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Should high creatine kinase discourage the initiation or continuance of statins for the treatment of hypercholesterolemia?

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Abstract

Patients with high low-density lipoprotein cholesterol (LDLC) and asymptomatic high creatine kinase (CK) (≥250 but <2500 IU/L, 10× the laboratory upper normal limit [UNL]) are often not started on statins or have statins stopped because of concern about myositis-rhabdomyolysis. In the current report, we prospectively examined the hypothesis that asymptomatic patients with high CK (≥250 but <2500 IU/L) tolerate statins well at doses reducing LDLC to target, less than 100 mg/dL, without development of myalgia-myositis. We assessed outcomes of 3 groups of patients referred to us because of asymptomatic high CK (≥250 but <2500 IU/L)—1 group (n = 29) on statins at referral and continued on statins, 1 group (n = 20) not on statins and started on statins, and 1 group (n = 19) not on statins and not given statins—all restudied 1 month after entry and then every 3 months. Of the 68 patients, 59 (87%) had CK greater than 1 to 3 times the UNL, 7 (10%) had CK greater than 3 to 5 times the UNL, and 2 (3%) had CK greater than 5 to 10 times the UNL. After 1.2 months of follow-up in 29 statin→statin patients, median CK fell from 353 to 301 (P = .0018) and was 287 (P = .015) after 4 months. After 1.3 months of follow-up in 20 no statin→statin patients, median CK fell from 397 to 292 (P = .0094) and was 419 after 4.1 months. After 1.1 months of follow-up in 19 no statin→no statin patients, median CK fell from 392 to 323 (P = .14) and was 271 (P = .029) after 4.2 months. By repeated-measures analysis, there were no differences in entry CK among the 3 treatment groups; CK fell (P = .04) in the no statin→no statin patients. Despite high baseline CK (48 patients with CK 1-5× the UNL, 1 with CK 5-10× UNL), no patients during follow-up on statins developed CK greater than 10 times the UNL (2500 IU/L), none discontinued statins or reduced statin dose because of myalgia-myositis, and there was no rhabdomyolysis. High pretreatment CK, particularly 1 to 5 times the UNL, should not be an impediment to start or continue statins to lower LDLC.

1. Introduction

Patients with high low-density lipoprotein cholesterol (LDLC) who are found to have asymptomatic creatine kinase (CK) levels greater than 250 IU/L (the laboratory upper normal limit [UNL]) but less than 10 times [1] the UNL (2500 IU/L) are often not started on statins or have their statins stopped by their physicians [1-3] because of concern about symptomatic myositis or rhabdomyolysis. Creatine kinase levels depend in part on age, sex, race, muscle mass, and physical activity [4]. Lovastatin may increase exercise-induced skeletal muscle injury [5]; but using the downhill walking model, CK levels did not differ between subjects receiving atorvastatin 10 or 80 mg [6].

Brewster et al [2] recently noted that "eligible subjects with mildly elevated serum CK activity are often excluded before randomization in statin trials, but patients may potentially be misclassified as having hyperCKemia when inappropriate reference limits are used." In a stratified random sample of the Netherlands population, the calculated upper reference limits for CK (97.5th percentile) for nonblack and black women and men were 2 to 5 times higher than those recommended by the assay manufacturer [2]. Brewster et al [2] reported that 13% of white Europeans, 23% of South Asians, and 49% of black people had serum CK activities greater than the manufacturer-provided limits. Brewster et al [2] concluded that "… upward adjustment of the upper reference limit is necessary for all population

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subgroups studied. The use of appropriately established reference intervals may improve the use of statins and particularly benefit the control of dyslipidemia in those with relatively high baseline CK activity."

