Determinants and effects of vitamin D supplementation on serum 25-Hydroxy-vitamin D levels in patients with rheumatoid arthritis

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Abstract

Objective

Osteoporosis (OP) and increased risk of fracture are relevant features in patients with rheumatoid arthritis (RA). Low levels of serum vitamin D are frequently reported and correlate with a higher RA activity. This study evaluated factors related with the prescription of vitamin D supplements in RA patients and variables influencing the achievement of adequate vitamin D levels.

Methods

Study population was made up by 1168 consecutive RA patients from 22 Italian rheumatology centers. Demographic and clinical variables data were collected and 25OH serum vitamin D was measured in all patients. Insufficient serum 25OH vitamin D levels were defined as values lower than 20 ng/mL.

Results

The majority of patients (56.0%) was not taking vitamin D supplements. Among the 514 supplemented patients, 196 (38.1%) were taking insufficient dosages (≤440 IU/day). Variables related with the prescription of supplements were older age, female sex, previous bone density assessment and OP diagnosis. Among the 318 patients using daily supplements ≥800 IU, 88 patients (27.7%) did not reach adequate levels of vitamin D. In these patients a higher HAQ score (OR for 1 point=1.62, 95% CI: 1.06–2.49; p=0.03) and poor sun exposure (OR=2.38, 95% CI: 1.05–5.55; p=0.04) were predictors of vitamin D insufficiency.

Conclusion

Vitamin D deficiency is common in patients with RA, even in patients who are regularly using supplements. Vitamin D supplementation is often ineffective even at the recommended dose of 800 IU/day in more disabled patients.

Key words

drug therapy, epidemiology, osteoporosis, rheumatoid arthritis, vitamin D

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Introduction

Osteoporosis (OP) and fragility fractures are well-recognised complications of rheumatoid arthritis (RA). Register-based prevalence data have shown a two-fold increase in OP prevalence in pre- and postmenopausal women and in men with RA (1, 2). These results are consistent with a two-fold increase in the risk of fractures in subjects with RA compared to age and sex-matched controls (3). Based on these data and the prevalence of the disease across general population, RA is one of the items of the FRAX® to estimate the 10-year risk of fracture regardless of corticosteroid use and other forms of secondary OP (4).

Vitamin D supplementation is considered a cornerstone for the management of OP in patients with RA for several reasons. Low vitamin D levels are highly prevalent in these subjects (5, 6), with vitamin D deficiency reported in more than half of patients (7). In addition, an increased disease activity has been related to lower levels of serum vitamin D metabolites in patients with early RA (7, 8). In patients with active RA, vitamin D levels were reported to be inversely associated with disease activity (DAS28) and disability (HAQ score) (9). This finding seems to be even more relevant in patients treated with anti-osteoporotic drugs, since subjects with serum 25OHD lower than 20 ng/ml have shown severely hampered therapeutic response both in terms of mineral density changes and anti-fracture efficacy (10).

In order to implement appropriate educational programs it is important to understand the attitude of rheumatologists in administering vitamin D to RA patients and whether prescribed doses are adequate. In this paper we report the results of a large survey coordinated by the Italian Society of Rheumatology (SIR) among Italian rheumatologists.

Materials and methods

From June 2007 to May 2008, 1191 consecutive patients (1014 women and 177 men) were recruited at 22 rheumatology centres uniformly distributed across Italy to participate to a cross-sectional survey on RA. Patients who were seen for a follow up visit, fulfilling the 1987 revised criteria for RA and aged between 30 and 75 years were considered eligible for the study. The exclusion criteria were presence of insulin-dependent diabetes and severe hepatic or renal impairment, as in these patients vitamin D prescription habits might be also influenced by other kinds of specialist physicians. Patients who reported gastrointestinal diseases or previous gastrectomy were excluded as well for possible malabsorption. All subjects were outpatients; they were neither bedridden, nor even home-confined. Patients were interviewed and examined at each clinical centre to collect data about their disease and treatment.

