out by performing monthly pregnancy tests (human chorionic gonadotropin in urine). According to the informed consent form, patients committed themselves to use adequate contraception for the entire duration of the trial. This provision did not apply to women who had had no menstruation for at least 1 year or had undergone surgical sterilization. The study was approved by the local ethics committee.

Random sampling was performed in a double-blinded manner by our statistician, who was not involved in the treatment or testing of patients. The STATISTICA 7 software (uniform random number generator) was used. The screening examination was performed at time point V1 by 1 of 3 doctors in charge of treatment. After 1 week (V2), suitable test persons with a serum calcifediol level <80 nmol/L (32 ng/mL) were randomized to a verum or a placebo group. Depending on their serum calcifediol levels, the verum group received 2400 IU (serum calcifediol levels <60 nmol/L) or 1200 IU (serum calcifediol levels 60 to 80 nmol/L) of cholecalciferol (vitamin D3) daily, dissolved in a triglyceride solution. The placebo group received the triglyceride solution without cholecalciferol. Persons with higher vitamin D levels (serum calcifediol levels >80 nmol/L) at V2 were excluded from the trial.

Serum calcifediol levels were re-evaluated at week 5 (V3) and week 13 (V4) to adapt the dose of cholecalciferol. The adapted dose was communicated to the patients by telephone after their laboratory data had been obtained. To ensure the double-blind nature of the trial, the doctors in charge of treatment were unaware of the patients' serum calcifediol levels and other laboratory data. These were inspected by another physician who was not in charge of treatment. The doctors in charge of treatment were then informed by the statistician about required changes in the patients' cholecalciferol dose. After each modification of treatment in a member of the verum group, a member of the CG received a change in placebo treatment as well. When serum calcifediol levels reached >120 nmol/L, the substitution was put on hold for safety reasons. The aim was to keep calcifediol levels between 80 and 120 nmol/L for the duration of the trial. A further examination was scheduled for week 25 (V5), at which vitamin D or placebo was stopped and several parameters were controlled. Finally a follow-up examination (V6) was performed at week 49 (Table 1). At the start of the trial, patients were given a telephone number at which they could contact a competent person and report adverse events. Patients were asked about potentially unreported adverse events at every visit.

The main hypothesis was tested using a visual analog scale (VAS; 0 to 100; lower scores indicated less pain) to determine the severity of pain during the preceding 7 days (VAS7). The time point for the primary outcome was week 13 (V4) and the change of the VAS over time. Additional parameters were as follows:

- Health-related quality of life was evaluated using the Short Form Health Survey 36 [5] (SF-36; scales 0 to 100, lower scores indicate poorer social, psychological, and emotional quality of life).
- Anxiety and depression were evaluated on the Hospital Anxiety and Depression Scale–local version [15] (score 0 to 21 for either anxiety and depression, higher scores indicate greater limitation relating to anxiety or depression). A score between 8 and 11 of 21 points on 1 scale denotes a potential for an anxiety or depressive disorder. When the score exceeds 11 of 21 points, an anxiety or depressive disorder is very likely to be present [4].
- Disease-related impairment was evaluated on the Fibromyalgia Impact Questionnaire [6] (FIQ; score: 0 to 80, the higher the score, the greater the impact of FMS on the person's quality of life). FIQ is used to monitor the progress of FMS. Individual questions such as "How do you feel when you get up in the morning?" are scored on a visual analog scale (0 to 10, higher score indicates greater limitation).
- Somatization was evaluated on the somatization subscale of the checklist for symptoms by Derogatis [10] (Symptom Checklist-90-Revised). Headache, fainting sensation, vertigo, heart and chest pain, back pain, nausea, indigestion, muscle pain, breathing difficulties, hot flushes, cold chills, hypesthesia or dysesthesia in various parts of the body, globus sensation, sensation of weakness in various parts of the body, and a feeling of heaviness in the arms or legs were evaluated. Symptom Checklist-90-Revised is a useful instrument to measure a patient's progress or the outcome of treatment.
- Sociodemographic data, medication (especially pain medication), and smoking behavior were evaluated at V2. Changes in concomitant medication were assessed at every visit.