Myalgia–mild myositis is a common clinical complaint in patients receiving statin monotherapy [3,7,8] or in patients on combined fibric acids and statins [9]. In the observational Prediction of Muscular Risk in Observational Conditions (PRIMO) study of 7924 patients receiving high-dosage statin therapy in a usual care French outpatient setting, muscular symptoms were reported by 832 patients (10.5%), with a median time of onset of 1 month after starting statins [10]. More severe than myositis, myopathy with CK at least 10 times the laboratory UNL, although uncommon, is significantly associated with statin monotherapy [7]. When CK is more than 10 times the UNL, particularly if myalgia-myositis symptoms are present, statins are commonly stopped [1,3]. Rosuvastatin for up to 52 weeks was rarely (≤0.1% of patients) associated with treatment-related myopathy with CK at least 10 times the UNL; asymptomatic CK levels of at least 2500 IU/L were observed in 0.2% to 0.4% of patients [11]. In studies of 10 to 80 mg atorvastatin, including 9416 patients, the incidence of treatment-associated myalgia was 1.9% and was not related to the atorvastatin dose; CK greater than 2500 IU/L was observed in only 1 patient and was not associated with myopathy [12]. Myositis rates with statin monotherapy have been reported to be 33 per 100 000 person-years, with mean time to event of 2 years [7]. In an assessment of 32,225 diabetic and nondiabetic patients, Nichols and Koro [13] reported that 95% of statin-associated events were myalgia–mild myositis. The National Lipid Association Statin Safety Task Force report [3], in reviewing CK levels and statin use, concluded that "… patients with tolerable muscle complaints, or who are asymptomatic with a CK <10 times ULN [upper limit of normal], may continue statin therapy at the same or reduced doses."

In the current report, we examined the hypothesis that asymptomatic patients with high CK (≥250 but <2500 IU/L, >1× but <10× UNL) tolerate statins well at doses reducing LDLC to target, less than 100 mg/dL, without development of myalgia-myositis. We prospectively assessed outcomes of 3 groups of patients referred to us because of asymptomatic high CK (≥250 but <2500 IU/L): 1 group (n = 29) on statins at referral and continued on statins, 1 group (n = 20) not on statins and started on statins, and 1 group (n = 19) not on statins and not given statins.

2. Patients and methods

2.1. Study design

2.1.1. Patients

Approval to analyze data prospectively collected as part of our routine clinical cholesterol management program was given by the Jewish Hospital Institutional Review Board. All patients referred to the Jewish Hospital Cholesterol Center for diagnosis and management of hyperlipidemia have routine measurement of CK and blood lipids at their initial visit, first follow-up visit 1 month later, and second follow-up visit 3 months later. All patients also have routine measurement of thyroxine (T4) and thyroid-stimulating hormone (TSH) at their initial visit. In the current observational study, we prospectively assessed outcomes of 3 groups of patients referred to us because of asymptomatic high CK (≥250 but <2500, >1× but <10× UNL): 1 group (n = 29) on statins and continued on statins (statin→statin), 1 group (n = 20) not on statins and started on statins (no statin→statin), and 1 predominantly hypertriglyceridemic group (n = 19) not on statins and not given statins (no statin→no statin) (Tables 1-3). At each visit, use and dose of statins (Table 1) or other lipid-lowering therapy were documented by investigators. Patients with high entry CK (Tables 1-3) were included in the data set in the temporal order of their referral, without any known selection bias.

2.2. Cases

During the past 5 years, at their initial, entry visit, CK was measured in 1692 patients consecutively referred to our Cholesterol Center for diagnosis and treatment of hyperlipidemia. No patients with a previous history of myalgia associated with statin use were excluded. Of these 1692 patients, 201 (12%) had high baseline CK (≥250 but <2500 IU/L) and, at study entry, were asymptomatic without myalgia-myositis. Of these 201 patients, 68 had completed at least 2 sequential follow-up visits (1 month, 4 months after entry) in our center; and these 68 patients were the focus of the current study. At the initial visit, a detailed history was taken of previous and current statin (Table 1) and other lipid-lowering drug use; and their medication was recorded at each subsequent visit. After an overnight fast, blood was drawn for measurement of plasma cholesterol, triglyceride, LDLC, and high-density lipoprotein cholesterol, along with CK, glucose, insulin, renal, thyroid, and liver function tests. Patients were scheduled to return for reevaluation 1 month

Table 1
Statin use at study entry, at first follow-up on statins (1.1-1.3 months later), and at second follow-up on statins (4.1-4.2 months later)

