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ORIGINAL ARTICLE

Vitamin D supplementation in a healthy, middle-aged population: actual practices based on data from a French comprehensive regional health-care database

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BACKGROUND/OBJECTIVES: The debate surrounding recommendations for vitamin D supplementation in middle-aged patients (that is, 20–60 years of age) with low serum concentrations of 25-hydroxyvitamin D (25(OH)D) is growing. Our aim was to describe practices regarding vitamin D supplementation in this age group, which are basically unknown.
SUBJECTS/METHODS: We performed an analysis using exhaustive reimbursement data from the individuals in Rhône-Alpes area, a French region regrouping more than 6 million of inhabitants. The data were collected from the French Insurance Health-care System. Patients who were 20–60 years of age, had no severe comorbidities, had a 25(OH)D assay between 1 December 2008 and 31 January 2009 were identified. Those who received a subsequent prescription for vitamin D were included in this analysis. We described patterns of vitamin D supplementation by frequency and daily dose.
RESULTS: The sample in this study included 1311 patients. The mean age was 47.7 years (s.d.: 9.5) and the median age was 50.2 years. Most of the participants (that is, 85.9%) were women. A total of 372 distinct prescription patterns for vitamin D supplementation were observed. The two most frequent (that is, 32.6% in total) involved a unique dispensation of a high dose of either 200 000 (17.5%) or 100 000 IU (15.1%). Most prescribed supplements were based on vitamin D3 (65%), and the most prescribed forms were high dose ampoules (81.6%). Only 48.9% of the participants were given a maintenance prescription after the initial loading phase.
CONCLUSIONS: Our results reveal a significant variability in the prescriptions for vitamin D supplementation from physicians in the French population. Moreover, less than half of the patients receive maintenance therapy after the initial loading phase of supplementation.

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Keywords: adult; middle aged; Vitamin D; Vitamin D deficiency; pharmacoepidemiology

INTRODUCTION

Interest in the benefits of vitamin D is growing. Indeed, research interest has focused both on vitamin D's benefits in the bone[1] and other areas (for example, cancer disease,[2] diabetes[3,4] or multiple sclerosis[5]). Most developed countries, including France, have set national guidelines for the systematic supplementation of vitamin D in infants and children[6] and in the elderly.[7] The French Groupe de Recherche et d'Informations sur l'Ostéoporose (GRIO) recently recommended the inclusion of vitamin D supplementation in a systematic approach in all patients over 65 years of age as they consider the risk of low 25-hydroxyvitamin D (25(OH)D) levels to be quite high in this population.[7] Guidelines have also been developed for patients who have specific conditions and truly need to have a sufficient level of 25(OH)D; this includes patients taking antiosteoporotic drugs and patients with renal insufficiency.[7,8] For middle-aged people (that is, 20–60 years of age), however, no consensual guidelines have been established[9] despite several epidemiological studies that have reported a significant prevalence of low 25(OH)D serum concentrations, especially in people with risk factors (for example, night work). For instance, the National Health and Nutrition Examination Survey (NHANES) reported that 41.6% of American adults in 2005–2006 had 25(OH)D serum levels less than 50 nmol/l,[10] and in the French Nutrition and Health Survey (ENNS, Etude Nationale Nutrition Santé 2006–2007), 42.5% of French adults had similar levels of 25(OH)D.[11] In a previous study of 247 consecutive patients who were 19–60 years of age, had no comorbidities and were consulting their general practitioner, we found that 80% had a 25(OH)D serum concentration of less than 50 nmol/l.[12] Indeed, several studies have clearly established the prevalence of low 25(OH)D serum levels. However, the main source of debate is the therapeutic target concentration of 25(OH)D, which is reported to be between 50 and 75 nmol/l.[13,14] Note that this wide range has mostly been defined from data collected in studies with the elderly.[9] Nevertheless, regardless of the concentration selected as the therapeutic target in the case of 25(OH)D insufficiency or deficiency, the treatment requires a loading phase followed by a maintenance phase; the actual prescription can come in the form of a large variety of compounds with a daily to quarterly administration since the metabolite, that is, 25(OH)D, has a

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half-life of about 1 month.[7] Given the absence of consensual guidelines for this middle-aged population, we expect some variations in the loading phase and relatively similar practices for the maintenance phase once the expected target 25(OH)D concentration has been reached. We did not find any study in the literature that describes actual vitamin D prescription patterns in this age group. The objective of this study was to describe the type and frequency of vitamin D supplementation delivered to patients who had underwent a 25(OH)D assay, were middle aged and had no severe comorbidities.

