Low Plasma Vitamin D Levels and Muscle-Related Adverse Effects in Statin Users

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ABSTRACT: **Background:** Treatment with HMG-CoA reductase inhibitors (statins) is often complicated by muscle-related adverse effects (MAEs). Studies of the association between low plasma vitamin D levels and MAEs have yielded conflicting results.

Objectives: To determine if low plasma vitamin D level is a risk factor for MAEs in statin users.

Methods: Plasma levels of 25(OH) vitamin D were measured as part of the routine evaluation of unselected statin-treated patients attending the coronary and lipid clinics at our hospital during the period 2007–2010. Medical data on muscle complaints and statin use were retrieved from the medical files. Creatine kinase (CK) levels were derived from the hospital laboratory database.

Results: The sample included 272 patients (141 men) aged 33–89 years. Mean vitamin D level was 48.04 nmol/L. Levels were higher in men (51.0 ± 20.5 vs. 44.7 ± 18.9 nmol/L, $P = 0.001$) and were unaffected by age. MAEs were observed in 106 patients (39%): myalgia in 95 (35%) and CK elevation in 20 (7%); 9 patients (3%) had both. There was no difference in plasma vitamin D levels between patients with and without myalgia (46.3 ± 17.7 vs. 48.9 ± 21.0 nmol/L, $P = 0.31$), with and without CK elevation (50.2 ± 14.6 vs. 47.8 ± 20.3 nmol/L, $P = 0.60$), or with or without any MAE (50.4 ± 15.0 vs. 47.8 ± 10.2 nmol/L, $P = 0.27$). These findings were consistent when analyzed by patient gender and presence/absence of coronary artery disease, and when using a lower vitamin D cutoff (< 25 nmol/L).

Conclusions: There is apparently no relationship between plasma vitamin D level and risk of MAEs in statin users.

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KEY WORDS: vitamin D, statin, HMG Co-A reductase inhibitor, creatine phosphokinase, myalgia, myopathy, muscle-related adverse effect (MAE)

HMG-CoA reductase inhibitors (statins) reduce mortality and morbidity in patients with coronary artery disease. They are one of the most widely used medications worldwide. However, statins have been associated with muscle-related adverse effects, such as myalgia and creatine kinase elevation [1,2]. Muscle-related adverse effects are the most common reason for statin discontinuation and, therefore, an important barrier to cardiovascular risk reduction [3]. The exact mechanism underlying this complication has not been elucidated. Potential risk factors implicated to date include genetic predisposition, high drug dose, low body mass index, female gender, hypothyroidism, alcohol abuse, polypharmacy, low plasma vitamin D level, concomitant use of fibrates and other medications, reduced production of specific regulatory proteins, and reduced renal and hepatic function [1-5].

Muscle cells have vitamin D receptors [5], and low plasma levels of vitamin D 25(OH) are associated with proximal muscle weakness, hypotonia, prolonged time to peak muscle contraction and relaxation, as well as generalized musculoskeletal pain [4-6]. Recent studies suggest that vitamin D deficiency, a common finding in the general population [7-9], may be associated with an increased risk of statin-related muscle complaints [10] and that symptomatic myositis-myalgia in statin-treated patients with vitamin D deficiency may reflect an interaction between vitamin D deficiency and statins in skeletal muscle. Myositis may result from an autoimmune disease [11] which may be preventable by vitamin D supplementation [12]. Some researchers proposed that statin-related myalgia may be correctable by oral administration of vitamin D [13], although their findings were not confirmed by others [14]. The possible effect of background factors, such as gender, comorbidity, environment, and ethnicity in this context, is still unknown.

The aim of the present study was to examine the possible relationship between plasma vitamin D level and muscle complications in statin users in Israel and to explore the possible impact of patient gender and the presence of coronary artery disease on this association.

