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Statin-Associated Myopathy in a Pediatric Preventive Cardiology Practice

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Abstract

Objectives—To describe muscle-related statin adverse effects in real-world pediatric practice.

Study design—Using prospectively collected quality improvement data from a pediatric preventive cardiology practice, we compared serum creatine kinase (CK) levels among patients prescribed and not prescribed statins, and pre/post statin initiation. Multivariable mixed-effect models were constructed accounting for repeated measures, examining the effect of statins on log-transformed CK levels (lnCK) adjusted for age, sex, weight, season, insurance type, and race/ethnicity.

Results—Among 1,501 patients seen over 3.5 years, 474 patients (14±4 years, 47% female) had at least one serum CK measured. Median (IQR) CK levels of patients prescribed (n=188 patients, 768 CK measurements) and not prescribed statins (n=351 patients, 682 CK measurements) were 107 (83) IU/L and 113 (81) IU/L, respectively. In multivariable-adjusted models, lnCK did not differ based on statin use ($\beta=0.02$ [SE 0.05], $p=0.7$). Among patients started on statins (n=86, 130 pre-statin and 292 post-statin CK measurements), median CK levels did not differ in adjusted models (β for statin use on lnCK=0.08 [SE 0.07], $p=0.2$). There was a clinically insignificant increase in CK over time ($\beta=0.08$ [SE 0.04], $p=0.04$ per year). No muscle symptoms or rhabdomyolysis were reported among patients with high CK levels.

Conclusions—In a real-world practice, pediatric patients using statins did not experience higher CK levels, nor was there a meaningful CK increase with statin initiation. These data suggest the limited utility to checking CK in the absence of symptoms, supporting current guidelines.

Keywords

Statins; child; adolescent; creatine kinase; myopathy; lipid; cholesterol

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Statins (HMG-CoA reductase inhibitors) are recommended for children and adolescents with severe lipid disorders that are not sufficiently responsive to lifestyle modification to reduce the risk of future atherosclerotic cardiovascular disease (ASCVD) events.(1) However, the benefits of statins in high risk youth must be weighed against potential adverse effects, particularly because children who are prescribed these medicines often have a genetic hyperlipidemia, and are likely to take statins for decades. Muscle toxicity, including muscle pain (and rarely rhabdomyolysis), are the most commonly cited adverse effects of statin therapy.(2) Fear of muscle toxicity is a commonly cited reason for delaying or not initiating statin therapy, and minor muscle aches and pains may lead children and adolescents to discontinue statins. It is important to understand the extent of muscle-related adverse effects due to statins in youth to avoid inadvertent lost opportunities to reduce future ASCVD.

Muscle-related adverse effects of statins can present as asymptomatic increases in serum creatine kinase (CK), myalgia (muscle complaints without CK elevations), myositis (muscle symptoms accompanied by CK elevations), and rhabdomyolysis (muscle aches or weakness with CK levels > 10 times the upper normal limit, and evidence of renal compromise).(3, 4) In clinical trials of adult patients the incidence of myopathy with minor muscle pain, marked elevations in CK, and rhabdomyolysis are quite rare, occurring at rates of 190, 5, and 1.6 per 100,000 patient years, respectively.(5) Notable rates of myopathy in clinical practice studies in adults vary widely from 0.1% to as high as 33%, possibly do to a higher incidence of comorbidities and less frequent monitoring.(6–8) In a meta-analysis of randomized controlled trials of statins in children and adolescents with familial hyperlipidemias, no patients experienced rhabdomyolysis and rates of myopathy were low. (9) Recent trials have confirmed these findings.(10, 11) However, the incidence of statin-associated muscle toxicity in children and adolescents in clinical practice outside of controlled trials is not well described. In this review of data collected for a quality improvement project we aimed to describe CK levels and muscle-related symptoms in real-world pediatric preventive cardiology practice.

METHODS

Patient data were collected from September 2010 to March 2014 in a referral pediatric preventive cardiology clinic at Boston Children's Hospital using the Subspecialty Standardized Clinical Assessment and Management Plan (SCAMP®), a quality improvement initiative focusing on pediatric patients with lipid abnormalities. The Subspecialty Lipid SCAMP provides guidance about the evaluation and treatment of children and adolescents with lipid abnormalities, prospectively capturing clinical data and provider decision-making to iteratively improve quality of care.(12, 13) This dataset was used to describe clinical characteristics including anthropometrics, family history, medical conditions, and laboratory values. Muscle symptoms were collected, where available, from the SCAMP dataset and from the electronic medical record.