MATERIALS AND METHODS

We performed an analysis using the Rhône-Alpes area data from the Extraction, Recherches, Analyses pour un Suivi Médico-Economique (ERASME) database, which is administered by the French Insurance Health-care System.[15] This database contains all of the medical reimbursements for all employees and their families in the Rhône-Alpes area (that is, 6.1 million inhabitants, which is 10% of the French population). Among the individuals whose data are compiled in this database, all patients from 20 to 60 years of age who had a 25(OH)D assay between 1 December 2008 and 31 January 2009 were identified. This database is limited to a 24-month follow-up period; thus, we restricted our analysis to 7 months before and 7 months after the assay in order to ensure that we had valid and comparable data for all of the patients. Among these patients, we selected those who had a prescription and a reimbursement for vitamin D supplementation during the 7 months following the assay. The exclusion criteria included vitamin D supplementation during the 7 months preceding the assay, pregnancy and death or assignment to another insurance health-care system during the 7-month period following the assay. We also excluded patients with major chronic diseases as those patients often have specific needs and are likely to receive treatments that are not typical among our target population. Those patients were identified through their 'Affection de longue durée' status as declared by their general practitioner and approved by a physician employed by the National Healthcare Insurance. These chronic diseases as coded according to the International Classification of Disease, 10th version (ICD-10) classification system[16] included stroke; bone marrow failure and other chronic cytopenia; chronic artheriopathy with ischemic manifestations; complicated bilharziasis; severe heart disease; chronic active liver disease and cirrhosis; primary or HIV acquired immunodeficiency; type I and type II diabetes; severe neuromuscular disease, including myopathy and severe epilepsy; severe and chronic hemoglobinopathy; hemophilia; severe arterial hypertension; coronary heart disease; chronic respiratory failure; Alzheimer's disease; Parkinson's disease; metabolic inherited disease; cystic fibrosis; severe and chronic renal disease; paraplegia; vasculitides; systemic lupus erythematosus; scleroderma; rheumatoid arthritis; long-term psychiatric disease; chronic ulcerative colitis; Crohn's disease; multiple sclerosis; evolutive scoliosis; severe spondylarthritis; complications with organ transplant; tuberculosis; leprosy; and cancer.

To describe the cohort, we anonymously extracted the following demographic data from the database: date of birth, gender, global data on health-care use,[17] number of distinct pharmacy prescriptions, number of visits to specialists, number of distinct Anatomical Therapeutic Chemical classes for reimbursed drugs, number of medical imaging exams, number of sick leaves prescribed by a doctor, number of prescriptions for physiotherapy and prescriptions for vitamin D supplementation. Available pharmaceutical formulations included high dose ampoules of 80 000, 100 000 and 200 000 IU of vitamin D3 (cholecalciferol) and ampoules of 600 000 IU of vitamin D2 (ergocalciferol). In addition, many other pharmaceutical formulations designed for daily vitamin D3 intake were prescribed; they ranged from 200 IU tablets to multidose bottles containing up to 2 000 000 IU of vitamin D2 or D3 with daily doses containing up to 1000 IU each (that is, the specific dose was defined by the intake of a prescribed daily number of drops from the bottle). The vitamin D supplementation patterns were determined based on the temporal succession of reimbursements for the prescriptions of specific doses of vitamin D and from the form for each reimbursed treatment (that is, both daily doses and high dose ampoules), the cumulative dosage and the type of vitamin D (that is, cholecalciferol, ergocalciferol, alfacalcidol or calcitriol) prescribed over the 7-month follow-up period. When multidose vials were prescribed, the whole quantity of vitamin D contained in the package was considered. High dose ampoules of vitamin D are usually prescribed as a single treatment or repeated at intervals that generally vary from 2 weeks to 3 months; the latter is sometimes called 'stosstherapy'.[18] We classified patients into the following three categories: those who received 'stosstherapy' only, those who received pharmaceutical forms designed for daily doses (that is, 'daily dose therapy') and those who received both types of medications either concurrently or sequentially (that is, 'mixed therapy'). Even though there may be differences between vitamin D_3 and vitamin D_2, we considered the two forms to be equivalent because neither has been solely identified as the best means for correction of 25(OH)D deficiency.[19,20]