2.1. Statistical analysis

Descriptive statistics were used to summarize basic data. Percentages were computed for categorical variables. Depending on

Table 1
Time points and examinations.

	Week 0	Week 1	Week 5	Week 13	Week 25	Week 49
Medical history	x					
Physical examination	x					
Medical checkup			x	x	x	
Blood pressure, pulse, weight	x		x	x	x	
Human chorionic gonadotropin testing in women of reproductive age	x		x	x	x	x
Randomization		x				
Receiving medication		x	x	x		
Adaptation of dose			x		x	
Full blood count, glutamic oxaloacetic transaminase, glutamate-pyruvate transaminase, Gamma-glutamyltransferase, bilirubin, alkaline phosphatase, blood urea nitrogen, creatinine, Na, K, Ca, phosphate	x		x	x	x	
25-Hydroxycholecalciferol	x		x	x	x	x
Health-related quality of life (Short Form Health Survey 36)		x			x	x
Somatization subscale of the Symptom Checklist-90-Revised		x		x	x	x
Depression/anxiety (Hospital Anxiety and Depression Scale–Depression)		x		x	x	x
Disease-related impairment (Fibromyalgia Impact Questionnaire)		x	x	x	x	x
Bowel function		x	x		x	x
Socioeconomic factors		x				
Smoking		x				
Intensity of pain (visual analogue scale-past 7 days)		x	x	x	x	x
Updating of medical history						x

the scaling of variables, we calculated means and standard deviations or medians and ranges. To test whether the study groups were comparable with respect to basic variables, we computed χ^2 tests for categorical variables and Mann-Whitney U tests for continuous variables. Repeated-measures analyses of variance were applied to the main outcome factors, ie, the intensity of pain, health-related quality of life (SF-36), depression and anxiety (Hospital Anxiety and Depression Scale), severity of fibromyalgia symptoms (FIQ), and somatization (subscale of the Symptom Checklist-90-Revised). The assumptions for these tests are normal distribution of independent variables and equal variances among the groups of independent variables. Normal distribution was checked visually by the inspection of histograms. The validity of the assumption of equity of variances was established by performing Levene tests. The level of significance was set at $P \geq .05$.

3. Results

The study was composed of 42 patients, of whom 12 (3 in the CG and 9 in the TG) were dropouts. Patients were not required to state reasons for terminating their participation. Finally, 30 patients remained in the study, of whom 15 (50%) belonged to the TG and 15 (50%) belonged to the CG. Subjects were randomized in a computer-assisted manner. The fact that both groups contained the same number of active participants was a coincidence. The small sample size was due to the preliminary character of the study, which was performed to report the initial promising results of an ongoing investigation comprising a larger patient population.

Ninety percent of our patients (n = 27) were women. The mean age of the patients was 48.37 years (±5.301; minimum 35, maximum 55). At the time of inclusion in the study, the TG and CG did not differ significantly with respect to age, gender, mother tongue, training, profession, and body mass index (normal weight 40%, overweight persons 33.3%, obesity grade I 23.3%, obesity grade II 3.3%).

One of the inclusion criteria was the number of pressure-sensitive tender points on the body, which was required to exceed 10. In all, we investigated 18 defined tender points. The entire group had an arithmetic mean of 14.47 (±1.980; minimum 11, maximum 18) tender points. TG had a mean of 14.93 points (±1.981; minimum 12, maximum 18), whereas CG had a mean of 14.00 (±1.927; minimum 11, maximum 18). The 2 groups did not differ significantly ($P = .202$).

3.1. Month of inclusion

The time of the year was significantly correlated with variations in serum calcifediol levels. Nearly the entire random sample was recruited in the winter (Fig. 1).

