Significant association between statin-associated myalgia and vitamin D deficiency among treated HIV-infected patients

Leonardo Calza[a], Eleonora Magistrelli[a], Vincenzo Colangeli[a], Marco Borderi[a], Ilaria Contadini[a], Isabella Bon[b], Maria Carla Re[b] and Pierluigi Viale[a]

Background: Several studies have shown a significant association between vitamin D deficiency and an increased risk of statin-related symptomatic myalgia in the general population, but there are no data among HIV-infected persons.

Methods: A retrospective, cohort study was conducted to assess the incidence of symptomatic myalgia and elevation in serum creatine kinase level among HIV-positive adults on combination antiretroviral therapy and treated with atorvastatin or rosuvastatin for at least 12 months between 2011 and 2015 in our outpatient unit.

Results: A total of 545 patients (mean age 53.4 years) were enrolled into the study. Atorvastatin was prescribed in 55.8% of patients and rosuvastatin in 44.2%. After a mean duration of statin therapy of 29 months, an isolated symptomatic myalgia was diagnosed in 42 patients (7.7%) and a myalgia associated with elevated creatine kinase level in 25 (4.6%). The mean concentration of 25-hydroxyvitamin D was significantly lower in patients with myalgia (19.4 ng/ml) and with creatine kinase elevation and myalgia (22.8 ng/ml) than in those without muscle toxicity (32.1 ng/ml; $P = 0.017$ and 0.024, respectively). In stratified multivariable-adjusted logistic regression models, there was a statistically significant association between vitamin D deficiency and occurrence of symptomatic myalgia ($P = 0.009$) or creatine kinase elevation and myalgia ($P = 0.046$). Other factors significantly associated with development of myalgia were duration of statin therapy more than 24 months, history of myalgia, and age older than 60 years.

Discussion: In our observational study, vitamin D deficiency was significantly associated with a statin-induced myalgia among HIV-infected patients on combination antiretroviral therapy, in conformity with data of the general population.

AIDS 2017, **31**:681–688

Keywords: antiretroviral therapy, myalgia, myopathy, statin, vitamin D

Introduction

The combination antiretroviral therapy (cART) has remarkably reduced the mortality of patients with HIV-1 infection, but the significant increase in their life expectancy has been accompanied by an increasing incidence of several metabolic disturbances such as hypercholesterolemia and mixed hyperlipidemia. At the same time, atherosclerotic cardiovascular diseases occur more frequently and earlier in HIV-positive people

[a]Unit of Infectious Diseases, Department of Medical and Surgical Sciences, and [b]Unit of Microbiology, 'Alma Mater Studiorum' University of Bologna, S. Orsola-Malpighi Hospital, Bologna, Italy.

Correspondence to Leonardo Calza, MD, Department of Medical and Surgical Sciences, Clinics of Infectious Diseases, 'Alma Mater Studiorum' University of Bologna, S. Orsola-Malpighi Hospital, via G. Massarenti 11, I-40138 Bologna, Italy.

Tel: +39 051 2143353; fax: +39 051 343500; e-mail: leonardo.calza@unibo.it

Received: 25 November 2016; revised: 12 December 2016; accepted: 12 December 2016.

DOI:10.1097/QAD.0000000000001397

ISSN 0269-9370

receiving cART than in general population, so a prompt correction of the cART-induced dyslipidemia is essential for an appropriate clinical management of HIV-infected people [1–4].

Statins [3-hydroxy-3-methylglutaryl coenzyme A (HMG Coa) reductase inhibitors] are the most effective therapy to treat hypercholesterolemia and they can significantly reduce the incidence of cardiovascular events in the general population [5]. Clinical trials and observational studies have reported a significant lipid-lowering effect of statins in HIV-infected study participants too [6–8], in association with several pleiotropic benefits and anti-inflammatory properties [9–12].

In spite of their proven metabolic, cardiovascular, and inflammatory benefits, statin treatment has been associated with a poor compliance in various patient populations, and the occurrence of muscle toxicity and myalgia are reported to be the main factor associated with poor statin compliance. The incidence of myalgia ranges about from 10 to 25% among study participants treated with statins in clinical practice, and a recent meta-analysis shows that approximately 10–13% of statin-treated patients complain of muscle symptoms in clinical trials [13].

A vitamin D deficiency has been associated with the occurrence of statin-induced myalgia in the general population [14,15], even though the results are conflicting about the cross-sectional association of vitamin D and myalgia in study participants taking statins [16]. High rates of hypovitaminosis D have been reported among HIV-infected patients like the general population, and the overall estimated prevalence of 25-hydroxyvitamin D deficiency in people living with HIV ranges from 70 to 84% [17–19]. So a correlation between low serum concentration of vitamin D and increased risk of statin-induced myalgia could be suspected also in HIV-positive patients, but at the moment there are no studies investigating this potential association.

A retrospective, observational study was performed to evaluate the incidence of muscle toxicity in a cohort of HIV-infected patients receiving cART and starting a lipid-lowering treatment with atorvastatin or rosuvastatin, and to investigate a potential correlation of muscle toxicity with hypovitaminosis D and other predictive factors.

Methods

We performed an observational, retrospective cohort analysis of HIV-1-infected patients on cART who were prescribed atorvastatin or rosuvastatin at our clinics of infectious diseases from January 2011 to December 2015. Eligible patients were 18 years or older and prescribed atorvastatin at 20 mg or rosuvastatin at 10 mg daily for any indication, including primary and secondary prevention of coronary heart disease and treatment of hypercholesterolemia.