	Rosuvastatin	Atorvastatin	Simvastatin	Lovastatin	Pravastatin	Fluvastatin	Any statins
29 Patients had statins at baseline	11 (38%)	10 (34%)	5 (17%)	1 (3%)	2 (7%)	1 (3%)	29 (100%)
At 1st follow-up	17 (59%)	9 (31%)	1 (3%)	0	2 (7%)	1 (2%)	29 (100%)
At 2nd follow-up	17 (59%)	9 (31%)	1 (3%)	0	2 (7%)	1 (2%)	29 (100%)
20 Patients had no statins at baseline	—	—	—	—	—	—	—
At 1st follow-up	8 (40%)	3 (15%)	4 (20%)	0	2 (10%)	3 (15%)	20 (100%)
At 2nd follow-up	8 (40%)	3 (15%)	4 (20%)	0	2 (10%)	3 (15%)	20 (100%)

Table 2
Statin therapy in patients with high entry CK and LDLC

CK	On statin at baseline		No statin at baseline			
	Continue on statin		On statin at follow-up		No statin at follow-up	
	n	CK (IU/L)	n	CK (IU/L)	n	CK (IU/L)
At baseline	29	353 (291, 494) 83% in >1-3× UNL 14% in >3-5× UNL 3% in >5-10× UNL	20	397 (341, 531) 90% in >1-3× UNL 10% in >3-5× UNL 0% in >5-10× UNL	19	392 (299, 469) 89% in >1-3× UNL 5% in >3-5× UNL 5% in >5-10× UNL
At 1st follow-up	29	301 (160, 434)†	20	292 (234, 489)†	19	323 (205, 393) NS
Duration	29	1.2 (1.0, 1.4) mo	20	1.3 (1.0, 1.5) mo	19	1.1 (0.9, 1.3) mo
At 2nd follow-up	29	287 (184, 494)*	20	419 (317, 531) NS	19	271 (161, 419)*
Duration	29	4.2 (3.5, 4.7) mo	20	4.1 (3.6, 4.7) mo	19	4.2 (3.1, 5.1) mo

By repeated-measures analysis, there were no differences in baseline CK among 3 treatment groups ($P = .76$); CK reductions were significant on follow-up in the no statin→no statin group ($P = .039$).

LDLC	n	LDLC (mg/dL)	n	LDLC (mg/dL)	n	LDLC (mg/dL)
At baseline	27	116 (97, 152)	19	162 (148, 189)	14	127 (105, 160)
At 1st follow-up	27	77 (67, 85)§	19	94 (73, 113)§	14	127 (101, 153) NS
Duration	27	1.2 (1.0, 1.4) mo	19	1.2 (1.0, 1.4) mo	14	1.2 (0.9, 1.3) mo
At baseline	28	114 (92, 150)	19	162 (148, 189)	14	127 (105, 160)
At 2nd follow-up	28	81 (66, 105)‡	19	96 (71, 115)§	14	113 (107, 142) NS
Duration	28	4.2 (3.5, 4.7) mo	19	4.1 (3.3, 4.4) mo	14	4.2 (3.5, 5.1) mo

Data are median (interquartile range). Significance of change: NS indicates not significant, $P > .05$; *$P \le .05$; $^{\dagger}P \le .01$; $^{\ddagger}P \le .001$; $^{\S}P \le .0001$ by paired Wilcoxon test.

and 4 months after their initial visit (Tables 2,3). At every outpatient visit, patients were interviewed by the principal investigators who used the National Heart, Lung, and Blood Institute categories for clinical muscle problems: myalgia, mild myositis, severe myositis, and rhabdomyolysis [13].

Creatine kinase was measured by a kinetic 340-nm spectrophotometric method (LabCorp, Columbus/Dublin, OH).

2.3. Statistical analyses

All statistical analyses were performed using SAS (version 9.1; SAS, Cary, NC). Changes in CK (Tables 2,3) and in LDLC (Table 2) over time were compared using nonparametric paired Wilcoxon tests. The nonparametric Kruskal-Wallis test was used to compare CK levels among the 3 study groups at entry and after 1-month follow-up.