Clinical evaluation

Disease related variables included age at disease onset, number of swollen joints (28 joints), and the Health Assessment Questionnaire Disability Index (HAQ) (11). Subjects were asked about disease-modifying anti-rheumatic drugs (DMARDs) and glucorticoid use as well as about use of other medications. Vitamin D supplements taken during the previous year were carefully evaluated and expressed as mean daily dose. At the time of recruitment, patients were assessed by ever having undergone bone measurement and the results of such testing. Hologic (17 centres) and Lunar (2 centres) instruments were used for DXA evaluations of Bone Mineral Density (BMD) at the lumbar spine and/or femoral neck in 449 patients. A further group of 25 patients was evaluated by calcaneal quantitative ultrasound (Achilles, GE-Lunar). OP was defined as a BMD or a calcaneal stiffness index value more than 2.5 SD below the T-score. To evaluate sun exposure we used a previously validated questionnaire (12). This variable was dichotomised according to those subjects who used to avoid sun exposure (less than 10 m/day) versus those subjects with a longer sun exposure. ACR criteria were used to classify a patient as in remission (13). Finally, information was recorded about menopausal status and patients' current smoking habits.

Measures

At the time of the inclusion in the study height and weight were measured to calculate body mass index (BMI= kg/m^2). C-reactive protein (CRP), rheumatoid factor (RF) and routine biochemistry measurements were performed locally. Individual aliquots of serum samples were collected from each patient and sent on dry ice by courier to the laboratory of the University of Verona and kept at -70° until measurement of 25OHD performed by commercial ELISA kit (IDS Co. Bolden, UK) with inter-assay coefficient of variation ranging from 5 to 15%. The volume of the serum sample from 23 patients was inadequate for the measurement with the auto-analyzer. As pooled serum samples showed expected seasonal variations, 25OHD values were adjusted for seasonal sampling time by ANCOVA based on definition of winter (December-February), spring (March-May), summer (June-August) and autumn (September-November). According to the recently defined threshold for an adequate serum level of vitamin D, insufficient serum 25OHD levels were defined as values below 20 ng/mL (14). The study was approved by local Ethical Committees and informed written consent was obtained from all participants.

Statistical analysis

The first step was to compare patients taking vitamin D with patients who were not using supplements. Among patients taking ≥800 IU/day (800-880 IU/day) of vitamin D a further analysis was performed to compare patients with 25OHD insufficiency to patients showing serum 25OHD values higher than 20 ng/mL. Comparisons were performed using Student's *t*-test for continuous variables and the chi-square test for categorical variables.

The role of recorded variables on the odds of being supplemented was assessed by multivariable stepwise logistic analysis. All variables which showed significant differences (p<0.05) in the univariate analysis were included in the multivariate analysis. In a second model, the "previous bone measurement" variable was replaced by the "previous OP diagnosis" variable. In the subgroup of patients taking ≥800 IU/day of vitamin D a stepwise logistic analysis was performed to assess whether any registered variables were predictive of serum 25OHD values lower than 20 ng/mL. In this model, variables that met the significance threshold (p<0.05) in the univariate analysis, such as HAQ and avoiding sun exposure were entered. Other variables not showing a significant difference but deemed of clinical relevance as possible determinants of serum 25OHD were entered into the model, with backwards stepwise elimination until all remaining variables showed a statistical significance (p<0.05). These variables were age, sex, disease duration, number of swollen joints, CRP, BMI, corticosteroid treatment and disease remission. All statistical tests were 2-sided at the 5% level and performed using SPSS Software (version 17.0; Inc, Chicago, USA).

Table I. Demographic and clinical characteristics of 1168 patients with rheumatoid arthritis: total study population and subsamples for vitamin D supplementation. Values are expressed as mean ± SD or number (percentage).