Exclusion criteria were statin treatment for less than 12 months if the discontinuation was not caused by toxicity, no regular clinical or laboratory data of follow-up, acute or chronic renal failure, acute hepatitis, liver cirrhosis, myopathy, pregnancy, and one or more of the following laboratory abnormalities at baseline: alanine aminotransferase or aspartate aminotransferase more than 80 U/l, creatinine more than 1.5 mg/dl, creatine kinase more than 145 U/l. Liver cirrhosis was excluded by liver biopsy or elastometry. The hepatitis B virus and hepatitis C virus (HCV) coinfections were diagnosed by the persistent positivity of hepatitis B s antigen or HCV serum antibodies associated with HCV-RNA positivity.

Muscle toxicity was defined as myalgia, creatine kinase elevation, or creatine kinase elevation and myalgia. Myalgia was defined as muscle pain documented in the medical record associated with a serum creatine kinase concentration lower than the upper limit of normal (ULN), or rather less than145 U/l. Creatine kinase elevation was defined as a serum creatine kinase concentration higher than the ULN without muscle pain. Creatine kinase elevation and myalgia were defined as a serum creatine kinase concentration higher than the ULN associated with muscle pain. Rhabdomyolisis was defined as a serum creatine kinase level at least10 times the ULN and evidence of end organ damage (or rather elevated creatinine level, myoglobinuria, or electrolyte alterations), in conformity with the definition of the American College of Cardiology, American Heart Association, and National Heart Lung and Blood Institute [20]. History of myalgia was obtained from a medical record review starting 12 months before initiation of the statin therapy.

The patient's medical record was examined for evidence of one or more of the following data: myalgia, creatine kinase elevation, and creatine kinase elevation and myalgia. The following demographic, clinical, and laboratory data were also gleaned from a medical record review at the start of therapy and at 12-week intervals during the follow-up: sex, age, race, physical examination, BMI, arterial pressure, clinical manifestations, spot urinalysis, and serum levels of triglycerides, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, glucose, complete liver and kidney function tests, creatine kinase, aldolase, $CD4^+$ and $CD8^+$ T-lymphocyte count, HIV RNA, 25-hydroxyvitamin D, parathormone, calcium, and phosphorus. All the plasma samples were analyzed for HIV RNA level using the automated COBAS AmpliPrep Instrument for specimen processing and the COBAS

TaqMan Analyzer for amplification and detection (Roche CobasAmpliPrep/Cobas TaqMan HIV-1 tests version 2.0; Roche Diagnostics, Mannheim, Germany) and the limit of quantification was less than 20 copies/ml.

Comorbidities were examined with specific attention to diseases, which can favor the incidence of muscle toxicity such as diabetes mellitus, hypothyroidism, renal disease, hepatic disease, alcoholism, intravenous drug dependence, or history of muscle pain. Current alcohol use and intravenous drug dependence were defined as a daily alcohol consumption more than 30 g and at least one intravenous drug use within 6 months before starting the dual regimen, respectively.

Concomitant medications were also registered, focusing on those which may interact with statins and increase the risk of statin-associated muscle toxicity such as antiretroviral drugs, fibrates, calcium channel blockers, amiodarone, digoxin, macrolides, azoles, rifampin, colchicine, cyclosporine, and nefazodone.

Data are presented as mean ± SD for descriptive data, while comparisons between groups were performed by Student *t*-test or Fisher exact test (where appropriate). The significance of changes in all the considered variables was assessed using the paired Student *t*-test. A bivariate analysis of collected data was performed to determine the significance of dependent and independent variables. The *t*-test was employed to compare the study participants who experienced muscle toxicity with those who did not experience these adverse events. The χ^2 or Fisher exact test was employed to assess the correlation with sex, age more than 60 years, race, liver disease, chronic hepatitis C, renal disease, history of myalgia, alcoholism, intravenous drug dependence, diabetes mellitus, hypothyroidism, concomitant medications, 25-hydroxyvitamin D level, and duration of statin therapy more than 24 months. Significant variables with $P \leq 0.05$ were included in a multivariate logistic regression analysis to predict the occurrence of muscle toxicity (GraphPad Statistical Software, San Diego, California, USA).

The adherence to the current therapy was carefully checked on the outpatient visits by self-reported questionnaires. The study was approved by the Ethic Committee of the S.Orsola-Malpighi Hospital and all participants signed an informed consent after receiving information about the purpose of the study.

Results

Study inclusion criteria were met by 545 patients who were enrolled in the study: atorvastatin (20 mg daily) was prescribed in 304 study participants (55.8%) and rosuvastatin (10 mg daily) in 241 (44.2%). Mean age ± was 53.4 ± 13.7 years, 441 patients (80.9%) were men, and 501 (91.2%) were white. The mean current $CD4^+$ lymphocyte cell count ± SD was 549 ± 208 cells/μl, the mean duration ± SD of current ART was 4.7 ± 2.8 years and 516 study participants (94.7%) had plasma HIV RNA less than 50 copies/ml. Current cART included two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and one nonnucleoside reverse transcriptase inhibitor (NNRTI) in 60 patients (11%), two NRTIs and one ritonavir-boosted protease inhibitor in 466 (85.5%), and two NRTIs and one integrase strand transfer inhibitor (INSTI) in 19 (3.5%). The mean duration of follow-up ± SD after the beginning of statin treatment was 29.2 ± 12.7 months. The very low number of study participants treated with an INSTI-based regimens was because of the very low prevalence of hypercholesterolemia associated with INSTI use and the rare need of statin therapy in these patients.