3.2. Calcifediol

At V1, serum calcifediol levels were below 24 ng/mL in 70% (n = 21) and between 24 and 32 ng/mL in 30% (n = 9). In terms of arithmetic means, the baseline value was 19.95 (±6.07) ng/mL, and the median value 20.83 ng/mL (minimum 8.5, maximum 29.00). The 2 study groups did not differ significantly ($P = .401$) with regard to baseline serum calcifediol levels. Changes in serum calcifediol levels are shown in Table 2 and Fig. 2. Initially, serum calcifediol levels were slightly increased in the CG as well. As a result, serum levels in both groups were quite similar between week 13 and week 25, but still were significantly different in statistical terms at all of these time points. After discontinuation of the medication at the final follow-up (V6, week 49), calcifediol levels were nearly identical.

After week 13, a total of 7 members (47%) of the TG had serum calcifediol levels >48 ng/mL (>120 nmol/L), which necessitated discontinuation of the medication in accordance with the protocol. The mean serum level in these patients was 69.17 ng/mL (SD: 13.768; minimum 55, maximum 93.29); at week 25 it was still 47.81 ng/mL (SD: 13.756, minimum 28, maximum 71.50). In the CG, 26.7% (n = 5) of subjects had serum calcifediol levels >32 ng/mL at week 13. Four of them were recruited for the study in March, and 1 in January. Two members of the TG did not achieve serum calcifediol levels >32 ng/mL at week 13. Baseline values of these patients were 16.78 ng/mL (42 nmol/L) and 13.16 ng/mL (33 nmol/L), respectively. At V5 (week 25), both had serum levels within or even above the target range (38.7 ng/mL and 48.50 ng/mL).

3.3. Intensity of pain—VAS

The mean initial VAS score of all participants was 65.2 (±17.3), whereas the median VAS score was 70 (minimum 34, maximum 100). The TG experienced a consistent reduction of pain, ie, an improvement in the VAS score, whereas VAS scores remained more or less constant in the CG. Both groups experienced increases in VAS scores (Table 3, Fig. 3) at week 25 (V5).

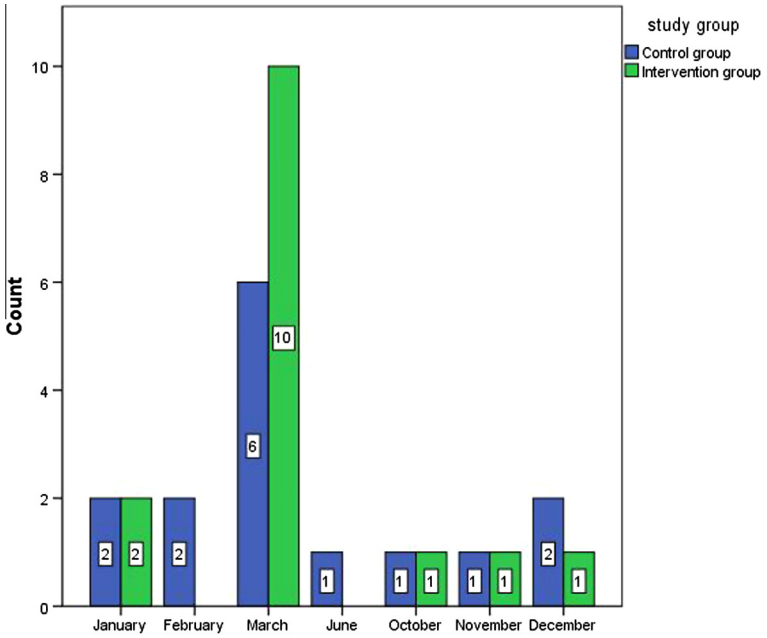

Fig. 1. Number of persons and time of inclusion.

Table 2
Calcifediol levels (ng/mL) at time points 1 to 5.