Patients were included in this analysis if they had at least one serum CK measurement, and were excluded if they had no recorded clinical data or had a condition that could affect CK

levels (chronic renal disease, childhood cancer, heart transplant or inflammatory disease). CK levels were routinely measured as recommended by the SCAMP and based on provider preference in patients prescribed statins or if providers anticipated starting statins at an upcoming visit. Patients were initially categorized into two groups: on statins (clinical and laboratory data that occurred in patients who initiated therapy before and during the data capture period), and off statins (clinical and laboratory data that occurred in patients prior to statin therapy or in patients who had CK levels drawn but were never started on statins). Patients started on statins during the observation period therefore contribute data to both groups. Patients who started on statins during the observation period were further subdivided into pre-statin (data captured before statin therapy was initiated) and post-statin therapy (data captured after statin therapy was initiated) groups. The upper limit of normal (ULN) for CK levels was defined as 175 IU/L for males and 150 IU/L for females as per Boston Children's Hospital laboratory reference values. Rates of muscle-associated complaints and symptoms were recorded to compare patients on versus off statin therapy. This analysis was approved by the Boston Children's Hospital institutional review board and individual consent was waived.

The following clinical variables were collected as part of clinical care and recorded in the SCAMP quality improvement dataset: age, sex, race and ethnicity (self-reported at visit check-in), family history of hypercholesterolemia or early ASCVD (defined as fatal or non-fatal ASCVD in a first-degree relative ≥ 55 years in males or ≥ 65 years in females¹), medical conditions (elevated blood pressure, clinical suspicion of insulin resistance, Type I or II diabetes mellitus), height, weight, BMI, as well as their associated z-scores calculated from the age-sex derived Center for Disease Control database, blood pressure, insurance type (public vs. private), and adequate physical activity levels determined by the clinician based on patient/family self-report as approximately ≥ 5 hours per week. Obesity was defined as BMI $\geq 95^{\text{th}}$ percentile (<18 years of age) or BMI $\geq 30 \text{ kg/m}^2$ (≥ 18 years of age) and overweight was defined as BMI 85^{th} - 94^{th} percentile for age and sex (<18 years of age) or between 25 - 29 kg/m^2 (≥ 18 years of age). These data were captured on the SCAMP form at the time of the initial visit by the medical provider.

Laboratory values including CK, fasting (≥ 8 hours) total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) levels were obtained at baseline and follow-up visits. Patients had blood samples drawn at Boston Children's Hospital or at their local labs, as convenient for the patient. CK levels ≥ 3 standard deviations (SD) above the mean were confirmed in the patient's medical record.

Statin-associated myopathy was defined as 1) any descriptions of myopathy recorded by the provider in the SCAMP or 2) CK levels $>3\times$ or $>10\times$ ULN.

Statistical Analyses

Patient characteristics for all patients were described with means (SD), medians (interquartile range, IQR) and frequencies, as appropriate for distribution. Linear mixed-effects models with restricted maximum likelihood estimation (REML) were constructed to test the association of statin therapy with serum CK levels in the overall study sample.

Subject ID was specified as a random effect, an unstructured covariance structure was selected, and two successive models were run: (1) adjusted for age and sex, (2) additionally adjusted for season at time of CK measurement as physical activity might vary based on time of year, weight category (obese, overweight and normal), insurance type (public or private) and race/ethnicity as fixed effects. In order to test the association of statin therapy with the odds of developing high CK levels (>ULN vs. normal), generalized linear mixed-effect models fit by maximum likelihood (Laplace Approximation), binomial distribution (logit link), with subject ID as a random effect and age and sex as fixed effect were conducted. Regression models failed to converge when the elevated CK group was divided into further subgroups (e.g. >3x or >10x ULN) due to low event rates and are therefore presented descriptively only.

For patients who initiated statin therapy during the SCAMP data capture, age and sex adjusted linear mixed effect models with subject ID as a random effect were constructed to test the association of statin therapy with serum CK levels among the same set of patients prior to and after initiation of statins. In addition, age and sex-adjusted linear mixed models for longitudinal data, allowing random intercepts for each patient, were employed to determine the rate of change in CK levels over time after initiating statins. Models allowing both random slopes and intercepts did not improve model fit (as determined by Akaike information criterion [AIC] when using maximum likelihood estimation) and therefore only the more parsimonious model with random intercepts was run. Analyses utilized the *nlme*(14) and *lme4*(15) packages and R foundation for Statistical Computing statistical software (version 3.3.1, Vienna, Austria).