Muscle toxicity was reported by 100 patients (18.3%), without significant difference between patients receiving atorvastatin or rosuvastatin. Particularly, muscle toxicity was reported by 63 out of 304 patients (20.7%) treated with atorvastatin and by 37 out of 241 (15.3%) treated with rosuvastatin ($P = 0.082$). Overall, myalgia was reported by 42 patients (7.7%), creatine kinase elevation by 33 (6.1%), and creatine kinase elevation and myalgia by 25 (4.6%), whereas no patient developed rhabdomyolysis. Of the 100 study participants who developed muscle toxicity, 10% occurred in 34.2 days, 25% in 153.7 days, 50% in 412.7 days, 75% in 674.2 days, and 90% in 1815.7 days. Muscle toxicity led to discontinuation of statin treatment in 68 out of the 100 patients (68%) and there were 44 discontinuations (44%) because of muscle toxicity within the first 12 months of therapy. Particularly, discontinuation occurred in 23 out of 42 patients (54.8%) with myalgia, 20 out of 33 (60.1%) with creatine kinase elevation, and 25 out of 25 (100%) with creatine kinase elevation and myalgia. Nine out of the 32 patients who continued statin treatment had their statin dose lowered and seven patients were switched to another statin (pravastatin in four cases and fluvastatin in three cases).

Demographic, clinical, and laboratory characteristics of study patients depending on the occurrence of muscle toxicity are summarized in Table 1. Baseline characteristics were similar between patients who experienced muscle toxicity and those who tolerated statin treatment with the exception of age, 25-hydroxyvitamin D concentration, and total duration of statin therapy. Myalgia was significantly more likely to occur in older patients (mean age, 58.6 vs. 52.5 years; $P = 0.041$). The mean baseline plasma concentration of 25-hydroxyvitamin D was significantly lower in patients who developed myalgia and creatine kinase elevation and myalgia than in those who did not develop these toxicities (19.4 and 22.8 vs. 32.1 ng/ml; $P = 0.017$ and 0.024, respectively), whereas it was similar in patients who developed isolated

Table 1. Baseline characteristics of the 545 patients enrolled in the study depending on the development of muscle toxicity.

	No muscle toxicity	Myalgia	*P* value	CK elevation	*P* value	CK elevation and myalgia	*P* value
No. of patients	445	42		33		25	
Men, no. (%)	362 (81.3)	35 (83.3)	0.547	26 (78.8)	0.289	18 (72)	0.433
White study participants, no. (%)	409 (91.9)	39 (92.8)	0.711	30 (90.9)	0.381	23 (92)	0.793
Age (years), mean (SD)	52.5 (20.2)	58.6 (19.6)	0.041	54.2 (21.3)	0.813	55.8 (18.4)	0.113
HIV transmission risk category, no. (%):							
IDU	83 (18.6)	8 (19)	0.409	6 (18.2)	0.829	4 (16)	0.298
MSM	209 (47)	19 (45.2)	0.288	16 (48.5)	0.549	10 (40)	0.581
Heterosexual	153 (34.4)	15 (35.7)	0.276	11 (33.3)	0.507	11 (44)	0.433
$CD4^+$ cell count nadir (cells/μl), mean (SD)	166 (93)	145 (88)	0.092	172 (102)	0.287	139 (83)	0.177
Current $CD4^+$ lymphocyte count (cells/ μl), mean (SD)	566 (213)	532 (209)	0.184	578 (234)	0.273	547 (233)	0.388
Duration of HIV infection (years), mean (SD)	16.2 (7.6)	17.5 (8.4)	0.481	15.8 (7.9)	0.499	14.9 (7.5)	0.083
Duration of current ART (years), mean (SD)	4.8 (2.6)	4.6 (2.9)	0.717	4.4 (2.5)	0.606	4.7 (2.1)	0.277
Cumulative exposure to ART (years), mean (SD)	14.7 (8.6)	13.6 (7.8)	0.183	14.3 (9.1)	0.422	15.3 (9.3)	0.188
Patients with HIV RNA < 50 copies/ml, no. (%)	426 (95.7)	40 (95.2)	0.691	29 (87.9)	0.726	21 (84)	0.083
Patients with chronic hepatitis C, no (%)	46 (10.3)	6 (14.3)	0.109	5 (15.1)	0.091	4 (16)	0.288
Patients with chronic hepatitis B, no (%)	9 (2)	2 (4.8)	0.512	2 (6.1)	0.106	1 (4)	0.466
Total cholesterol (mg/dl), mean (SD)	221 (58)	217 (62)	0.692	235 (49)	0.199	229 (41)	0.177
LDL cholesterol (mg/dl), mean (SD)	153 (30)	146 (34)	0.503	148 (37)	0.419	155 (36)	0.312
HDL cholesterol (mg/dl), mean (SD)	44 (12)	42 (14)	0.913	43 (16)	0.287	46 (17)	0.819
Triglycerides (mg/dl), mean (SD)	245 (102)	234 (87)	0.482	239 (92)	0.622	248 (110)	0.552
Creatinine (mg/dl), mean (SD)	1.02 (0.48)	1.03 (0.41)	0.874	0.97 (0.44)	0.307	0.95 (0.41)	0.589
Phosphorus (mg/dl), mean (SD)	3.4 (1.4)	3.1 (1.1)	0.372	3.5 (1.6)	0.842	3.3 (1.7)	0.713
Calcium (mg/dl), mean (SD)	9.3 (3.7)	9.1 (3.8)	0.388	8.8 (3.6)	0.378	8.9 (4.2)	0.377
CK (U/l), mean (SD)	88 (36)	92 (46)	0.077	97 (41)	0.114	92 (49)	0.471
25-hydroxyvitamin D (ng/ml), mean (SD)	32.1 (14.9)	19.4 (9.6)	0.017	25.6 (13.7)	0.085	22.8 (15.4)	0.024
Parathormone (pg/ml), mean (SD)	39.4 (21.3)	32.6 (17.8)	0.611	44.2 (23.4)	0.276	45.3 (24.1)	0.081
Total duration of statin therapy (months), mean (SD)	27.2 (11.2)	36.7 (18.9)	0.006	26.4 (10.7)	0.078	29.2 (12.3)	0.085