Repeated-measures analyses were carried out using the mixed model (Tables 2 and 3). Creatine kinase was the response variable, with initial CK value, treatment groups (statin→statin, no statin→statin, and no statin→no statin), and interaction of time × group as fixed effects. The classified follow-up time was an indicator of repeated measures, with AR(1) covariance structure within subject.

3. Results

Of 1692 patients studied in the temporal sequence of their referral to us for diagnosis of hyperlipidemia and lipid-lowering therapy, all having entry baseline CK measures, 201 (12%) currently asymptomatic patients had high CK (≥250 but <2500 IU/L, >1× but <10× UNL). Of these

Table 3
Long-term follow-up of 21 patients with high CK levels on statins at baseline and remaining on statins

	At baseline	1st follow-up	2nd follow-up	1-y follow-up	Last follow-up
Statin→statin group (n = 21)					
Median duration (mo)		1.2	4.3	10.7	29.5
CK (IU/L)	357 (274, 723)	241 (167, 434)	314 (186, 494)	285 (154, 506)	221 (154, 483)
P value (CK change from baseline, paired Wilcoxon test)		.008	.047	.005	.021
No statin→statin group (n = 16)					
Median duration (mo)		1.2	4.0	11.1	20.9
CK (IU/L)	402 (367, 531)	292 (234, 489)	420 (322, 531)	372 (293, 410)	328 (216, 480)
P value (CK change from baseline, paired Wilcoxon test)		.004	.93	.08	.23

Long-term follow-up of 16 patients with high CK levels, no statins at baseline, on statins throughout follow-up. CK median (interquartile range) exhibited. By repeated-measures analysis, there were no differences in baseline CK between 2 treatment groups ($P = .83$); CK reductions on follow-up were significant in the statin→statin group ($P = .03$).

201 patients with high baseline CK, 68 completed at least 2 sequential follow-up visits (1 month, 4 months after entry) in our center. There were 58 men and 10 women—51 white, 12 black, and 5 others—with ages from 23 to 82 years. At study entry, 29 patients had already been treated with a statin, which was subsequently continued (statin→statin group); 20 were not taking statins, which were subsequently started (no statin→statin group); and 19 were not taking statins, and they did not receive statins on follow-up (no statin→no statin) (Table 2).

Table 1 summarizes the distribution of statin use at study entry in 29 patients on statins at entry and on follow-up at 1 and 4 months, and in 20 patients with no statins at entry, but then placed on statins and studied during follow-up at 1 and 4 months. Rosuvastatin and atorvastatin were the most frequently used statins at the time of study entry, with an increase in rosuvastatin use as the most commonly used statin during follow-up (Table 1). Of the 29 patients in the statin→statin group, 26 had no change in statin dose on follow-up, 3 had statin doses increased, and none encountered myalgia-myositis. Of the 20 patients in the no statin→statin group, none encountered myalgia-myositis during follow-up; and none had their statin doses reduced.

Of the 68 subjects, 2 (both in the no statin→statin group) had high TSH (6.0, 7.8 mIU/L [UNL, 5.5]) at study entry, with both having normal T4 (7.0, 8.8 μg/dL [lower normal limit, 4.5]).

Creatine kinase levels at baseline and at the first follow-up, the change in CK between baseline and the first follow-up, and duration of follow-up did not differ ($P > .10$) among the 3 patient groups.

Using the 3 groups' (statin→statin, no statin→statin, and no statin→no statin) CK data at initial visit, 1-month follow-up, and 4-month follow-up, the repeated-measure models revealed no group differences in entry CK ($P = .76$); CK reduction slopes were significant only in the no statin→no statin group ($P = .039$) (Table 2).