PATIENTS AND METHODS

Plasma 25(OH) vitamin D level was measured as part of the routine evaluation in unselected statin-treated patients attending the coronary and lipid clinics of our hospital from January 2007 through December 2010. Exclusion criteria were conditions known to predispose to myalgia, CK elevation, or vitamin D insufficiency such as hypothyroidism, renal failure (creati-

CK = creatine kinase

nine > 1.2 mg/dl), active participation in competitive sports, known myopathy, vitamin D supplementation, acute coronary syndrome, and elevated baseline plasma CK level. Patients referred for myalgia or CK elevation were excluded as well. A detailed medical history was obtained from the patients' clinic files, with emphasis on statin use, muscle complaints, concomitant medications, and vitamin supplementation. CK levels were derived from the hospital's computerized laboratory database. We also recorded laboratory values of total plasma cholesterol, triglyceride, high density lipoprotein-cholesterol, and glucose, as well as findings on renal and liver function tests. Plasma 25(OH) vitamin D was considered low when recorded values were below 30 nmol/L (commonly described as vitamin D deficiency) [15,16]. MAEs were defined as typical myalgia, as described previously [3], and CK levels more than twice the upper limit of normal (> 400 IU/L) on at least two laboratory tests.

STATISTICAL ANALYSIS

Nominal data were described as numbers and percentages, and continuous data as means and standard deviations. Comparisons of continuous parameters between groups were performed using Student's *t*-test, and between nominal parameters with chi-square and Fisher's exact tests. A *P* value < 0.05 was considered significant. To assess the possible relationship between plasma vitamin D level and risk of MAEs, we compared vitamin D levels and the frequency of low vitamin D level in patients with and without CK elevation, myalgia, or any MAE. Logistic regression analysis was used to identify independent risk factors for MAEs. All statistical analyses were performed using SPSS-19 software.

RESULTS

The study sample included 272 patients (141 men) aged 33–89 years (median 66.0 years). Plasma vitamin D levels ranged between 10 nmol/L and 102 nmol/L (mean 48.04 nmol/L). Vitamin D levels were higher in men (51.0 ± 20.5 vs. 44.7 ± 18.9 nmol/L, $P = 0.001$) and were unaffected by patient age or gender, presence of hypertension or diabetes mellitus, family history of premature coronary artery disease, or smoking status. MAEs were recorded in 106 patients (39%): myalgia in 95 (35%) and elevated CK levels in 20 (7%); 9 patients (3%) had both. CK elevation was more common in men (11% vs. 3%, $P = 0.01$, Fisher's exact test). There was no association between patient gender and myalgia or any MAE, or between any of the other background variables (age, presence of coronary artery disease, hypertension, diabetes mellitus, family history of premature coronary artery disease, smoking status) and CK elevation, myalgia, or any MAE.

MAE = muscle-related adverse effect

Table 1. Patient characteristics by presence/absence of muscle-related adverse effects

	No MAE (n=166)	MAE (n=106)	*P* value
Age (yr)	69.3 ± 10.0	66.3 ± 10.2	0.203
Male gender	53	49	0.463
Hypertension	58	65	0.278
Diabetes	28	27	0.821
Smoking	22	19	0.567
CAD	67	60	0.210
Family history of premature CAD	29	30	0.836
Vitamin D level (nmol/L)	50.4 ± 15.0	47.8 ± 10.2	0.269
Vitamin D < 30 nmol/L	20	13	0.166

Data on age and vitamin D level are presented as mean ± SD. All other data are percentages

MAE = muscle-related adverse effect, CAD = coronary artery disease

Patients were categorized by the presence or absence of a muscle-related statin complication. The patients' characteristics are depicted in Table 1. There were no significant differences between the groups in gender distribution, plasma vitamin D level, or prevalence of traditional coronary risk factors. Additionally, no significant differences were found in plasma vitamin D levels between patients with and without myalgia (46.3 ±1 7.7 vs. 48.9 ± 21.0 nmol/L, $P = 0.31$) or with and without CK elevation (50.2 ± 14.6 vs 47.8 ± 20.3 nmol/L, $P = 0.6$). These results held true on separate analyses by gender and by age (above or below the study median of 66 years).

Analysis of the frequency of MAEs yielded no difference in rates of myalgia, CK elevation, or any MAE between patients with vitamin D levels higher or lower than 30 nmol/L. Even very low plasma levels of vitamin D (< 25 nmol/L, n=34) had no effect on the prevalence of MAEs. Patients with coronary artery disease (n=172) had similar rates of myalgia and CK elevation to those of the entire study group. The prevalence of MAEs in patients with plasma vitamin D ≥ 70 nmol/L was comparable to that in patients with plasma vitamin D < 70 nmol/L (36.4% vs. 39.5%, $P = 0.7$).

