Statin-Associated Myopathy in a Pediatric Preventive Cardiology Practice

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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-/poststatin initiation. Multivariable mixed-effect models were constructed accounting for repeated measures, examining the effect of statins on log-transformed CK (lnCK) levels adjusted for age, sex, weight, season, insurance type, and race/ethnicity.

Results Among 1501 patients seen over 3.5 years, 474 patients (14 ± 4 years, 47% female) had at least 1 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 levels did not differ based on statin use ($\beta = 0.02$ [SE 0.05], $P = .7$). Among patients started on statins (n = 86, 130 prestatin and 292 poststatin CK measurements), median CK levels did not differ in adjusted models (β for statin use on lnCK = .08 [SE .07], $P = .2$). There was a clinically insignificant increase in CK over time ($\beta = .08$ [SE .04], $P = .04$ 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. *(J Pediatr 2017;185:94-8).*

Statins (hydroxy-methylglutaryl-coenzyme A 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 from 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 because of 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 hypercholesterolemia, no patients experienced rhabdomyolysis and rates

ASCVD	Atherosclerotic cardiovascular disease
BMI	Body mass index
CK	Creatine kinase
ID	Identification
lnCK	Log-transformed CK
SCAMP	Subspecialty Standardized Clinical Assessment and Management Plan
ULN	Upper limit of normal

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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 1 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 2 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 prestatin (data captured before statin therapy was initiated) and poststatin 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 male patients and 150 IU/L for female patients as per Boston Children's Hospital laboratory reference values. Rates of muscle-associated complaints and symptoms were recorded to compare patients on vs 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 nonfatal ASCVD in a first-degree relative ≤55 years in male subjects or ≤65 years in female subjects[1]), medical conditions (elevated blood pressure, clinical suspicion of insulin resistance, type I or II diabetes mellitus), height, weight, body mass index (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 ≥95th percentile (<18 years of age) or BMI ≥30 kg/m^2 (≥18 years of age) and overweight was defined as BMI 85th-94th percentile for age and sex (<18 years of age) or between 25 and 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, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol levels were obtained at baseline and follow-up visits. Patients had blood samples drawn at Boston Children's Hospital or at their local laboratories as convenient for the patient. CK levels ULN ≥3 SDs 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× or >10× ULN.

Statistical Analyses

Patient characteristics for all patients were described with means (SD), medians (IQR), and frequencies, as appropriate for distribution. Linear mixed-effects models with restricted maximum likelihood estimation were constructed to test the association of statin therapy with serum CK levels in the overall study sample. Subject identification (ID) was specified as a random effect, an unstructured covariance structure was selected, and 2 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. 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 (eg, >3× or >10× ULN) because of 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 when using maximum likelihood estimation), and, therefore, only the more parsi-