P values concern comparison between patients without muscle toxicity and each other group. ART, antiretroviral therapy; CK, creatine kinase; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

creatine kinase elevation and in those who did not (Fig. 1).

The vitamin D level was also measured within the same month as myalgia occurred in 27 out of 42 patients (64.3%) and this mean concentration ± SD was similar to the baseline mean concentration ± SD reported in this group (20.3 ± 8.6 vs. 19.4 ± 9.6 ng/ml; $P = 0.712$). Among patients with creatine kinase elevation and myalgia the vitamin D level was also measured within the same month as toxicity occurred in 13 out of 25 patients (52%) and this mean concentration ± SD was similar to the baseline mean concentration ± SD reported in this group (21.6 ± 11.8 vs. 22.8 ± 15.4 ng/ml; $P = 0.507$). So the baseline vitamin D deficiency is usually predictive of a persistent vitamin D deficiency at the moment of muscle toxicity occurrence.

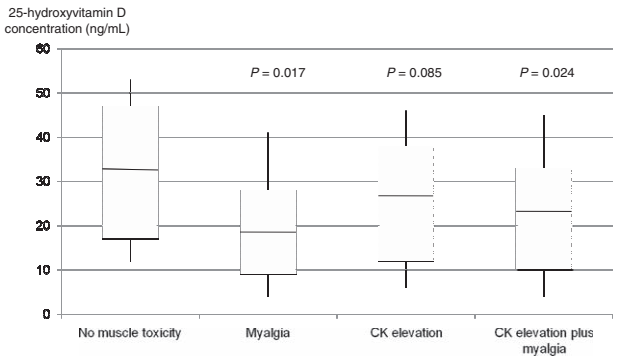

Fig. 1. Vitamin D levels in the study groups. Box plot showing mean values of 25-hydroxyvitamin D serum concentration in patients with and without muscle toxicity (*P* values concern comparison between patients without muscle toxicity and each other groups. CK, creatine kinase.

The mean duration of statin therapy was significantly higher in patients who developed myalgia than in those who did not develop myalgia (36.7 vs. 27.2 months; $P = 0.006$), whereas it was similar in patients who developed creatine kinase elevation or creatine kinase elevation and myalgia and in those who did not experience muscle toxicity (Table 1).

The prevalence of comorbidities was similar between persons who developed muscle toxicity and those who did not with the exception of history of myalgia. In fact, a history of muscle pain was reported in a significantly higher percentage of cases among patients who experienced myalgia (69%) and creatine kinase elevation and myalgia (44%) than in those who tolerated the statin treatment (11%; $P = 0.022$ and 0.037, respectively). On the contrary, the prevalence of this condition was similar in patients who developed isolated creatine kinase elevation and in those who did not experience muscle toxicity (Table 2).

Table 2. Concomitant comorbidities of the 545 patients enrolled in the study depending on the development of muscle toxicity.

	No muscle toxicity	Myalgia	*P* value	CK elevation	*P* value	CK elevation and myalgia	*P* value
No. of patients	445	42		33		25	
Diabetes mellitus, no. (%)	36 (8.1)	3 (7.1)	0.647	4 (12.1)	0.287	3 (12)	0.807
Hypothyroidism, no. (%)	31 (6.9)	1 (2.4)	0.064	3 (9.1)	0.188	1 (4)	0.532
Renal disease, no (%)	19 (4.3)	1 (2.4)	0.509	2 (6.1)	0.271	0	
Hepatic disease, no. (%)	25 (5.6)	3 (7.1)	0.449	3 (9.1)	0.617	1 (4)	0.098
Alcoholism, no. (%)	41 (9.2)	2 (4.8)	0.058	2 (6.1)	0.156	2 (8)	0.072
Intravenous drug dependence, no. (%)	7 (1.6)	1 (2.4)	0.913	0		0	
History of myalgia, no. (%)	49 (11)	29 (69)	0.022	7 (21.2)	0.068	11 (44)	0.037

CK, creatine kinase.

Among concomitant medications with potential pharmacokinetic interactions with statins, the most frequent was a ritonavir-boosted protease inhibitor, which was taken by 466 patients (85.5%). However, the prevalence of concomitant protease inhibitor-based cART was similar among study participants who developed muscle toxicity (82%) and those who did not develop this adverse event (86.3%; $P = 0.139$). The frequency of other concomitant therapies with potential drug–drug interactions was also similar among study participants with muscle toxicity and those without this adverse event (Table 3).

So in the comparison between HIV-infected patients with myalgia and those with no muscle toxicity, the bivariate analysis found statistically significant differences in age, 25-hydroxyvitamin D level, duration of statin therapy, and history of myalgia. In the comparison between HIV-infected patients with creatine kinase elevation and myalgia and those with no muscle toxicity, the bivariate analysis found statistically significant differences in 25-hydroxyvitamin D level and history of myalgia. In the comparison between HIV-infected patients with isolated creatine kinase elevation and those with no muscle toxicity, the bivariate analysis did not find statistically significant differences.