	All Patients (n=1168)	Non-supplemented (n=654)	Supplemented (n=514)	*p*-value*
Age (years)	58.9 ± 11.1	56.4 ± 11.4	62.1 ± 9.9	<0.001
Female sex (%)	994 (85.1)	522 (79.8)	472 (91.8)	<0.001
BMI (kg/m^2)	25.2 ± 4.4	25.4 ± 4.4	24.7 ± 4.4	0.007
Tobacco use (%)	243 (20.8)	137 (20.9)	106 (20.6)	0.9
Avoiding sun exposure (%)	319 (27.3)	160 (24.5)	159 (30.9)	0.01
RA measures:				
Disease duration (months)	138 ± 104	129 ± 104	150 ± 103	0.004
Swollen joints count (n)	2.95 ± 4.8	3.23 ± 5.17	2.55 ± 4.24	0.01
RF positive (%)	739 (63.3)	446 (68.2)	293 (57.0)	<0.001
CRP (mg/dl)	2.6 ± 5.6	3.1 ± 6.9	1.9 ± 3.2	<0.001
HAQ (score)	1.13 ± 0.84	1.06 ± 0.82	1.22 ± 0.86	0.002
Disease remission (%)	267 (22.9)	141 (21.6)	126 (24.5)	0.2
Medication:				
DMARDs (%)	1030 (88.2)	567 (86.7)	463 (90.1)	0.09
Biologics (%)	543 (45.5)	297 (45.4)	246 (47.8)	0.4
Corticosteroids (%)	1010 (86.5)	539 (82.4)	471 (91.6)	<0.001
OP measures:				
Bone measurement (%)	474 (40.6)	220 (33.6)	254 (50.0)	<0.001
OP diagnosis (%)	170 (37.9)	61 (27.7)	109 (47.6)	<0.001
Vit. D insufficiency (%)	504 (43.1)	339 (51.8)	151 (29.4)	<0.001

*Comparison between non-supplemented and supplemented patients.

Results

Study population characteristics are reported in Table I. From the original cohort of 1191 patients, 23 patients were excluded because 25OHD measurement was not performed. The final sample included 1168 patients. Six hundred and fifty-four patients (56.0%) were not taking vitamin D supplements. Among 514 patients taking supplements, 318 (61.9%) were using dosages ≥ 800 IU/day, while 196 (38.1%) were taking dosages ≤440 IU/day. The mean age in the whole sample was 58.9 years (standard deviation 11.1) with a significant older age (p<0.001) and a higher prevalence of female subjects (p<0.001) in supplemented patients. The mean disease duration was significantly longer in supplemented patients (p=0.004), as well as the proportion of subjects taking corticosteroids (p<0.001). Variables exploring the disease activity such as CRP and the number of swollen joints were all indicative of a higher RA activity in non-supplemented patients, even if the proportion of patients in clinical remission was not significantly different between patients taking vitamin D supplements and patients who were not. HAQ mean score was higher in patients using vitamin D supplementation (p=0.002). Supplemented patients more frequently underwent bone testing (p<0.001) and a greater proportion of these sub-

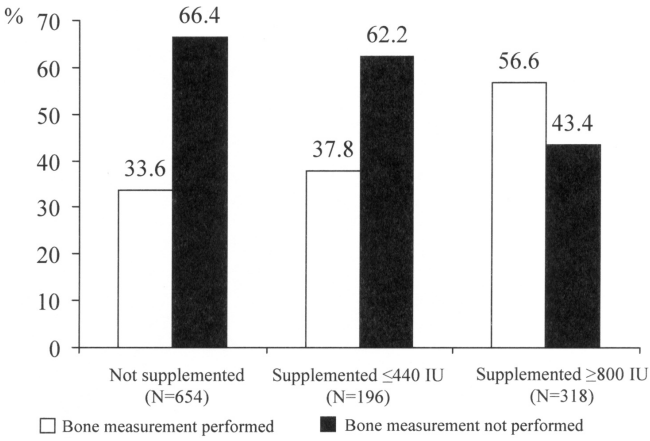

Fig. 1. Proportion of patients who underwent bone measurement by vitamin D supplementation category.
p-values were determined by chi-square test.
Patients not supplemented *vs*. patients supplemented: $p<0.001$; patients treated with lower dosages (≤440 IU/day) vs patients treated with higher dosages (≥800 IU/day): $p<0.001$.

Table II. Logistic regression analysis for the probability to be supplemented with vitamin D performed on 1168 patients with rheumatoid arthritis.

