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Analysis of vitamin D levels in patients with and without statin-associated myalgia — A systematic review and meta-analysis of 7 studies with 2420 patients ☆

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ABSTRACT

Introduction: Vitamin D (vit D) deficiency may be associated with an increased risk of statin-related symptomatic myalgia in statin-treated patients. The aim of this meta-analysis was to substantiate the role of serum vitamin D levels in statin-associated myalgia.
Methods: The search included PUBMED, Cochrane Library, Scopus, and EMBASE from January 1, 1987 to April 1, 2014 to identify studies that investigated the impact of vit D levels in statin-treated subjects with and without myalgia. Two independent reviewers extracted data on study characteristics, methods and outcomes. Quantitative data synthesis was performed using a fixed-effect model.
Results: The electronic search yielded 437 articles; of those 20 were scrutinized as full texts and 13 studies were considered unsuitable. The final analysis included 7 studies with 2420 statin-treated patients divided into subgroups of patients with (n = 666 [27.5%]) or without (n = 1754) myalgia. Plasma vit D concentrations in the symptomatic and asymptomatic subgroups were 28.4 ± 13.80 ng/mL and 34.86 ± 11.63 ng/mL, respectively. The combination of data from individual observational studies showed that vit D plasma concentrations were significantly lower in patients with statin-associated myalgia compared with patients not manifesting this side effect (weighted mean difference −9.41 ng/mL; 95% confidence interval: −10.17 to −8.64; $p < 0.00001$).
Conclusions: This meta-analysis provides evidence that low vit D levels are associated with myalgia in patients on statin therapy. Randomized controlled trials are necessary to establish whether vitamin D supplementation reduces the risk for statin-associated myalgia.

1. Introduction

Statins are very effective agents in both primary and secondary prevention of cardiovascular (CV) events in high-risk patients [1–4]. According to the available studies in patients with CV disease (CVD), statin therapy significantly reduces all-cause mortality, CV mortality,

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morbidity, recurrent CV events and ischemic stroke [5–8]. Therefore, the number of people treated with statins has been increasing during the past several years, and it is predicted that it will increase further due to an increase of high risk patients, population aging and expanded indications [9–11].

However, side effects, most frequently muscle aches (i.e., myalgia), are commonly observed in patients treated with statins, and these side effects greatly affect statin therapy adherence [12–17]. It is therefore important to increase our understanding of the pathology underlying statin adverse effects and how to manage or prevent them in statin-intolerant patients [12,13]. Observational studies show that myalgia can occur even in 15–20% of patients on statin therapy [12–14]. Its occurrence is much more prevalent in daily clinical practice than reported in randomized controlled trials (RCTs; 3–5%), since patients prone to these adverse events may have been excluded from participation during the run-in phase prior to randomization, and due to selection of patients in trials with lesser complexity of illness and comorbidities [12,13]. Muscle-related adverse effects often lead to cessation of statin use, with consequent failure to lower low-density lipoprotein cholesterol (LDL-C) to target levels for primary and secondary prevention of CVD [12–15]. Genetic predisposition, high drug dose, low body mass index (BMI), female gender, hypothyroidism, parathyroid dysfunction, underlying fibromyalgia or polymyalgia rheumatica, autoimmune phenomena, disturbances in muscle metabolism, alcohol abuse, low plasma vitamin D (vit D) level, drug interaction, as well as renal and hepatic dysfunction have been suggested as etiological factors [18,19].

Vitamin D receptors are present on muscle cells [19], and low plasma levels of vit D are associated with hypotonia, proximal muscle weakness, prolonged time to peak muscle contraction and relaxation, as well as non-specific musculoskeletal pain [20]. In recent studies, it has been shown that vit D deficiency may be associated with an increased risk of statin-related muscle complaints [12,18,21] and some hypothetical mechanisms underlying statin-associated myalgia have been proposed. One of them concerns a reduction in muscle mitochondrial levels of coenzyme Q10 (CoQ10) that has a role in muscle energy production, subsequent to inhibition of the mevalonate pathway by statins [22]. However, according to a recent meta-analysis, CoQ10 supplementation does not prevent statin-related myopathy [23]. A second concern is increased beta-oxidation. In patients on high doses of statins, skeletal muscle levels of plant sterols might be increased by nearly 50%, which by inhibiting acetyl coenzyme A carboxylase, reduces fat synthesis, increases beta-oxidation, and results in muscle injury [24]. Others have suggested that individual genetic susceptibility plays an important role in statin-associated myalgia [25]. Finally, a potential mechanistic link for vit D is that the metabolism of some statins depends on cytochrome P450 3A4 (CYP3A4), which displays 25-hydroxylase activity in vitro [26]. Therefore, vit D deficiency may lead to 'preferential shunting' of CYP3A4 for vit D hydroxylation, in an effort to maintain levels of vit D (25[OH]D) within a physiological range, thereby reducing the availability of CYP3A4 for statin metabolism, which ultimately results in increased serum statin levels [26]. However, not all studies show consistent results with regard to vit D levels and statin-associated myalgia [12,13,18].