	Group	Mean	SD	N
Week 1 (time point 1)	CG	20.89	6.274	15
	TG	19.00	5.908	15
	Total	19.94	6.066	30
Week 5 (time point 2)	CG	22.80	8.773	15
	TG	32.31	6.747	15
	Total	27.56	9.083	30
Week 13 (time point 3)	CG	28.21	12.370	15
	TG	50.96	20.634	15
	Total	39.59	20.327	30
Week 25 (time point 4)	CG	33.99	12.370	15
	TG	48.86	11.048	15
	Total	41.42	13.783	30
Week 49 (time point 5)	CG	26.31	11.725	15
	TG	26.34	6.934	15
	Total	26.32	9.464	30

CG = control group; TG = treatment group.

A 2 (groups) × 4 (time points) variance analysis revealed a significant ($P = .025$) group effect, ie, an actual treatment effect. The follow-up time point was not included in the calculation. Values for the 2 groups were again similar at this time point and did not differ significantly ($P = .999$). There were no statistically significant correlations between changes in serum calcifediol levels and VAS within groups, but as mentioned earlier, the number of subjects was rather low (n = 15 per group).

3.4. Changes in somatization

The 2 groups did not differ significantly ($P = .413$) with respect to somatization (Symptom Checklist-90-Revised). No major changes were observed over time ($P = .139$).

3.5. Depression and anxiety

At the time of inclusion in the study, a large percentage of patients were in somewhat poor clinical condition. With regard to an anxiety disorder, no significant differences were noted between groups ($P = .343$) or over time ($P = .929$). Also with regard to depression, no statistically significant difference was observed in terms of progression over time ($P = .501$), or a potential difference between groups ($P = .641$).

3.6. SF-36

The SF-36 scores showed no statistically significant time ($P = .231$) or group ($P = .812$) effect with respect to the physical health summary. The mental health summary also revealed no significant time ($P = .783$) or group ($P = .363$) effect. However, a group-specific significance was noted ($P = .022$) on the physical role functioning scale, a subscale of SF-36. From week 1 to the week 25, the TG improved significantly ($P = .014$), whereas the placebo group remained unchanged ($P = .480$) (calculated for raw data levels, nonparametric). For the remaining 7 subscales, no significant differences were noted over time or between groups.

3.7. FIQ

FIQ scores (Table 4) varied significantly for both groups, but no group-specific effects were observed ($P = .615$). In general, a slight improvement in total scores was noted in both groups ($P = .020$). Regarding the question of morning fatigue, a significantly better outcome was observed in the TG ($P = .007$), which showed the greatest group differences in serum calcifediol levels at time point 3 (Fig. 4).

3.8. Adverse events

One person in the TG had mild hypercalcemia (2.71 mmol/L) and a serum calcifediol level of 63.6 ng/mL at V3. The study medication was interrupted, and the patient's serum calcium levels returned immediately to the normal range. Apart from that, we found only transient adverse events, none of which were directly related to the study medication, and all of which resolved without any change in the study medication. We observed once-only occurrences of flu-like syndrome, diarrhea, laryngitis, and sciatic pain in the TG.