The continuous variables were described in terms of mean, median and s.d.. The categorical variables were described as number of patients and sample proportions. χ^2 tests with a threshold of 0.05 were used for proportion comparison. To compare the different vitamin D supplementation patterns, we converted observed patterns into average daily doses by dividing the sum of all doses prescribed over the 7-month follow-up period by the number of days in that follow-up period and rounding the results to hundreds of IU. As some evidence indicates that daily doses may not produce the same outcome as 'stosstherapy' due to adherence[21] and pharmacokinetics,[22] we separately analyzed the three groups of patients (that is, those who were prescribed only the daily dose therapy, those who were prescribed only 'stosstherapy' and those who received 'mixed therapy').

RESULTS AND DISCUSSION

In the ERASME database, 3023 patients had underwent a 25(OH)D assay during the 2-month inclusion period (that is, December 2008–January 2009), and 1311 were included in our study after the removal of patients who met the exclusion criteria (that is, not between 20 and 60 years of age ($n = 96$), those with a history of recent vitamin D supplementation ($n = 454$) and those who were not prescribed a vitamin D supplementation after their 25(OH)D assay ($n = 1162$)). The relevant characteristics of the 1 311 patients included in the study are shown in Table 1. Note that 85.9% were women, and the mean age was 47.7 years (s.d. 9.5); moreover, the median age was 50.2 years. These demographic characteristics were similar to that of the group who received no supplementation after their assay. The total amount of vitamin D prescribed per

Table 1. Baseline characteristics of the study population

Baseline characteristics of supplemented patients (n = *1311)*	
Age, n *(%)*	
20–<30	84 (6.41)
30–<40	208 (15.9)
40–<50	348 (26.5)
50–60	671 (51.2)
Female gender, *n (%)*	1126 (85.9)
Number of specialist visited, n *(%)*	
⩽1	816 (62.2)
2–4	382 (29.1)
>4	113 (8.6)
Presence of medical imaging, *n* (%)	557 (42.5)
Presence of prescription for physiotherapy, *n* (%)	301 (22.9)
Presence of incident sick leaves, *n* (%)	214 (16.3)
Number of recorded distinct dates of pharmacy prescription, n *(%)*	
⩽5	796 (60.7)
6–10	401 (30.6)
>10	114 (8.7)
Number of different ATC drug classes reimbursed, n *(%)*	
⩽2	825 (62.9)
3–4	441 (33.6)
>4	45 (3.4)

Abbreviation: ATC, Anatomical Therapeutic Chemical.

patient over the 7-month follow-up period ranged from a minimum of 30 000 IU to a maximum of 2 280 000 IU, and the median was 260 000 IU. Interestingly, the dose increased with age. The average daily dose per patient over the 7-month period ranged from 140 to 10 600 IU/day (Figure 1), and the median was 1600 IU/day.

In our study, a total of 372 patterns of vitamin D supplementation with vitamin D_2 and/or vitamin D_3 were observed (Table 2). The two most frequent patterns were found in 32.6% of the patients and were a single administration of a high dose, that is, either 200 000 IU vitamin D3 (17.5%) or 100 000 IU vitamin D3 (15.1%) shortly after the assay. Two other patterns that were far less common in terms of frequency of prescription were a single administration of a high dose of either 600 000 IU D2 (5.6%) or 400 000 IU D3 (5.3%). However, in total, these four patterns represented the regimens prescribed to 43.5% of the patients. Over the 7-month follow-up period, 81.6, 12.0 and 6.3% of the patients received 'stosstherapy' only, mixed therapy and daily doses therapy only, respectively. Regarding maintenance therapy, 51.1% of the patients received 'stosstherapy' during the first month following the assay but were given no further supplementation. Among those, 39.1, 35.4, 10.6, and 3.3% were given 100 000, 200 000 IU, 600 000 IU and 400 000 IU, respectively. Increasing age was associated with higher use of mixed therapy; indeed, 65% of patients receiving mixed therapy were 50–60 years of age as compared with the proportion of 50–60 years aged patients representing 49% of treated patients for each other type of therapy ($P<0.05$, Table 3). Female gender was also associated with higher rates of mixed therapy; that is, 93% of patients receiving mixed therapy were women as compared with women representing 81% for daily dose forms and 85% for stosstherapy (Tables 3, $P<0.05$).