Taking into account the divergent data, we performed a meta-analysis to investigate whether there are differences of vitamin D (25[OH]D) levels between statin-treated subjects with and without myalgia.

2. Methods

2.1. Data sources

This study was designed in conformity to the guidelines of the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [27]. We searched PubMed, Web of Science and Scopus, using keywords such as: statin, vitamin D level, statin-induced myalgia, statin-associated myalgia, myopathy, muscle pain, muscle function, side effect, adverse effect, adverse events, statin intolerance and supplementation. Data were collected from January 1, 1987 to April 1, 2014. Bibliographies of all retrieved articles were searched for additional relevant publications. Meeting abstracts were searched in Web of Science. Two reviewers (MM and AS) assessed each article independently to diminish the probability of duplication, analyzing reviews, case studies and uncontrolled trials. Disagreements were resolved by consensus and discussion with a third party (MB).

2.2. Study selection

2.2.1. Inclusion criteria

Study design had to meet the following criteria: (1) observational (prospective, retrospective) studies or cross-over trial; (2) population enrolled: adults aged ≥ 18 years, (3) available data regarding the measurement of vit D and information on myalgia, and (4) exclusion of other comorbid conditions associated with myalgias (hypothyroidism, renal failure, decompensated liver disease, rheumatic diseases, muscle diseases, neuropathy/polyneuropathy, and peripheral arterial disease).

2.2.2. Exclusion criteria

Studies were excluded if: (1) no data was presented regarding vit D level or information on statin-associated myalgia, (2) the study was not conducted in statin-treated subjects, (3) no numerical values were provided, (4) we were unable to obtain adequate

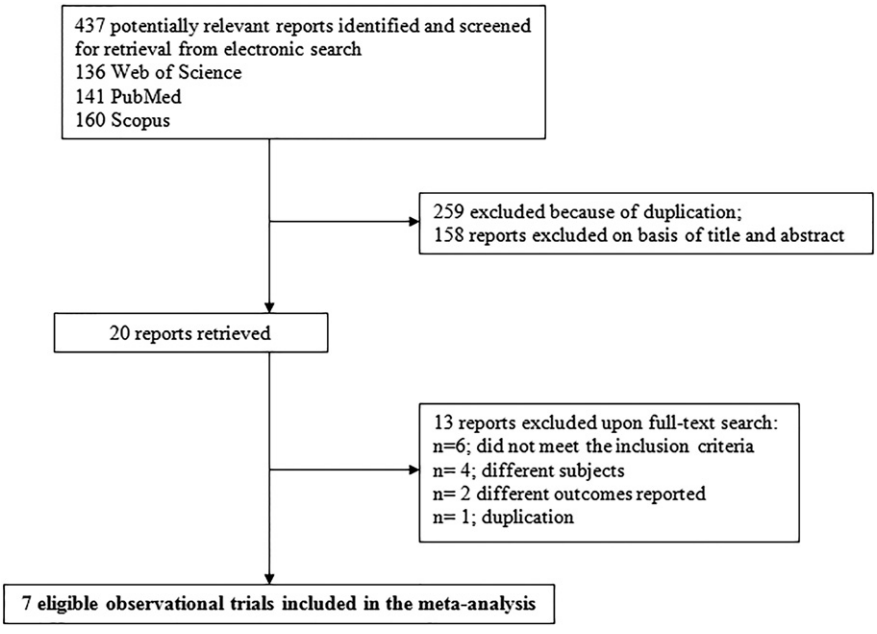

Fig. 1. Flow diagram of the study selection process.