RESULTS

Of the 1,501 patients included in the database, 474 patients had CK levels and met other criteria for analysis [Figure 1; available at www.jpeds.com]. Included patients had a mean (SD) age of 14.3 ± 4.0 years; 47% were female, 65% were Caucasian and 7% were African-American [Table]. The analyzed patients had 1,450 serum CK lab values, an average of 3.1 (SD 2.4, range 1-14) serum CK levels per patient. Among the 302 patients with more than 1 CK value, there was a mean (SD) of 18 (11) months of follow-up per patient, totaling 5569 patient-months of follow-up. Baseline clinical characteristics are shown in the Table. There were 768 CK lab values among 188 patients on statin therapy, and 682 lab values among 351 patients not on statins in our cohort [Figure 1]. Patients initiated on statin therapy could be included in both groups if they had CK levels obtained pre and post therapy. There were 86 patients who initiated statin therapy during the observation period (130 CK levels off statins and 292 CK levels on statins).

Among the 474 included patients, the median (IQR) serum CK values among those on statins (n=188 patients, 768 CK measurements) versus not on statins (n=351 patients, 682 CK measurements) were 107 (83) IU/L and 113 (81) IU/L, respectively [Figure 2]. Subdividing patients into four mutually exclusive groups, the median (IQR) CK levels were 113 (86) IU/L (552 CK results) for patients never on statins, 113 (57) IU/L (130 CK results) for those prior to starting statins, 100 (66) IU/L (292 CK results) for those post starting statins, and 112 (86) IU/L (476 CK results) for patients always on statins during the

observation period. There was no observable difference in CK levels among patients on statins compared with not on statins in age and sex-adjusted regression models (β for statin use on $\ln\text{CK}=0.02$ [SE 0.04], $p=0.7$) and multivariable models adjusted for age, sex, weight category, season at time of CK measurement, insurance type and race/ethnicity (β for statin use on $\ln\text{CK}=0.02$ [SE 0.05], $p=0.7$).

Among the 474 included patients, the percent of abnormal CK values did not substantially differ among patients on statins compared with patients not on statin therapy. Among those on statins ($n=188$ patients, 768 CK measurements), 20% (153) of values were 1-3x ULN and 2.2% (17) were $>3x$ ULN. Similarly, among those not on statin therapy ($n=351$ patients, 682 CK measurements), 22% (150) and 2.5% (17) were 1-3x ULN and $>3x$ ULN, respectively. Four patients included in the dataset had at least one CK value $>10x$ ULN noted during routine monitoring after 6 or more months on statins. All were asymptomatic. The abnormal CK levels were variably addressed by encouraging fluids, limiting physical activity, holding statins and repeating CK levels based on clinician and patient/family preference; CK levels normalized in all cases without additional intervention. All four patients were on statin therapy at the time of the last clinical interaction. The odds ratio (OR) for an elevated CK ($>ULN$) among statin users as compared with patients not on statins was not elevated (OR=0.97 [95% 0.6-1.5] $p=0.9$), in age and sex adjusted mixed effect model accounting for repeated measures.

Median CK level for each patient prior to and after initiation of statin therapy are outlined in [Figure 3; available at www.jpeds.com]. In the adjusted linear mixed effects model, there was no observed difference between pre and post-statin CK values for those patients who began statin therapy during the data capture period in age and sex adjusted or multivariable adjusted models (β for statin use on $\ln\text{CK}=0.08$ [SE 0.06], $p=0.2$ and β for statin use on $\ln\text{CK}=0.08$ [SE 0.07], $p=0.2$, respectively). Among the 86 patients starting statins during the observation period (130 CK measures pre and 292 CK measures post), the OR for elevated CK levels ($>ULN$ compared with normal [ref]) after initiating statin therapy as compared with prior to statin use was not significantly elevated in our study sample; OR=1.4 ([95% 0.9-2.2]; $p=0.3$) in age and sex-adjusted regression models. There were too few CK levels $>3x$ or $>10x$ ULN to conduct further elevated CK group inference testing.