	OR	95% CI	*p*-value
Age (1 year)	1.05	1.03–1.08	<0.001
Female sex	5.01	2.04–12.31	<0.001
BMI (1 unit)	0.99	0.94–1.04	0.7
Avoiding sun exposure (yes *vs*. no)	1.04	0.61–1.78	0.9
Disease duration (1 month)	1.00	0.99–1.01	0.2
Swollen joints count (1 joint)	0.96	0.91–1.02	0.2
RF positive (yes *vs*. no)	1.12	0.69–1.84	0.6
CRP (1 mg/dL)	0.96	0.91–1.02	0.2
HAQ (1 point)	1.01	0.74–1.39	0.9
Corticosteroids (yes *vs*. no)	1.20	0.58–2.48	0.6
Bone measurement (yes *vs*. no)	1.69	1.26–2.27	0.001

Table III. Demographic and clinical characteristics of 318 patients with rheumatoid arthritis taking vitamin D supplement at dosages ≥ 800 IU/day, stratified by 25OH-vitamin D insufficiency. Values are expressed as mean ± SD or number (percentage).

	Vitamin D insufficiency <20 ng/ml (n=88)	Serum 25OH-Vitamin D >20 ng/ml (n=230)	*p*-value
Age (years)	61.3 ± 9.4	61.1 ± 10.2	0.9
Female sex (%)	83 (94.3)	207 (90.0)	0.3
BMI (kg/m^2)	25.1 ± 4.9	24.7 ± 4.3	0.5
Smoking (%)	16 (18.2)	47 (20.4)	0.8
Avoiding sun exposure (%)	35 (39.8)	56 (24.3)	0.01
RA measures:			
Disease duration (months)	151 ± 102	142 ± 94	0.5
Swollen joints count (n)	3.46 ± 6.14	2.57 ± 3.69	0.1
RF positive (%)	52 (59.1)	138 (60.0)	0.9
CRP (mg/dL)	1.9 ± 3.3	1.8 ± 3.2	0.9
HAQ (score)	1.5 ± 0.9	1.1 ± 0.8	0.001
Disease remission (%)	13 (14.8)	55 (23.9)	0.1
Medication:			
DMARDs (%)	79 (89.8)	210 (91.3)	0.8
Biologics (%)	40 (45.4)	104 (45.2)	0.9
Corticosteroids (%)	78 (88.6)	209 (90.7)	0.6
OP measures:			
Bone measurement (%)	50 (56.8)	130 (56.5)	0.9
OP diagnosis (%)	44 (50.0)	110 (47.8)	0.8

jects had a diagnosis of osteoporosis ($p<0.001$). As expected, serum 25OHD mean values were significantly higher in patients supplemented with vitamin D in comparison with non supplemented patients (28.5±17.4 ng/mL *vs*. 21.3±10.5 ng/mL; $p=0.001$), with a high prevalence of vitamin D deficiency in patients not taking supplements (51.8% *vs*. 29.4%; $p<0.001$).

Figure 1 depicts rates of patients who underwent bone measurement based on the prescription of vitamin D. Patients using vitamin D supplements more frequently underwent bone testing in comparison with patients who were not supplemented ($p<0.001$). Similarly, patients taking higher dosages (≥800 IU/day) had more frequent bone assessments than patients who were using lower dosages (≤440IU/day) ($p<0.001$).

In Table II results of the multivariable analysis performed to evaluate the predictors of vitamin D supplementation are shown. Independent predictors of the prescription of a vitamin D supplement were age, female sex and a previous diagnosis of OP. When the variable "bone measurement" was replaced by "OP diagnosis", this was also a significant predictor of supplementation (OR=2.38; 95% CI: 1.40–4.03; $p<0.001$).

Table III shows the univariate analysis performed on 318 patients taking daily vitamin D supplements ≥800 IU. Patients were stratified into serum 25OHD values above (230 pts) or below 20 ng/mL (88 pts). Patients with 25OH insufficiency showed a higher mean HAQ score ($p=0.001$) and a greater proportion of subjects who avoided sun exposure ($p=0.01$), while no difference was found with regard to the other variables.

Table IV reports the results of the logistic model performed on the subgroup of patients on ≥800 IU/day vitamin D supplements using 25OHD insufficient level as dependent variable. HAQ score and sun exposure acted as significant variables on the odds of having serum 25OHD values lower than 20 ng/mL.

Discussion

Inflammation, decreased functional capacity and corticosteroids have been identified as independent risk factors for OP in RA patients (15, 16). Inadequate levels of vitamin D have been frequently reported in RA patients (5-7) and this is often related to raised PTH levels and increased bone loss. Vitamin D deficiency is a well established risk factor for falling (17). The risk of falling is higher in patients with RA (18) and this may be related with vitamin D deficiency.