Table 1
Characteristics of the studies included in the meta-analysis.

Study	n (M/F)		Age (years)		Vitamin D levels (ng/mL)		BMI (kg/m[a])		Diabetes t.2 n (%)		Statin		Other therapy		Design
	SIM	AS	SIM	AS	SIM	AS	SIM	AS	SIM	AS	SIM	AS	SIM	AS	
Duell and Connor (2008) [33]	38 (NS)	61 (NS)	59.3 ± 10.4	58.4 ± 12.3	20.5 ± 10.0	30.1 ± 12.5	NS[b]	NS	NS	NS	All types		NS	NS	Cross-sectional study
Ahmed et al. (2009) [21]	128 (52/76)	493 (274/219)	60.0 ± 11.0	58.0 ± 12.0	28.6 ± 13.2	34.2 ± 13.8	29.6 ± 7.6	28.5 ± 5.5	11 (9)	44 (9)	Rosuvastatin, atorvastatin, pravastatin		NS	NS	Cross-sectional study
Linde et al. (2010) [34]	39 (21/18)	25 (16/9)	59.5 ± 10.0	59.3 ± 13.8	28.2 ± 11.6	24.3 ± 10.5	27.9 ± 5.7	27.5 ± 5.5	NS	NS	All types		9[a]	0	Retrospective cohort study
Backes et al. (2011) [35]	26/31	72 (44/28)	62.4 ± 10.5	58.3 ± 13.0	21.4 ± 9.7	21.8 ± 12.1	30.8 ± 4.7	30.3 ± 6.9	19 (33)	23 (36)	All types		NS	NS	Retrospective cohort study
Riphagen et al. (2012) [36]	22 (NS)	53 (NS)	65 (35–84)[c]		18.0[d]	15.2[d]	26.6 (19.5–41.5)[c]		17 (20)		Simvastatin rosuvastatin, atorvastatin, pravastatin		NS	NS	Prospective observational study
Eisen et al. (2014) [37]	106 (52/54)	166 (88/78)	66.3 ± 10.2	69.3 ± 10.0	19.1 ± 4.1	20.2 ± 6.0	NS	NS	27 (25)	28 (17)	All types		NS	NS	Retrospective cohort study
Palamaner Subash Shantha et al. (2014) [38]	276 (NS)	884 (NS)	55.9[e]		22.3 ± 7.1	33.8 ± 4.5	NS	NS	394 (34)		All types[f]		NS	NS	Retrospective cohort study

Abbreviations: SIM — statin-induced myalgia; AS — asymptomatic; BMI — body mass index.
[a] Niacin, fenofibrate, diltiazem or verapamil.
[b] Not stated.
[c] Median age/BMI (range) including 9 patients with myositis.
[d] Median serum 25(OH)D level.
[e] Mean age.
[f] Atorvastatin (60%) and simvastatin (29%) were the predominant statins used by our study population.

details of study methodology or results from the article or the investigators, or (5) the study was ongoing.

2.3. Statistical analysis

Meta-analysis was conducted using the Cochrane Program Review Manager version 5.1. Plasma vit D (25[OH]D) levels were collated in ng/mL. If vit D levels were collated in nmol/L they were converted to ng/mL by dividing by 2.5. Mean and SD values in statin-treated subgroups with and without myalgia were extracted. In case of reporting values in median and interquartile range, the mean and SD were estimated using the recommendations of Hozo et al. [28]. In case of showing vitamin D levels indirectly with a graph, the software GetData Graph Digitizer 2.24 [29] was applied to digitize and extract the data. A fixed-effect model and the generic inverse variance method were used to calculate the combined effect size. In order to evaluate the influence of each study on the overall effect size, sensitivity analysis was conducted using the one-study remove approach [30]. The objective of this analysis was to assess the impact of individual studies, by estimating the weighted mean difference (WMD) in the absence of each single study. Heterogeneity analysis was performed using the Cochran Q test and I^2 index. Mean difference was used as the summary statistic for the meta-analysis.

Potential publication bias was explored using visual inspection of Begg's funnel plot asymmetry along with Begg's rank correlation and Egger's weighted regression tests. The "trim and fill" method of Duval and Tweedie [31] was used to adjust the analysis for the effects of publication bias. Comprehensive Meta-Analysis V2 software [32] was used for performing meta-regression and publication bias analyses.