On logistic regression analysis, none of the parameters (age, gender, diabetes mellitus, hypertension, family history, smoking habit, coronary artery disease) was found to be a predictor of MAEs, either in a model that included vitamin D status lower or higher than 30 nmol/L or a model in which a lower cutoff of 25 nmol/L vitamin D was used. Similar findings were observed on analysis of each MAE separately.

DISCUSSION

The present study shows that there is no apparent relationship between plasma vitamin D level and risk of MAEs in statin-treated adults. These results were consistent for both men

and women and for each side effect (myalgia, CK elevation) separately. Even very low levels of plasma vitamin D were not associated with muscle complications.

In an earlier study, Kurnik et al. [14] reported no association between low 25(OH) vitamin D levels and statin-induced myalgia. Their finding is similar to ours, although we added an objective parameter, CK elevation, another disturbing MAE of statins. By contrast, Ahmed et al. [10] reported lower vitamin D levels in patients with statin-related myalgia. The reason for the discrepancy is unclear. It may be due to differences in the population studied, the statin used, the intensity of cholesterol lowering, and the ethnic background of the subjects, or to possible related differences in the prevalence of subclinical genetic myopathies, certain single nucleotide polymorphisms [17], and CYP 3A4 activity [3]. Differences in environmental factors may be involved, such as nutrition or sun exposure (Israel has a sunny climate as compared to North America). Further studies of this issue are warranted. Moreover, we defined low plasma vitamin D as < 30 nmol/L, whereas Ahmed et al. [10] used a higher cutoff of 32 nmol/L, which may be less sensitive. Nevertheless, repeated analysis of our data using their criterion did not alter the results.

It is also noteworthy that myalgia is a subjective complaint and may thus reflect cultural and other parameters associated with pain perception and pain tolerance. The diagnosis of myalgia in our patients was made by the attending physician, usually after failure to identify another cause of the muscle pain and after statin discontinuation resulted in pain relief. Thus, it is unlikely that pain in our patients was non-specific, and the diagnosis of statin-related myalgia was probably better established than in reports using other criteria. In addition, our further examination of the possible effect of low plasma vitamin D levels on CK elevation, an objective indicator of statin-related muscle complications, yielded no apparent association between these factors in statin users.

Interestingly, the finding that most of our patients with MAEs had either myalgia or CK elevation but not both may suggest that the two side effects have different underlying mechanisms, although neither was associated with low plasma vitamin D.

The relatively low plasma vitamin D level in our patients is not surprising and is comparable with recent findings in Israeli cohorts. For example, Oren et al. [9] reported a mean plasma vitamin D level of 57.16 ± 25.2 nmol/L, and Kurnik et al. [14] a median plasma vitamin D level of 54.4 nmol/L. The prevalence of vitamin D insufficiency in the cohort reported by Oren et al. [9] was 78%, which is close to that in our patients (84%).

It was recently suggested that myositis may be explained at least in part by autoinflammatory disease, and that anti-HMG Co-A reductase autoantibodies may be found in patients with statin-associated autoimmune myopathy but not in the vast majority of patients with statin exposure [11]. Vitamin D deficiency has been linked to autoinflammatory disease, including the risk of coronary artery disease, probably via its effect on inflammatory cytokines. This finding was supported by a positive response of autoinflammation to vitamin D supplementation [6,12,18-20]. Additionally, some data indicate that vitamin D may modulate pain sensation, but this has not been confirmed [19]. Although the lack of an association between low plasma vitamin D and myopathic complications in the present study does not support the hypothesis that low levels of vitamin D are an important risk factor for statin-related muscle adverse effects, it does not necessarily imply that administration of pharmacological doses of vitamin D, as suggested by Ahmed et al. [10], would have no effect on statin-related muscle complications, particularly those with an underlying autoinflammatory mechanism. However, exploring this issue was beyond the scope of the present study. Further research on the mechanisms of statin-related myalgia and CK elevation is necessary.

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