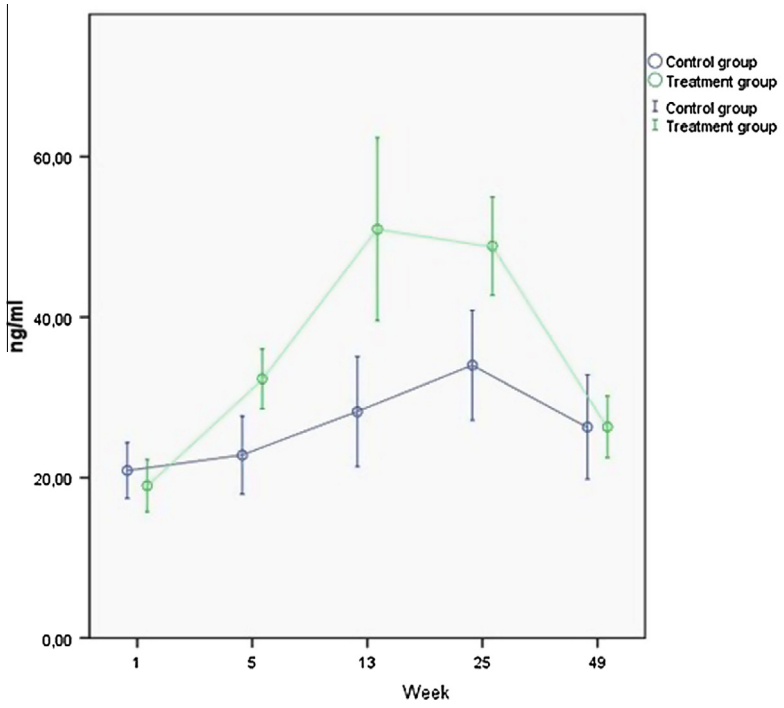

Fig. 2. Mean serum calcifediol levels over time, including error bars with standard deviation. Time points have been shifted to clarify the results (control group to the left, treatment group to the right).

Table 3
VAS7 at time points 1 to 5.

	Group	VAS7 mean	SD	N
Week 1 (time point 1)	CG	62.0	20.275	15
	IG	68.7	12.531	15
	Total	65.0	17.312	30
Week 5 (time point 2)	CG	71.8	22.720	15
	IG	57.6	13.056	15
	Total	65.6	20.050	30
Week 13 (time point 3)	CG	61.1	26.259	15
	IG	50.6	25.005	15
	Total	56.5	25.736	30
Week 25 (time point 4)	CG	64.5	16.142	15
	IG	53.4	29.313	15
	Total	59.6	23.043	30
Week 49 (time point 5)	CG	55.2	20.487	15
	IG	55.2	21.792	15
	Total	55.2	21.140	30

VAS7 = xxx; CG = xxx; IG = xxx.

4. Discussion

As shown in Fig. 2, calcifediol levels increased in the entire study population, a fact associated with the previously mentioned time point of recruitment. As a large percentage of the study participants were recruited in the winter or early spring, the active study period for most participants was the summer. Therefore, the CG treated with placebo had a mild increase in serum calcifediol levels during the study period. The reduction of mean scores on VAS (time frame of 7 days) in the TG is quite remarkable. Despite the small number of participants in each group (a mere 15), a statistically significant difference was noted from time point 1 to time point 4. The outcome on the physical role functioning scale of SF-36 also was correlated with VAS because this variable expresses the extent to which a person experiences limitations due to physical symptoms at work and in other activities.

The lowest values on VAS were noted at week 13, when the TG also had a markedly reduced score with regard to morning fatigue on FIQ (Fig. 4). The highest serum calcifediol levels also were noted at this time, ie, 3 months after inclusion in the study. On average we registered serum calcifediol values slightly above 50 ng/mL (125 nmol/L) in the TG. The study medication had to be temporarily discontinued in some probands because our study design did not permit serum calcifediol levels beyond 48 ng/mL (120 nmol/L) for safety reasons.

The relatively low mean reduction of 20 points on VAS (on a scale from 0 to 100) may have been due to the low maximum levels of calcifediol we had selected. Therefore, further studies comprising larger patient numbers and studies focused on the determination of optimal serum levels should be performed in the future.

It is interesting to compare our data with those reported by Warner and Arnspiger [24]. The authors used a different dosing regimen of vitamin D in patients with diffuse musculoskeletal pain, consisting of 50,000 IU per week given orally, without adjusting the vitamin D treatment to serum calcifediol levels. The duration of treatment was only 3 months. This resulted in a lower mean serum calcifediol level of 31.2 ± 6.2 ng/mL in the TG at the end of the treatment period. The authors concluded that treatment with vitamin D does not reduce pain in patients with diffuse pain and low vitamin D levels.