3. Results

3.1. Study characteristics

The electronic search provided 437 articles: 141 from PubMed, 136 from Web of Science and 160 from Scopus. Of those, 20 were scrutinized as full texts; 13 studies were considered unsuitable, while 7 [21,33–38] met the inclusion criteria and were included in the analysis (Fig. 1). The final meta-analysis included 2420 statin-treated patients divided into subgroups of patients with myalgia (n = 666 [27.5%]) or asymptomatic (n = 1754). Table 1 shows the baseline characteristics of the included studies.

3.2. Quantitative data synthesis

Plasma vit D concentrations in the symptomatic and asymptomatic subgroups were 28.4 ± 13.80 ng/mL and 34.86 ± 11.63 ng/mL, respectively. The combination of data from individual observational studies revealed a significantly lower plasma concentration of vit D in the statin-associated myalgia compared with the asymptomatic subgroup (WMD: −9.41 ng/mL, 95% confidence interval [CI]: −10.17 to −8.64; $p < 0.00001$). Forest plots summarizing the meta-analysis of observational studies comparing plasma vit D levels between myalgic and asymptomatic subjects are shown in Fig. 2. This pooled difference was found to be robust in the leave-one-out sensitivity analysis, removing one study at a time. This stability confirms that the significant difference between the studied groups is the overall effect of all included studies (Table 2).

3.3. Publication bias

Visual inspection of funnel plot asymmetry suggested potential publication bias for the comparison of plasma vit D levels between statin-associated myalgia and asymptomatic groups (Fig. 3). Although Begg's rank correlation test was not significant (tau with continuity correction = 0.29, z-value = 0.90, one-tailed p-value = 0.18), Egger's linear regression analysis suggested potential publication bias (intercept = 5.25, standard error = 1.01, 95% CI = 2.66 to 7.84, t-value = 5.21, df = 5, two-tailed $p = 0.003$). Duval and Tweedie "trim and fill" correction led to the imputation of 4 missing studies and a greater difference between the groups: WMD: −11.08 ng/mL; 95% CI: −11.70 to −10.46.

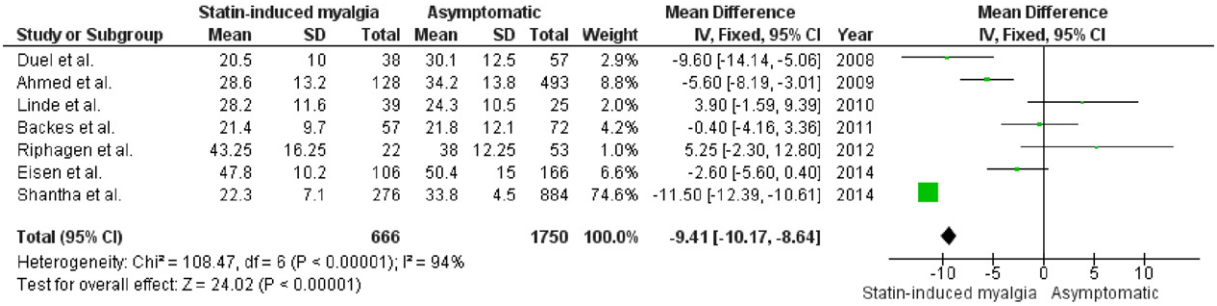

Fig. 2. Forest plots summarizing the meta-analysis of observational studies comparing plasma vitamin D levels between myalgic and asymptomatic subjects.

4. Discussion

This analysis involving 2420 statin-treated patients from 7 studies provides suggestive evidence that there is an association between plasma vit D levels and statin-associated myalgia. Patients with statin-associated myalgia had significantly lower levels of vit D compared to asymptomatic patients. To our knowledge, the present meta-analysis is the first to assess the association of vit D levels and statin-associated myalgia. This meta-analysis is hypothesis generating, and RCTs investigating the effect of vit D supplementation on the frequency and severity of statin-associated myalgia should be performed in order to test the validity of this association.