Absolute change in serum CK level from baseline is shown in Figure 4 (available at www.jpeds.com). When CK levels of patients on statins are assessed over time, CK levels increase marginally with statin use by 1.08 (95% CI 1.004, 1.18) IU/L per year (β for time after starting statins on $\ln\text{CK}=0.084$ [SE 0.04] increase per year, $N=86$, $p=0.04$).

Myopathies and Symptoms

Rates of associated myopathy including myalgia, myositis, and rhabdomyolysis across all statin users were examined. There were no reported episodes of rhabdomyolysis. Out of all new statin starts and patients already on statins at the time of the SCAMP initiation, only one patient reported muscle pain with elevated CK. These symptoms were mild, resolved with the application of heat, and then ceased without any change in the statin dose or type. This single report of mild symptoms was obtained from a total of 3,433 patient-months of follow-up on 171 patients treated with statins during the observation period (with over 1 CK

measurement or a baseline statin start date), giving an incidence of 0.3 minor events per 100 patient-years of follow-up.

DISCUSSION

In this study we examined serum CK levels and reported muscle symptoms in children and adolescents treated with statins compared with untreated levels including a subset analyses of the same pediatric patients prior to and after statin initiation, and change in CK levels over time on statins. We found no clinically meaningful differences in CK levels off vs. on statins, or after statin initiation. CK levels increased very slightly over time on statins (~1 IU/L per year), a clinically insignificant change. A single report of muscle symptoms was noted in a patient with elevated CK and resolved without intervention. Four patients had CK elevation >10x ULN while on statin therapy, without accompanying symptoms; these patients were managed expectantly and at the last clinical encounter remained on statins with normal CK levels.

Understanding of statin-related muscle toxicity in the pediatric patient population comes primarily from randomized controlled trials of statins in children and adolescents with Familial Hypercholesterolemia. In a meta-analysis of statin trials in children and adolescents treated with statins, muscle-associated symptoms and elevated serum CK levels were reported at very low prevalence.(9) Of the 21 included studies, 5 reported CK levels; there was no increased risk for CK levels > 10X ULN. There were no cases of rhabdomyolysis. There are limited data representing clinical practice outside of the clinical trial setting. One survey of young adults taking statins over ~10 years reported muscle symptoms in 9.3% (19/205 patients); no CK levels were collected in this report.(16) Early data from a UK pediatric FH registry reported no significant CK elevations in 111 children on statins.(17) Neither study reported episodes of rhabdomyolysis. The National Heart Blood and Lung Institute (NHLBI) Expert Panel in 2011 recommends a baseline CK measurement prior to statin initiation and regular monitoring of myopathy-associated symptoms by patients and parents.(1) CK levels are recommended when patients experience symptoms. However, some practices regularly measure CK levels in asymptomatic patients as part of ongoing clinical monitoring. Increased physical activity levels are recommended to reduce cardiovascular risk but complicate the interpretation of CK levels and muscle symptoms in children on statins. Concerns have been raised about adverse effects of statins in children, particularly in light of the growing evidence of the early origins of ASCVD.(18) Our study provides greater understanding of the prevalence of statin-associated adverse effects and their relation to serum CK levels in clinical practice, outside the confines of clinical trials this understudied group. The findings support recommendations for the judicious use of CK levels, given that our clinical experience in monitoring of CK levels in asymptomatic pediatric patients on statin therapy did not provide any useful additional information.

This analysis has several limitations. Although our cohort was relatively large for pediatric statin patients, it was not large enough to reliably detect rare events (e.g. rhabdomyolysis). This analysis was a review of clinical experience collected as part of a quality improvement effort, not a clinical trial, so our comparison group was not randomly ascertained. Similarly, symptoms were not systematically collected in patients not prescribed statins. During this

time, physical activity was not systematically collected as part of the quality improvement dataset and therefore we were not able to adjust for activity level among our patients, who were receiving advice to participate in regular moderate to vigorous physical activity. Additionally, serum CK levels were more likely to be drawn in patients with symptoms on statins, skewing the number of values towards those on statin therapy. We were not able to examine dose or statin type because most patients were on one of two low dose statins (simvastatin or atorvastatin), limiting the variability in statin type and dose. The design of the QI dataset did not capture medication or dose changes during follow-up. Frequency of follow-up differed among patients on versus not on statin therapy. Furthermore, the patients included in this study were referred to and cared for in a pediatric subspecialty lipid clinic and do not reflect a primary care practice; most children on statins are cared for by subspecialists. The majority of patients were Caucasian and our results may not be generalizable to other ethnicities.