The variables found to be significant in the bivariate analysis (age, 25-hydroxyvitamin D level, duration of statin therapy, and history of myalgia) were included in a multivariate logistic regression analysis to assess their effect on the occurrence of myalgia and creatine kinase elevation and myalgia.

Factors significantly associated with the occurrence of muscle toxicity by the multivariate logistic regression analysis are listed in Table 4. Older patients (age ≥ 60 years), patients with history of myalgia, patients with a low baseline serum concentration of 25-hydroxyvitamin D (<30 ng/ml), and patients with a long duration of statin treatment (>24 months) were significantly more likely to develop myalgia while taking atorvastatin or rosuvastatin in association with cART (Fig. 2). At the same time, patients with history of myalgia and patients with a low baseline serum concentration of 25-hydroxyvitamin D (<30 ng/ml) were significantly more likely to develop creatine kinase elevation and myalgia while taking atorvastatin or rosuvastatin in association with cART. There were no factors significantly associated with the occurrence of isolated creatine kinase elevation.

The adherence to the statin treatment was high in all groups and comparable between patients with muscle

Table 3. Concomitant therapies of the 545 patients enrolled in the study depending on the development of muscle toxicity.

	No muscle toxicity	Myalgia	*P* value	CK elevation	*P* value	CK elevation and myalgia	*P* value
No. of patients	445	42		33		25	
Atorvastatin, no. (%)	241 (54.1)	29 (69)	0.208	20 (60.6)	0.175	14 (56)	0.062
Rosuvastatin, no. (%)	204 (45.9)	13 (31)	0.058	13 (39.4)	0.391	11 (44)	0.672
NNRTIs, no. (%)	47 (10.6)	5 (11.9)	0.344	4 (12.1)	0.842	4 (16)	0.408
PIs, no. (%)	384 (86.3)	36 (85.7)	0.721	27 (81.8)	0.287	19 (76)	0.471
Fibrates, no. (%)	6 (1.3)	0	0.933	0	0.503	0	0.388
Calcium channel blockers, no. (%)	49 (11)	3 (7.1)	0.077	5 (15.1)	0.068	4 (16)	0.149
Amiodarone, no. (%)	8 (1.8)	0	0.663	1 (3)	0.269	0	0.581
Digoxin, no. (%)	5 (1.1)	0	0.822	0	0.571	1 (4)	0.088
Macrolides, no. (%)	17 (3.8)	1 (2.4)	0.066	0	0.881	1 (4)	0.305
Ketoconazole, no. (%)	2 (0.4)	0	0.771	0	0.709	0	0.328
Rifampin, no. (%)	4 (0.8)	0	0.419	0	0.381	1 (4)	0.118
Colchicine, no. (%)	2 (0.4)	0	0.318	0	0.179	0	0.271
Nefazodone, no. (%)	2 (0.4)	0	0.248	0	0.617	1 (4)	0.447

CK, creatine kinase; NNRTIs, nonnucleoside reverse transcriptase inhibitors; PIs, ritonavir-boosted protease inhibitors.

Table 4. Multivariate logistic regression analysis assessing predictors of muscle toxicity.

Variables	Myalgia *P* value	CK elevation *P* value	CK elevation and myalgia *P* value
Age ≥ 60 years	0.032	0.068	0.092
History of myalgia	0.014	0.173	0.039
25-hydroxyvitamin D level < 30 ng/ml	0.009	0.155	0.046
Duration of statin therapy >24 months	0.025	0.208	0.311
Chronic hepatitis C	0.187	0.059	0.222
Concomitant therapy with PIs	0.088	0.068	0.183
Concomitant therapy with NNRTIs	0.106	0.215	0.481
Concomitant therapy with CCB	0.429	0.444	0.239

CCB, calcium channel blockers; CK, creatine kinase; NNRTIs, non-nucleoside reverse transcriptase inhibitors; PIs, ritonavir-boosted protease inhibitors.

toxicity and those without muscle toxicity. The percentage of patients with adherence at least 90% was 398 out of 445 (89.4%) among patients with no muscle toxicity, 37 out of 42 (88.1%) among those with myalgia ($P = 0.288$), 29 out of 33 (87.8%) among those with creatine kinase elevation ($P = 0.468$), and 20 out of 25 (80%) among those with creatine kinase elevation and myalgia ($P = 0.197$).

Discussion

The correlation between low serum 25-hydroxyvitamin D concentration and statin-induced musculoskeletal pain is debated still today, but it was proved by several observational cohort studies performed in the general population.

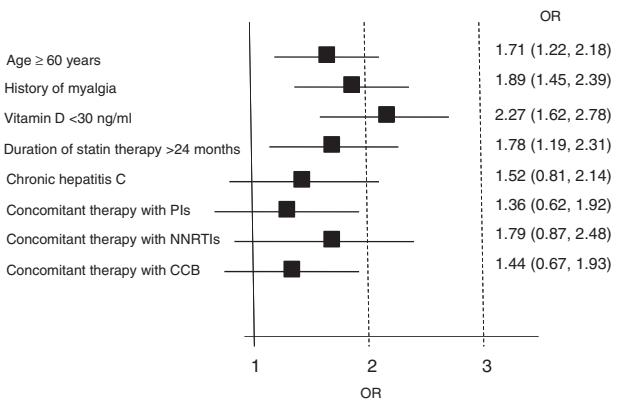

Fig. 2. Correlation between risk factors and occurrence of myalgia. Forest plot image showing predictors of myalgia. CCB, calcium channel blockers; OR, odd ratio; PI, protease inhibitor; NNRTIs, nonnucleoside reverse transcriptase inhibitors.