Threshold values of calcifediol levels in serum are widely discussed at the present time, especially with reference to bone metabolism. The problem of a rather low optimal calcifediol value is also a historical one: an evident vitamin D deficiency has been associated with specific diseases, as is true for many other vitamins as well. In the case of vitamin D, these diseases are rickets and osteomalacia. Therefore, until now recommendations for medication-based substitution were mainly focused on the efficacy of the substances with respect to these diseases. Serum calcifediol levels were deemed sufficient when (1) sufficient intestinal absorption of calcium could be stimulated, (2) the individual had normal parathyroid activity, and (3) no osteoporotic fractures occurred. This can be ensured from a rather low serum calcifediol level of about 32 ng/mL (80 nmol/L) onward [13]. In a randomized

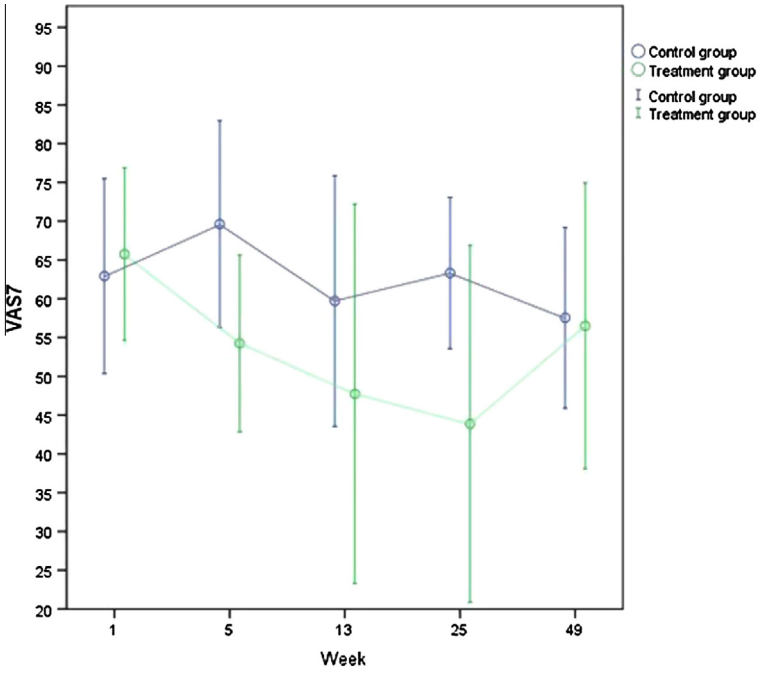

Fig. 3. Mean score of the severity of pain during the preceding 7 days using a visual analog scale (VAS7), including error bars with standard deviation. Time points have been shifted to clarify the results (control group to the left, treatment group to the right).

Table 4
FIQ score.

Group			FIQ score, week 1	FIQ score, week 5	FIQ score, week 13	FIQ score, week 25	FIQ score, week 49
CG	N	Valid	14	13	15	15	15
		Missing	1	2	0	0	0
	Mean		42.261	52.032	49.020	48.076	43.500
	Median		43.400	52.560	49.140	47.070	45.000
	Minimum		17.10	30.60	29.00	22.00	0.80
	Maximum		68.76	68.49	69.48	68.85	66.60
	SD		17.331	12.942	13.282	11.631	16.298
TG	N	Valid	14	12	13	14	14
		Missing	0	2	1	0	0
	Mean		43.437	48.272	40.977	44.207	35.790
	Median		45.750	46.994	42.111	45.123	38.244
	Minimum		26.00	27.10	14.04	12.00	0.98
	Maximum		62.70	67.86	69.48	65.79	61.70
	SD		11.715	10.305	17.911	16.143	21.461

FIQ = Fibromyalgia Impact Questionnaire; CG = control group; TG = tratment group.

placebo-controlled study conducted in Britain for a period of 5 years, increasing serum calcifediol levels from 21 to 30 ng/mL (53 to 74 nmol/L) was found to reduce osteoporotic fractures by 33%.