Our findings suggest limited utility to monitoring CK levels in asymptomatic pediatric patients on statins, supporting the recommendations of the NHLBI Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents.⁽¹⁾ Based on these data, and our clinical experience, we recommend checking a baseline CK level prior to starting statins, providing patient education on signs and symptoms of muscle adverse effects, and select repeat testing on statins in children and adolescents with muscle or urinary symptoms concerning for rhabdomyolysis, or in patients with concerns of an underlying muscle disorder.

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Figure 1 -
Patient flow chart. There were a total of 1,450 serum creatine kinase levels obtained from 474 patients available for analysis.

Figure 2 -
Boxplot of creatine kinase levels of patients on and not on statins displaying median, interquartile range (IQR), and outliers (log-scale).

Figure 3:

Creatine kinase (CK) levels of patient patients prior to and after being prescribed statins. CK levels are shown as the median value per patient to account for multiple CK levels per patient state (log-scale).

Figure 4 –.

Absolute change from baseline in serum CK level for individual patients after starting statins. CK: creatine kinase. Individual patient's CK levels are connected by lines.

Table -

Patient Characteristics.

Characteristics of patients included in the analysis are reported as percent (n), unless otherwise indicated.

Variable	N	Value
Age, years (mean $\pm$ SD)	474	14.3 $\pm$ 4.0
Female	474	47% (224)
<i>Race/Ethnicity</i>		
Caucasian	474	65% (309)
African-American	474	7% (33)
Asian	474	5% (26)
Other	474	10% (48)
Not reported	474	12% (58)
<i>Insurance type</i>		
Any public insurance	474	12% (55)
<i>ASCVD Risk Behaviors</i> *		
Inadequate exercise	462	48% (222)
Excess screen time	426	40% (170)
Nutritional concerns	458	62% (286)
Cigarette smoke exposure	456	10% (46)
<i>Family History</i>		
Early ASCVD (%)	422	65% (276)
Hypercholesterolemia (%)	222	98% (217)
<i>Medical Conditions</i>		
Elevated blood pressure or hypertension (%)	449	12% (52)
Diabetes Type 1 or 2 (%)	463	6% (29)
Suspected Insulin Resistance (%)	448	25% (114)
<i>Anthropometrics and blood pressure</i>		
Height, cm (mean $\pm$ SD)	474	158 $\pm$ 17
Weight, kg (mean $\pm$ SD)	474	64 $\pm$ 27
BMI (mean $\pm$ SD)	474	24.6 (7.5)
BMI z-score	340	1.4 $\pm$ 0.8
Overweight (%)	474	88 (19%)
Obese (%)	474	158 (33%)
Systolic BP, mmHg (mean $\pm$ SD)	469	115 $\pm$ 14
Diastolic BP, mmHg (mean $\pm$ SD)	468	66 $\pm$ 10
<i>Baseline Laboratory Values</i>		

Variable	N	Value
Fasting lipid profile		
TC, mg/dL (mean $\pm$ SD)	471	245 $\pm$ 61
LDL-C, mg/dL (mean $\pm$ SD)	467	172 $\pm$ 59
HDL-C, mg/dL (mean $\pm$ SD)	473	47 $\pm$ 12
TG, mg/dL median (IQR)	473	99 (104)
CRP, mg/dL (mean $\pm$ SD)	4	1.1 $\pm$ 0.5
Insulin, microU/dL (mean $\pm$ SD)	49	17 $\pm$ 15
HgA1C, % median (IQR)	174	5.5 (0.7)
Glucose mg/dL, median (IQR)	195	90 (12)
ALT unit/L (mean $\pm$ SD)	342	23 $\pm$ 18
AST unit/L (mean $\pm$ SD)	325	26 $\pm$ 13
TSH mcunit/ml (mean $\pm$ SD)	212	2.6 $\pm$ 1.4
VitD 25-OH (mean $\pm$ SD)	127	24 $\pm$ 9

ALT alanine-aminotransferase; ASCVD atherosclerotic cardiovascular disease; AST aspartate aminotransferase; BMI body mass index; BP blood pressure; CRP C-reactive protein; HgA1C hemoglobin A1C; LDL-C low-density lipoprotein cholesterol; HDL-C high-density lipoprotein cholesterol; TC total cholesterol; TG triglycerides.

* ASCVD risk factors were reported as assessed qualitatively by the treating clinician.