A cross-sectional study using the National Health and Nutrition Examination Survey between 2001 and 2004 evaluated the incidence of musculoskeletal symptoms and the vitamin D status in 5907 patients older than 40 years and treated with statins. Among study participants with low 25-hydroxyvitamin D level (<15 ng/ml) and using a statin there was a nearly two times higher risk of reporting musculoskeletal pain compared with nonstatin users [21]. Similarly, in a retrospective observational analysis including 20 women with prior myalgia-related statin intolerance, serum vitamin D levels were significantly lower in those who remained on alternative daily dosing compared with those who were tolerant of daily dosing [22].

A retrospective analysis of 450 patients who were prescribed high-dose simvastatin (80 mg daily) between 2006 and 2011 evaluated the correlation between serum vitamin D level and incidence of myalgia, myopathy, and rhabdomyolysis. The occurrence of myalgia was reported by 50 study participants (11.1%), whereas one patient developed rhabdomyolysis (0.22%). Factors significantly associated with the occurrence of myalgia were low vitamin D level, younger age, and history of muscle pain. The mean (SD) vitamin D concentration was 26.2 (12.9) ng/ml in patients experiencing myalgia vs. 36.3 (11.8) ng/ml in those who tolerated high-dose sinvastatin, while duration of statin therapy was not associated with the development of muscle pain [23].

Another retrospective cohort study assessed 1160 patients treated with statins out of 5526 consecutive study participants of a primary care outpatient clinic. Over a median follow-up period of 4.2 years, the incidence of statin-induced myalgia was 24% and the unadjusted cumulative incidence of this adverse event across quartile 1–4 of vitamin D concentration was 30.1, 24.5, 17.5, and 12.9%, respectively. After adjustment, the association of vitamin D level and myalgia was confirmed and a vitamin D concentration 15 ng/ml or less had a high predictive value for statin-induced muscular pain (positive predictive value of 81% and negative predictive value of 90%). Moreover, cut off 15 ng/ml or less showed a better predictive accuracy for myalgia when compared with cut off 5 ng/mL or less [24].

The association of low vitamin D levels with statin-induced myalgia in general population was also confirmed by a recent meta-analysis based on an electronic search yielding 437 articles, which investigated the effect of vitamin D levels in statin-treated patients. This final analysis included seven observational studies with 2420 patients divided into two subgroups: those with myalgia (666 study participants) and those asymptomatic (1754 study participants). Plasma vitamin D concentration ± SD was significantly lower in the symptomatic subgroup (28.4 ± 13.8 ng/ml) than in the asymptomatic one (34.86 ± 11.63 ng/ml). The pooled difference was found to be robust in the leave-one-out sensitivity analysis,

confirming the significant difference between the evaluated groups [25].

The pathogenetic mechanism leading to a more frequent occurrence of myositis and myalgia in patients treated with statins and with a low vitamin D concentration is debated still today. The vitamin D receptor is present in skeletal muscle; the vitamin D has several physiologic functions in muscle and its deficiency is known to cause myopathy and myalgia. So, the occurrence of muscle pain in the hypercholesterolemic, statin-treated patients with concurrent vitamin D deficiency could reflect a reversible interaction between vitamin D deficiency and statins on skeletal muscle. As a consequence, the supplementation with oral vitamin D2 and the normalization of serum vitamin D levels would result in myalgia improvement or resolution and statin tolerance [26,27].

The favorable effect of the vitamin D supplementation on the statin intolerance represented by muscle pain was evaluated by an observational, prospective study including 150 patients unable to tolerate one or more statins because of myositis or myalgia and with low serum concentration of vitamin D (<32 ng/ml). After 3 weeks of vitamin D supplementation (50 000 units twice a week) without statins, statins were restarted. After a median follow-up of 8.1 months, the serum vitamin D level normalized in the 78% of patients and the 87% of study participants were free of myositis/myalgia and tolerated the statins well [28].

Another observational study assessed 146 patients intolerant to two or more statins because of myalgia or myopathy and found to have a low serum vitamin D concentration (<32 ng/ml). The enrolled patients were treated with a vitamin D2 supplementation (50 000 to 100 000 units a week) and followed up for 24 months. The median vitamin D level rose from 23 to 55 ng/ml after a 24-month follow-up and the serum concentration normalized in 91% of the enrolled patients. On rechallenge with statins while on vitamin D supplementation, after 24 months 95% of the previously statin-intolerant study participants were free of myalgia and myopathy, so the muscle toxicity was safely resolved by the vitamin D supplementation [29].

However, other authors argue that this association has not been clearly demonstrated. In their opinion, given the quality and paucity of the observational studies examining this association, it seems to be premature at the moment to recommend vitamin D supplementation as treatment for the statin-induced myalgia, except those with a proven vitamin D deficiency [30].

The prescription of statins is increasing in recent years among HIV-infected patients, but the choice of the lipid-lowering drug is complicated owing to the reduced efficacy and the increased risk of toxicity showed in this population. Particularly, the higher risk of adverse events of statins in HIV-positive people treated with cART is associated with the potential pharmacokinetic interactions with some antiretroviral agents, such as protease inhibitors, leading to a higher plasma exposure to several statins [31,32]. Moreover, the high prevalence of hypovitaminosis D reported in HIV-infected patients [33] could favor the occurrence of myalgia and intolerance during the statin treatment, but at the moment there are no data about the potential correlation between vitamin D deficiency and statin-induced myalgia in HIV-infected people.