However, analysis of the Third National Health and Nutrition Examination Survey data has shown that optimal quantities in excess of 40 ng/mL (100 nmol/L) must be achieved in order to increase bone density [3]. This level also was recommended in a review conducted by Haroon et al. [12] in 2010. Ideal values are possibly even higher because these measurements are primarily based on bone metabolism. Currently, levels of 40 to 60 ng/mL (100 to 150 nmol/L) are recommended for the prevention of colorectal cancer or breast cancer [11].

The Institute of Medicine (United States) recommends for healthy persons a daily oral cholecalciferol intake of 400 IU (estimated average requirement) or 600 mg (recommended dietary allowance) to a permitted maximal daily dose of 4000 IU [19]. Hypercalcemia occurs no earlier than serum calcifediol levels beyond 142 ng/mL (355 nmol/L). Other toxic effects are very unlikely below this dose. In cases of maximal exposure to sunlight, 10,000 IU of cholecalciferol can be synthesized by the skin daily [23]. Thus the intake of 3000 to 4000 IU per day, which would result in correspondingly higher serum calcifediol levels and should be monitored by means of regular laboratory controls as recommended by Souberbielle et al. [21], would pose a calculable low risk to the patients.

The absence of changes in the remaining parameters investigated in our study may have been due to the small number of probands. However, the absence of an improvement in anxiety and depression, somatization, and the total scores of SF-36 also indicate that FMS constitutes a very extensive symptom complex that cannot be explained by a vitamin D deficiency alone. Prolonged intake of cholecalciferol over a longer period of time might reduce pain and improve these parameters as well.

A major limitation of the present study is, aside from the small number of participants, the highly selected patient population. In contrast to the study by Warner und Arnspiger [24], we only assessed patients with FMS and no signs of remarkable degenera-

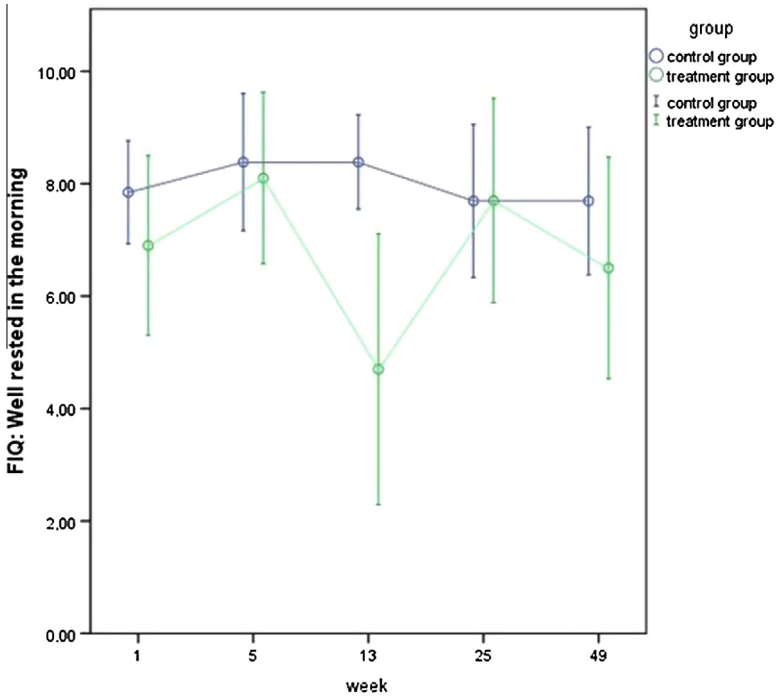

Fig. 4. Mean FIQ–Morning fatigue, including error bars with standard deviation. Time points have been shifted to clarify the results (control group to the left, treatment group to the right). FIQ = Fibromyalgia Impact Questionnaire.

tive changes of the spine. Hence, our results cannot be extrapolated to patients with chronic pain.

We believe that the data presented in the present study are promising. In addition to known therapies, oral substitution of vitamin D may be regarded as a relatively safe and economical treatment for patients with FMS. Vitamin D levels should be monitored regularly in these patients, especially in the winter season, and increased appropriately.

Conflict of interest statement

The authors declare no conflict of interest.

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