In some available studies, low serum concentrations of 25-hydroxyvitamin D (≤20 ng/mL) have been associated with myalgia and reduced muscle function [33–40]. Ahmed et al. [21] reported that 128 statin-treated patients with myalgia had significantly lower mean serum vit D level than 493 asymptomatic patients (28.6 ± 13.2 vs 34.2 ± 13.8 ng/mL). Serum vit D was lower in 64% patients with myalgia vs 43% of asymptomatic patients [21]. In another study Duell and Connor [33] showed that patients with statin-associated myalgia had a 32% lower mean serum vit D level in comparison to patients without myalgia, and mild and severe vit D deficiency were significantly more commonly observed among patients with statin-associated myalgias [33]. Also among patients with serum vit D level < 20 ng/mL, 62.1% had statin-associated myalgias vs 17.6% of patients with serum vitamin D level ≥ 30 ng/mL. Approximately one third of patients with statin-associated myalgia reported fewer symptoms after unblinded treatment with high dose ergocalciferol for 8–12 weeks [33]. These results are in line with the findings of the present meta-analysis and support an association between vit D metabolism and the incidence of statin-associated myalgia.

In addition, vit D supplementation has been shown to lower serum concentrations of atorvastatin while acting synergistically with the drug to decrease LDL-C and total cholesterol (TC) levels [41]. The effect of vit D levels (as well as its supplementation) in patients with statin-associated myalgia was investigated in several studies [21,33–38]. As a part of a cohort study evaluating the relationship between serum vit D levels and myalgia [21], 82 vit D deficient myalgic patients (vit D level: 20.8 ± 7.1 ng/mL) were prescribed 50,000 units of ergocalciferol weekly for 12 weeks. Thirty-five of these patients (92%) reported no further symptoms of myalgia [21], implying that statins and vit D deficiency interact additively or synergistically to produce myalgia that is reversible by vit D supplementation, while continuing statin therapy [21]. Similar results were obtained by Glueck et al. [42] who evaluated 68 adult patients with statin-associated myositis/myalgia and serum 25(OH) vit D levels < 32 ng/ml. Vit D supplementation was administered at the dose of 100,000 U/week for 3 weeks, then 50,000 U/week, and after 3 weeks, statins were re-started. After 3 months of follow-up, 91% previously statin-intolerant patients on vit D supplementation and re-instituted statins were asymptomatic [42].

Lee et al. [43] also highlighted the association of vit D deficiency with statin-associated myalgia, demonstrating successful reintroduction of statin therapy in a subgroup of patients following appropriate repletion of vit D levels. Among 11 patients with statin-associated myalgia, 8 were vitamin D insufficient < 60 nmol/L (24.04 ng/mL) and 3 of these were severely deficient of vitamin D < 30 nmol/L (12.02 ng/mL) [43]. Cessation of the statin with vit D replacement led to complete resolution of myalgia in 6 of the 8 patients and significant improvement of myalgia in another 2 during the 3 month observation. Six patients agreed to be rechallenged with the same statin therapy following vit D repletion, and statins were successfully titrated to higher than original doses to achieve lipid-lowering goals in 2 of these patients [43]. These results suggest an association between vit D deficiency and statin myalgia and that correcting vit D deficiency may allow for an adequate statin dose to achieve target lipid levels [43]. In large retrospective cohort study involving a population (n = 5526) of unselected patients from primary care practice, the prospective association of vit D and statin-associated myalgia was explored [38]. The authors attempted to identify a serum vit D cut-off with significant predictive accuracy to identify patients at risk for statin-associated myalgia. They showed that serum vit D cut-off level < 15 ng/mL had high accuracy in predicting this adverse effect. However, these results obviously need to be validated with

Table 2
Results of leave-one-out sensitivity analysis.

	SIM (*n*)	Quantitative data synthesis					Heterogeneity analysis		
		Asymptomatic (*n*)	Effect size	95% CI	*z*-Value	*p*-Value	Q	df (Q)	I^2
Overall effect	666	1754	−9.41	−10.17 to −8.46	24.02	<0.00001	108.47	6	94%
Leave-one-out sensitivity analysis									
Duell and Connor (2008)	628	1693	−9.40	−10.18 to −8.62	23.66	<0.00001	108.46	5	95%
Ahmed et al. (2009)	538	1257	−9.77	−10.58 to −8.97	23.83	<0.00001	99.38	5	95%
Linde et al. (2010)	627	1725	−9.67	−10.45 to −8.90	24.45	<0.00001	85.49	5	94%
Backes et al. (2011)	609	1678	−9.80	−10.58 to −9.01	24.49	<0.00001	85.49	5	94%
Riphagen et al. (2012)	644	1697	−9.56	−10.33 to −8.79	24.28	<0.00001	93.84	5	95%
Eisen et al. (2014)	560	1584	−9.89	−10.68 to −9.09	24.39	<0.00001	87.25	5	94%
Palamaner Subash Shantha (2014)	390	866	−3.25	−4.77 to −1.72	4.17	<0.0001	24.42	5	80%

Abbreviations: SIM — statin-induced myalgia.