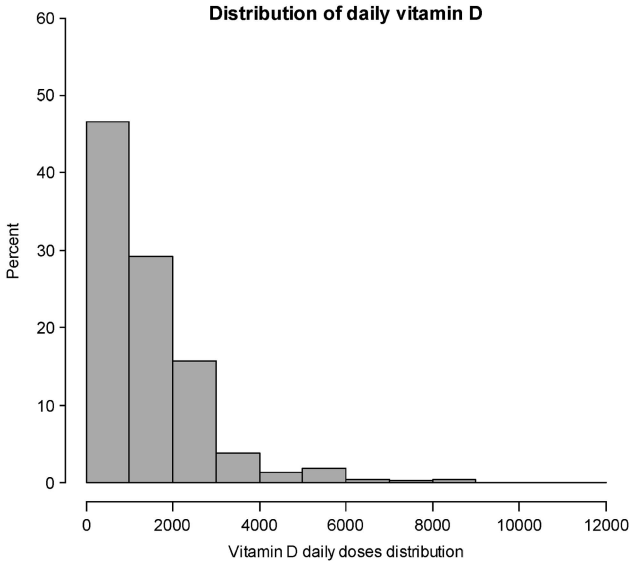

Figure 1. Histogram of average daily doses of vitamin D over the 7 months of follow-up.

Table 2. Supplementation patterns observed in the cohort study ($N=1311$)

Supplementation pattern n *(%) in 25(OH)* D_2 *or* D_3	
200 000 IU D3 at inclusion	230 (17.5)
100 000 IU D3 at inclusion	198 (15.1)
600 000 IU D2 at inclusion	74 (5.6)
400 000 IU D3 at inclusion	69 (5.3)
100 000 IU D3 at inclusion and 1 month later	40 (3.0)
100 000 IU D3 at inclusion and 2 months later	32 (2.4)
200 000 IU D3 at inclusion and 1 month later	22 (1.7)
200 000 IU D3 at inclusion and 200 000 IU D3, 2 months later	20 (1.5)
300 000 IU D3 at inclusion	20 (1.5)
60 000 IU D3 at inclusion	19 (1.4)
80 000 IU D3 at inclusion	18 (1.4)
200 000 IU D3 at inclusion and 200 000 IU D3, 1 month later	17 (1.3)
100 000 IU D3 at inclusion and 100 000 IU D3, 2 months later	13 (1.0)
200 000 IU D3 at inclusion and 100 000 IU D3, 2 months later	12 (1.0)
100 000 IU D3 at inclusion, 1 month later and 2 months later	12 (1.0)
Other pattern ($n=357$)	515 (39.3)

Globally, regarding the volume of drugs prescribed, most were single use ampoules (72.3%), and half of those contained 100 000 IU of vitamin D3. Almost all of the prescribed single use ampoules contained vitamin D3; in fact, only 5.7% contained vitamin D2. More precisely, most prescriptions were for cholecalciferol (64.5%) associated with calcium in fixed combined form or not (that is, 23.5% versus 41.0%, respectively). Vitamin D2, calcifediol and alfacalcidol were prescribed in 19, 14.3 and 1.7%, respectively, of the supplementation cases. Calcitriol was prescribed in just one case.

This study was based on an exhaustive regional database and showed that among all registered patients who were 20–60 years of age, 3 023 had a 25(OH)D assay during a 2-month winter period. Within this group, 40% did not receive any vitamin D supplementation, whereas 60% were given a prescription for vitamin D. No difference in age or gender was observed between the group who received supplementation and the group who did not. Among the patients who were prescribed a 25(OH)D assay followed by supplementation with vitamin D, most were women (86%) and half of them were between the ages of 50 and 60.

We observed enormous variability in the vitamin D prescription patterns for these middle-aged patients who were consulting with their general practitioners for non-severe illnesses; in fact, we noted more than 370 different patterns. For most patients, the loading phase consisted of a single high dose, that is, either 200 000 IU vitamin D3 (17.5%) or 100 000 IU vitamin D3 (15.1%), shortly after the assay.