At entry, the median (interquartile range) for CK was 353 (291-494) for the 29 statin→statin patients. Of the 29 patients in the statin→statin group, 24 (83%) had entry CK in the greater than 1 times to 3 times the UNL range, 4 (14%) had CK in the greater than 3 times to 5 times the UNL range, and 1 (3%) had CK in the greater than 5 times to 10 times the UNL range. At entry, CK was 397 (341-531) for the 20 no statin→statin patients, 18 (90%) had CK in the greater than 1 times to 3 times the UNL range, and 2 (10%) had CK in the greater than 3 times to 5 times the UNL range. At entry, CK was 392 (299-469) for the 19 no statin→no statin patients, 17 (89%) had CK in the greater than 1 times to 3 times the UNL range, 1 (5%) had CK in greater than 3 times to 5 times the UNL range, and 1 (5%) had CK in the greater than 5 times to 10 times the UNL range (Table 2). After 1-month follow-up in the 29 statin→statin patients, median CK fell from 353 to 301 ($P = .0018$), and then fell to 287 ($P = .015$, compared with study entry) at 4-month follow-up (Table 2). In the statin→statin group, entry LDLC fell from 116 to 77 mg/dL ($P < .0001$, compared with study entry, Table 2) after 1 month on statin therapy (median rosuvastatin dose, 15 mg/d; atorvastatin, 20 mg/d) and was 81 mg/dL after 4 months on therapy ($P = .0012$) (Table 2).

After 1-month follow-up in the 20 no statin→statin patients, median CK fell from 397 to 292 ($P = .0094$); and median CK was 419 after 4-month follow-up ($P = .75$, compared with study entry) (Table 2). The median LDLC fell from 162 mg/dL at study entry to 94 mg/dL after 1 month on statin therapy ($P < .0001$) (rosuvastatin, 10 mg/d) and was 96 mg/dL after 4 months on therapy ($P < .0001$) (Table 2).

After 1-month follow-up in the 19 no statin→no statin patients, median CK fell from 392 to 323 ($P = .14$), and fell to 271 ($P = .029$, compared with study entry) at 4-month follow-up (Table 2). The no statin→no statin group was predominantly hypertriglyceridemic and was treated with diet-fibric acids, without additional attempts to lower LDLC (Table 2).

Despite having high baseline CK (≥250 but <2500 IU/L) by selection, no patients in the statin→statin or no statin→statin group during 4-month follow-up developed CK more than 10 times the UNL (2500 IU/L), no patients discontinued statins because of myalgia-myositis, and there was no rhabdomyolysis.

In the statin→statin group, a subgroup of 21 patients had extended follow-up for a median of 29.5 months (Table 3). Median CK fell from 357 at entry to 241 at 1-month follow-up ($P = .008$), to 314 after 4 months ($P = .047$), to 285 after 12 months ($P = .005$), and to 221 after 29.5 months ($P = .021$) (Table 3). In the no statin→statin group, a subgroup of 16 patients had extended follow-up for a median of 20.9 months (Table 3). After 1-month follow-up, median CK fell from 402 to 292 ($P = .004$), was 420 at 4 months, 372 at 12 months, and 328 at 20.9 months (Table 3). Using these 2 groups' (statin→statin and no statin→statin) CK data at initial visit and up to 1-year follow-up (1, 4, 7, and 12 months), by repeated-measures analysis, there were no differences in initial CK levels between the 2 groups ($P = .83$); CK reduction slopes were significant in the statin→statin group ($P = .03$) (Table 3).

Despite having high baseline CK (≥250 but <2500 IU/L) by selection, no patients during 21- to 30-month follow-up on statins (Table 3) developed CK more than 10 times the UNL (2500 IU/L), none discontinued statins because of myalgia-myositis, statin doses were not reduced during follow-up, and there was no rhabdomyolysis.

4. Discussion

In the current study, 12% of patients consecutively referred for diagnosis of and therapy for hyperlipidemia had high CK (≥250 but <2500 IU/L, >1× but <10× UNL) at entry, comparable with findings in healthy Israeli men and women (19% and 4.6%) and to healthy subjects in the Netherlands where 13% of white Europeans, 23% of South

Asians, and 49% of black people had CK levels higher than the manufacturer-provided limits [2]. In agreement with Brewster et al [2] and Lev et al [14], we believe that an upward adjustment of the currently used upper reference limits for CK is necessary. Use of appropriate, upwardly adjusted CK reference intervals should improve the use of statins and particularly benefit the control of high LDLC in subjects with high baseline CK.