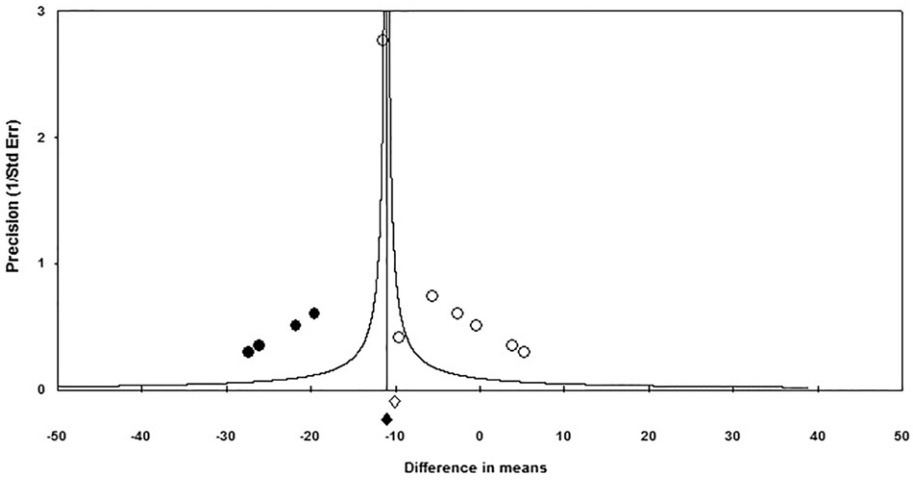

Fig. 3. Funnel plots detailing publication bias in the studies selected for analysis. Trim and fill method was used to impute for potentially missing studies. Open circles represent observed published studies; closed circles represent imputed unpublished studies. Open and closed diamonds represent observed and imputed effect size, respectively.

prospective randomized controlled trials (RCTs) with vit D supplementation at statin initiation and its effect on the future development of statin-associated myalgia [38].

In contrast to the above studies, there have also been studies which do not confirm the relationship between concentrations of vit D and risk of muscle-related side effects in statin-treated adults. Eisen et al. [37] noted that even very low levels of plasma vit D (mean was 48.04 nmol/L) were not associated with muscle complications. Additionally, they found no significant differences in plasma vit D levels between statin-treated patients with and without myalgia [37]. In two similar studies, Kurnik et al. [44] and Riphagen et al. [36] also reported no association between low vit D (25[OH]D) levels and statin-associated myalgia. In the study by Riphagen et al. there were a limited number of patients with very low serum vit D levels (52.5 nmol/L). In addition, there were no patients with serum vit D levels above 80 nmol/L [36]. This lack of a wide range of vit D levels might have hampered the finding of a relationship between vit D status and statin-associated myalgia [36].

The present meta-analysis has some limitations. The studies included were rather heterogeneous, because they were carried out in a variety of settings, with different methods, using various criteria and different comparator groups. The other limitations of all included studies were subjective reports of muscle symptoms and lack of matched blinded control groups. We were unable to examine a possible dose-dependent relationship between vitamin D, statins and symptoms, and possible differences in the effects of different statins given the relatively small number of studies and the limited data available. Our study was limited by the lack of available randomized, placebo-control studies.

In conclusion, our meta-analysis provides suggestive evidence for an association between low plasma vit D levels and myalgia in patients on statin therapy. These findings support the hypothesis that vit D supplementation might be a therapeutic option for statin intolerant patients with low vit D levels. However, the available data from mostly small, non-blinded, non-placebo controlled studies, and cohort observations which suggest that repletion of vit D levels might improve or resolve statin-associated myalgia, still warrants well-designed, large RCTs. This is pertinent since statins are the cornerstone for the prevention and treatment of coronary heart disease, and strategies to improve tolerance and compliance are essential [45].

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Some of the authors have given talks, attended conferences and participated in trials and advisory boards sponsored by various pharmaceutical companies.

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