Only 51.1% of patients received further vitamin D supplementation, that is, either by 'stosstherapy' or daily doses therapy, after this first loading dose despite the fact that most current available guidelines recommend that a loading dose (that is, at least 200 000 IU of vitamin D_3 over 1 month) should be followed by maintenance doses of vitamin D (that is, 100 000 IU every 3 months) in order to prevent deficiency recurrence.[7] The loading dose recommended by GRIO varies from 200 000 IU over 30 days when the 25(OH)D level is between 50 and 75 nmol/l to 400 000 IU over 60 days when a deficiency of less than 25 nmol/l is present; this is followed by a quarterly administration of 100 000 IU of vitamin D to prevent recurrence of 25(OH)D deficiency. Those recommendations have to be considered with regards to the safety of vitamin D supplementation. In a recent meta-analysis involving 50 randomized controlled trials,[19] vitamin D supplementation alone did not significantly increase the risk of developing hypercalcemia, hypercalciuria, renal insufficiency, cardiovascular disorders, gastrointestinal disorders, psychiatric disorders, skin disorders or cancer. A slight increase of

Table 3. Description of type of therapy according to age and sex

Type of therapy	*Stosstherapy*	*Daily dose therapy*	*Mixed therapy*	P-*value*
Age, n *(%)*				<0.05
20–<30	75 (7.0)	4 (4.8)	5 (3.2)	
30–<40	180 (16.8)	13 (15.7)	15 (9.5)	
40–<50	288 (26.9)	25 (30.1)	35 (22.1)	
50–60	527 (49.2)	41 (49.4)	103 (65.2)	
Gender, n *(%)*				<0.05
Female	912 (85.2)	67 (80.7)	147 (93.0)	
Male	158 (14.8)	16 (19.3)	11 (7.0)	

nephrolithiasis occurrence was observed only when vitamin D3 was associated with calcium (risk ratio 1.17, 95% confidence interval 1.02–1.34, $P = 0.02$).

Our results showed that half of the patients did not receive prescriptions for maintenance supplementation over the 7-month follow-up period after the loading dose. This lack of attempts to prevent recurring vitamin D deficiency may be a problem given that a number of factors that cause vitamin D deficiency are expected to continue over time in most cases, including ethnicity,[23] skin color, clothing choices, sun exposure and sun protection habits and body mass index.[24]

Most studies published on vitamin D supplementation were randomized trials conducted by specialists (for example, rheumatologists, endocrinologists, geriatricians or internists).[19] Furthermore, although national agencies have recently observed a dramatic increase in the prescription of 25(OH)D assays,[25] actual current practices regarding vitamin D supplementation are not precisely known. In a French survey conducted in 2010 that included 100 general practitioners,[26] the general practitioners declared the median dose they prescribed was 400 000 IU/year (that is, equivalent to daily doses of 1100 IU/day), ranging from 160 000 to 2 400 000 IU; note that the type of vitamin D used for supplementation was not specified.

Although this study was based on a large exhaustive database, the main limitation of this study is that no detailed information was available regarding the result of the assay and the possible risk factors for low 25(OH)D. We assume that a part of the variability in prescriptions is due to the magnitude of the deficiency. However, our data and findings are still of interest as a general practitioner typically prescribes a high dose of vitamin D after a 25(OH)D assay, especially a dose higher than 100 000 IU, when the patient has a deficiency and would need maintenance therapy. Another limitation is that over-the-counter drugs are not reimbursed by the French Health-care System and thus do not appear in the database. This also could lead to an underestimate of the vitamin D treatment for these patients.[27] However, most drugs used to correct vitamin D deficiency supplementation are not available without a medical prescription in France and are thus fully reimbursed. Therefore, this should not affect the assessment of our main objective, which was to describe the patterns of vitamin D prescription by physicians. Also note that our study results are generalizable only to other countries with comparable health-care systems, socio-economic situations and latitude.

The main strength of this study is the description of the actual prescription of vitamin D based on an exhaustive database of prescriptions from all physicians within a large French region; this precludes any selection bias of the physicians, unlike other descriptive studies based on samples of volunteer physicians.[28] Thus, we believe that this analysis provides a reasonably unbiased estimate of vitamin D supplementation prescription patterns during the winter months in the French primary care setting.[29]

To conclude, this work highlights the tremendous variability surrounding the practice of vitamin D supplementation in France, which represents a context of existing but debated recommendations. In addition to this variability, our results suggest that no maintenance treatment was prescribed in half of the supplemented patients. Further research is needed to confirm this trend and identify the factors associated with these practice patterns.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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