Beyond necessary upward adjustment of population-based reference intervals for CK [2,14], physicians need to know that even moderate exercise can substantially raise CK higher than "normal" reference intervals [15-17]. Creatine kinase levels increase substantially with duration and intensity of exercise training [18] and are increased 90-fold in ultramarathoners [19]. Moderate exercise also leads to large, delayed increases in CK [20]. Sport training and competition have profound effects on serum CK, optimally requiring sport-specific reference intervals [21].

Rarely, patients who develop muscle symptoms while receiving statin therapy have demonstrable weakness and histopathologic findings of myopathy despite normal serum CK levels. [22].

In the current study, asymptomatic patients with high CK (≥250 but <2500 IU/L) on statins and without statins at study entry had reductions in median CK after 1 month of continuing statins or initiating statins, respectively. After 4 months on statin therapy, median CK had fallen from 353 at study entry to 287 IU/L in patients whose initial statins were continued, and were not different (P = .75) from baseline (397 vs 419) in patients with no baseline statins who then started statins. Moreover, in a subgroup of 21 statin→statin patients with extended follow-up (median, 29.5 months), CK fell from 357 at entry to 221; and at 20.9-month follow-up in 16 no statin→statin patients, CK fell from 402 at entry to 328 IU/L. No patients with high CK at study entry who continued statins or started statins developed myositis or myopathy on follow-up; and none developed CK more than 10 times the UNL [1,3], a cutpoint where physicians commonly stop statins. Stable or falling CK was observed in both the statin→statin and no statin→statin groups at 1- and 4-month follow-up at statin doses that successfully reduced median LDLC to less than our target of 100 mg/dL, that is, to 81 mg/dL in the statin→statin group and to 96 mg/dL in the no statin→statin group. Creatine kinase levels were stable or decreased over time in all 3 treatment groups. One likely explanation for this fall in CK is regression to the mean [23].

Current guidelines [3] do not require checking a baseline CK in the usual patient started on a statin, unless risk factors for statin-induced myositis are present such as renal failure, concurrent use of a fibric acid, or concurrent use of drugs such as transplant rejection agents (Neoral, Novartis Pharmaceuticals, East Hanover, NJ, etc). Our current report supports that recommendation [3]. Because covert or overt hypothyroidism can promote myalgia-myositis with elevated CK in statin-treated patients [24], a baseline TSH should be obtained in all or most people started on a statin. Two of the 68 patients referred to us in the current study because of asymptomatic high CK (≥250 but <2500 IU/L) had high TSH with covert hypothyroidism (normal T4 levels).

Our study was observational, without randomization of subjects who had high CK at entry to statins or placebo. Although rosuvastatin and atorvastatin were the predominant statins at study entry and on follow-up, other statins were also used; and we cannot examine whether one statin or another is optimal in patients who present with high CK. Despite the large initial patient population, because of the lack of at least 2 completed serial follow-ups over an at least 4-month period, our 68-patient follow-up group was small for a safety study, a major limitation. Nevertheless, the current report provides at least a preliminary indication of statin safety and LDL lowering efficacy in patients with high baseline CK.

Physicians often measure CK in patients about to begin statins or already on statins. Many physicians will not start or continue statins to lower LDLC in asymptomatic patients with high CK (>250 but <2500 IU/L) because of concern about possible statin-induced myositis-rhabdomyolysis [1,3]. In our current prospective follow-up study of asymptomatic statin-treated patients (48 with entry CK 1-5× UNL, 1 with CK 5-10× UNL), no patients during follow-up on statins developed CK more than 10 times the UNL (2500 IU/L), none discontinued statins or reduced statin dose because of myalgia-myositis, and there was no rhabdomyolysis. High pretreatment CK, predominantly 1 to 5 times the UNL, as in the current report, should not be an impediment to start or continue statins to lower LDLC. In the current report, patients with CK 1 to 5 times the UNL tolerated statins very well with either significant decrements or nonsignificant changes in CK on statin therapy, without development of myositis-myalgia, at statin doses that reduce LDLC to target levels of less than 100 mg/dL.

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