Our retrospective, cohort study is the first study evaluating the correlation between statin-induced myalgia and low vitamin D concentration among study participants with HIV infection and receiving cART, to the best of our knowledge. In our work, the mean serum level of 25-hydroxyvitamin D was significantly lower in study participants with myalgia and with creatine kinase elevation and myalgia than in those without muscle toxicity. Moreover, in stratified multivariable-adjusted logistic regression models, there was a statistically significant association between vitamin D deficiency and the development of myalgia or creatine kinase elevation and myalgia. Therefore, the evaluation of serum vitamin D level is recommended in HIV-infected patients on cART with myalgia during a statin therapy, and the vitamin D supplementation could increase the statin tolerability in these study participants.

Obviously, there are several limitations to our study. First, the retrospective, observational design and the short observation period may have limited the accuracy of the analysis. Second, the patient population was predominantly men, whereas myopathy and myalgia are thought to be more frequent among women [34]. Third, the concomitant cART is not the same, and this difference could certainly influence the drug–drug interactions with statins. Fourth, only two statins (atorvastatin and rosuvastatin) were analyzed, and the role of other statins was not assessed. Finally, there is not a pharmacokinetic analysis assessing the plasma drug concentrations of statins which is usually associated with the risk of toxicity.

To conclude, low vitamin D levels seem to be associated with the development of statin-induced myalgia in HIV-infected patients under cART like in the general population, but additional, enlarged, and controlled studies are needed to examine the potential role of vitamin D deficiency in the reduced statin tolerance by HIV-infected people.

Acknowledgements

L.C. analyzed the data, wrote the article, and checked the final version of the article. E. M., V. C., M. B., I. C., and I.

B. contributed in the data collection and analysis. M.C. R. and P. V. revised the final version of the study.

Conflicts of interest

L.C. has received research grants from ViiV and Gilead, and has received honoraria for consulting (as advisory board member) and speaking from Janssen, Merck, and Bristol-Myers Squibb.

There are no conflicts of interest.