Table IV. Logistic regression analysis for the risk of 25OH-vitamin D insufficiency performed on 318 patients with rheumatoid arthritis taking vitamin D supplement at dosages ≥800 IU/day.

	OR	95% CI	*p*-value
Age (1 year)	0.98	0.95-1.02	0.4
Female sex	0.82	0.24-2.83	0.7
BMI (1 unit)	0.99	0.93-1.07	0.9
Avoiding sun exposure (yes *vs*. no)	2.38	1.05-5.55	0.04
Disease duration (1 month)	1.00	0.99-1.01	0.9
Swollen joints count (1 joint)	1.00	0-93-1.08	0.9
RF positive (yes vs no)	1.41	0.68-2.93	0.3
CRP (1 mg/dL)	0.97	0.87-1.08	0.6
HAQ (1 point)	1.62	1.06-2.49	0.03
Corticosteroids (yes vs no)	0.69	0.22-2.16	0.5
Disease remission (yes vs no)	0.90	0.35-2.29	0.8

In this study including a large group of patients from 22 rheumatology centres evenly distributed across Italy we have observed that most subjects (56.0%) do not receive vitamin D supplementation and a further 38.1% of supplemented patients are taking ≤440 IU/day, a dosage considered inadequate to reduce the risk of fracture and falling (19, 20). Most of these latter patients were actually prescribed a formulation combining 400–440 IU vitamin D with 500 mg calcium.

Even if the dose of vitamin D required to achieve adequate levels may vary among individuals according to baseline levels, dietary intake, BMI and sun exposure, this study shows that dosages more frequently used are insufficient in RA patients in whom adequate levels of 25OHD should be warranted also for the alleged immunomodulatory effect of vitamin D on disease activity (21).

We have observed that the most frequently supplemented patients (Table I) were older female patients taking corticosteroids with longer disease duration and who underwent a bone measurement or already had a diagnosis of OP. These correlations were confirmed by multivariate logistic analysis, including all relevant confounding factors. Having been tested by bone measurement was significantly related with supplementation with higher dosages. Thus, factors motivating the prescription of vitamin D supplements are basically risk factors for OP or awareness of the risk of OP in RA.

It is worth a mention that bone measurement was performed only in 40.6% of patients, despite RA is a recognised indication for a DXA evaluation (4). Interestingly, patients who had no bone measurement were often also those who were not prescribed vitamin D supplements. Clearly, poor awareness of the risk of osteoporosis and vitamin D deficiency are strongly related to each other.

Possibly, the most surprising finding of this study was the high proportion (27.7%) of patients treated with 800 or more IU daily vitamin D supplements in whom serum 25OHD levels below 20 ng/mL were observed. Logistic analysis demonstrated that disability level and poor sunshine exposure were the two main determinants of this poor therapeutic response. There are several possible explanations to account for these results. It was suggested that an extrarenal 25(OH) 1-α-hydroxylase activity on rheumatoid synovium may burn out a larger amount of 25OHD, which is its substrate (22). Furthermore, in a previous analysis performed on the same population it was observed that clinical measures of disease activity, such as number of swollen joints and DAS 28 together with a disability parameter like HAQ are inversely related to 25OHD levels (7). However, as it was shown in the same study, patients with longstanding and more severe disease or functional impairment spend less time at sunlight, a major source of vitamin D (23). Alternatively, it has been proposed that systemic inflammation itself may modulate serum 25OHD concentrations (24).

There are several limitations to this study. We accounted for the use of vitamin D supplements based on physician prescriptions and patient reports, but the real adherence was not verified. Dietary intake of vitamin D was not assessed even if it is conceivable that the contribution of dietary intake to the overall 25OHD levels is very limited since the traditional Italian diet is poor in vitamin D and foods are not fortified with vitamin D. Lastly, in 3 of the 22 centres where patients were recruited for this study, bone measurement equipment was not readily available.

In summary, this study confirmed that vitamin D deficiency is common in patients with RA, even in patients regularly taking supplements. Vitamin D supplements even at 800 IU daily are inadequate to achieve normal 25OHD levels (20 ng/mL) in more than a quarter of patients. In this setting and in terms of OP screening, patterns of management among rheumatologists still remain suboptimal and interventions for quality improvement are needed.

Centres participating in this study

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