References

1. Palella FJ, Baker RK, Moorman AC, Chmiel JS, Wood KC, Brooks JT, Holmberg SD, HIV Outpatient Study Investigators. **Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study.** *J Acquir Immune Defic Syndr* 2006; **43**:27–34.
2. Carr A, Samaras K, Burton S, Law M, Freund J, Chisholm DJ, Cooper DA. **A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors.** *AIDS* 1998; **12**:F51–F58.
3. Penzak SR, Chuck SK. **Hyperlipidemia associated with HIV protease inhibitor use: pathophysiology, prevalence, risk factors and treatment.** *Scand J Infect Dis* 2000; **32**:111–123.
4. Oh J, Hegele RA. **HIV-associated dyslipidaemia: pathogenesis and treatment.** *Lancet Infect Dis* 2007; **7**:787–796.
5. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, *et al*. **2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines.** *Circulation* 2014; **129 (25 Suppl 2)**:S1–S45.
6. Calza L, Manfredi R, Colangeli V, Pocaterra D, Pavoni M, Chiodo F. **Rosuvastatin, pravastatin, and atorvastatin for the treatment of hypercholesterolaemia in HIV-infected patients receiving protease inhibitors.** *Curr HIV Res* 2008; **6**:572–578.
7. Aslangul E, Assoumou L, Bittar R, Valantin MA, Kalmykova O, Peytavin G, *et al*. **Rosuvastatin versus pravastatin in dyslipidemic HIV-1-infected patients receiving protease inhibitors: a randomized trial.** *AIDS* 2010; **24**:77–83.
8. Singh S, Willig JH, Mugavero MJ, Crane PK, Harrington RD, Knopp RH, *et al*. **Comparative effectiveness and toxicity of statins among HIV-infected patients.** *Clin Infect Dis* 2011; **52**:387–395.
9. Ganesan A, Crum-Cianflone N, Higgins J, Qin J, Rehm C, Metcalf J, *et al*. **High dose atorvastatin decreases cellular markers of immune activation without affecting HIV-1 RNA levels: results of a double-blind randomized placebo controlled clinical trial.** *J Infect Dis* 2011; **203**:756–764.
10. Aslangul E, Fellahi S, Assoumou LK, Bastard JP, Capeau J, Costagliola D. **High-sensitivity C-reactive protein levels fall during statin therapy in HIV-infected patients receiving ritonavir-boosted protease inhibitors.** *AIDS* 2011; **25**:1128–1131.
11. Calza L, Trapani F, Bartoletti M, Manfredi R, Colangeli V, Borderi M, *et al*. **Statin therapy decreases serum levels of high-sensitivity C-reactive protein and tumor necrosis factor-α in HIV-infected patients treated with ritonavir-boosted protease inhibitors.** *HIV Clin Trials* 2012; **13**:153–161.
12. Calza L, Colangeli V, Magistrelli E, Contadini I, Bon I, Re MC, *et al*. **Significant decrease in plasma levels of D-dimer, interleukin-8, and interleukin-12 after a 12-month treatment with rosuvastatin in HIV-infected patients under antiretroviral therapy.** *AIDS Res Hum Retroviruses* 2016[Epub ahed of print].
13. Ganga HV, Slim HB, Thompson PD. **A systematic review of statin-induced muscle problems in clinical trials.** *Am Heart J* 2014; **168**:6–15.
14. Lee P. **Vitamin D insufficiency: a novel mechanism of statin induced myalgia.** *Clin Endocrinol (Oxf)* 2009; **71**:154–155.
15. Ahmed W, Khan N, Glueck CJ, Pandey S, Wang P, Goldenberg N, *et al*. **Low serum 25 (OH) vitamin D levels (<32 ng/ml) are associated with reversible myositis-myalgia in statin-treated patients.** *Transl Res* 2009; **153**:11–16.
16. Kurnik D, Hochman I, Vesterman-Landes J, Kenig T, Katzir I, LomnickyY, *et al*. **Muscle pain and serum creatine kinase are not associated with low serum 25(OH) vitamin D levels in patients receiving statins.** *Clin Endocrinol (Oxf)* 2012; **77**:36–41.
17. Dao CN, Patel P, Overton ET, Rhame F, Pals SL, Johnson C, *et al*. **Low vitamin D among HIV-infected adults: prevalence of and risk factors for low vitamin D Levels in a cohort of HIV-infected adults and comparison to prevalence among adults in the US general population.** *Clin Infect Dis* 2011; **52**:396–405.
18. Lambert AA, Drummond MB, Mehta SH, Brown TT, Lucas GM, Kirk GD, *et al*. **Risk factors for vitamin D deficiency among HIV-infected and uninfected injection drug users.** *PLoS One* 2014; **9**:e95802.
19. Zhang L, Tin A, Brown T, Margolick JB, Witt MD, Palella FJ, *et al*. **Vitamin D deficiency and metabolism in HIV-infected and -uninfected Men in the Multicenter AIDS Cohort Study (MACS).** *AIDS Res Hum Retroviruses* 2016[Epub ahead of print].
20. Pasternak RC, Smith SC Jr, Bairey-Merz CN, Grundy SM, Cleeman JI, Lenfant C, American College of Cardiology; American Heart Association; National Heart, Lung and Blood Institute. **ACC/AHA/NHLBI Clinical advisory on the use and safety of statins.** *Stroke* 2002; **33**:2337–2341.
21. Morioka TY, Lee AJ, Bertisch S, Buettner C. **Vitamin D status modifies the association between statin use and musculoskeletal pain: a population based study.** *Atherosclerosis* 2015; **238**:77–82.
22. Minissian M, Agarwal M, Shufelt C, Metha PK, Waldman T, Lentz G, *et al*. **Do women with statin-related myalgias have low vitamin D levels?** *BMC Res Notes* 2015; **8**:449.
23. Mergenhagen K, Ott M, Heckman K, Rubin LM, Kellick K. **Low vitamin D as a risk factor for the development of myalgia in patients taking high-dose simvastatin: a retrospective review.** *Clin Ther* 2014; **36**:770–777.
24. Palamaner Subash Shantha G, Ramos J, Thomas-Hemak L, Pancholy SB. **Association of vitamin D and incident statin induced myalgia: a retrospective cohort study.** *PLoS One* 2014; **9**:e88877.
25. Michalska-Kasiczak M, Sahebkar A, Mikhailidis DP, Rysz J, Muntner P, Toth PP, *et al*., Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group. **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.** *Int J Cardiol* 2015; **178**:111–116.
26. Glueck CJ, Abuchaibe C, Wang P. **Symptomatic myositis-myalgia in hypercholesterolemic statin-treated patients with concurrent vitamin D deficiency leading to statin intolerance may reflect a reversible interaction between vitamin D deficiency and statins on skeletal muscle.** *Med Hypotheses* 2011; **77**:658–661.
27. Linde R, Peng L, Desai M, Feldman D. **The role of vitamin D and SLCO1B1*5 gene polymorphism in statin-associated myalgias.** *Dermatoendocrinol* 2010; **2**:77–84.
28. Glueck CJ, Budhani SB, Masineni SS, Abuchaibe C, Khan N, Wang P, Goldenberg N. **Vitamin D deficiency, myositis-myalgia, and reversible statin intolerance.** *Curr Med Res Opin* 2011; **27**:1683–1690.
29. Khayznikov M, Hemachrandra K, Pandit R, Kumar A, Wang P, Glueck CJ. **Statin intolerance because of myalgia, myositis, myopathy, or myonecrosis can in most cases be safely resolved by vitamin D supplementation.** *N Am J Med Sci* 2015; **7**:86–93.
30. Gupta A, Thompson PD. **The relationship of vitamin D deficiency to statin myopathy.** *Atherosclerosis* 2011; **215**:23–29.
31. De Socio GV, Ricci E, Parruti G, Calza L, Maggi P, Celesia BM, *et al*. **Statins and aspirin use in HIV-infected people: gap between European AIDS Clinical Society guidelines and clinical practice: the results from HIV-HY study.** *Infection* 2016; **44**:589–597.
32. Calza L, Colangeli V, Manfredi R, Bon I, Re MC, Viale P. **Clinical management of dyslipidaemia associated with combination antiretroviral therapy in HIV-infected patients.** *J Antimicrob Chemother* 2016; **71**:1451–1465.
33. Mansueto P, Seidita A, Vitale G, Gangemi S, Iaria C, Cascio A. **Vitamin D deficiency in HIV infection: not only a bone disorder.** *Biomed Res Int* 2015; **2015**:735615.
34. Fernandez G, Spatz ES, Jablecki C, Phillips PS. **Statin myopathy: a common dilemma not reflected in clinical trials.** *Cleve Clin J Med* 2011; **78**:393–403.