Statin Use and the Risk of Type 2 Diabetes Mellitus in Children and Adolescents

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Abstract

Objective: There is increasing evidence of an association between statin use and type 2 diabetes mellitus (T2DM) in adults, yet this relationship has never been studied in children or adolescents and may have important implications for assessing risks and benefits of treatment in this population. We estimated the association between statin use and the risk of T2DM in children with and without a dyslipidemia diagnosis.

Methods: Propensity scores were used to match new users of statins with a minimum 50 percent of days covered (PDC) in the first year of use to up to 10 nonusers. Analyses were stratified by a dyslipidemia diagnosis based on recent evidence suggesting a potentially protective effect of familial hypercholesterolemia on T2DM. In sensitivity analyses, we varied this period of exclusion and PDC. Cox proportional hazard models compared the hazard of the outcome between the exposed and unexposed patients.

Results: A total of 21,243,305 patients met the eligibility criteria, 2085 (0.01%) of whom met the exposure definition and 1046 (50%) of whom had a dyslipidemia diagnosis. Statin use was associated with an increased risk of T2DM in children without dyslipidemia (hazard ratio 1.96, 95% confidence interval 1.20–3.22), but not in children with dyslipidemia (hazard ratio 1.11, 95% confidence interval 0.65–1.90). The results were consistent across variations in the exclusion period and PDC.

Conclusions: Statin use was associated with an increased likelihood of developing T2DM in children without dyslipidemia. Physicians and patients need to weigh the possible risk of T2DM against the long-term benefits of statin therapy at a young age.

Keywords: diabetes; dyslipidemia; familial hypercholesterolemia; pharmacoepidemiology; statin

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What's New

There was an increased risk of type 2 diabetes mellitus associated with statin use in children and adolescents without a diagnosis of dyslipidemia, but no increased risk in children and adolescents with dyslipidemia.

STATIN PRESCRIBING TO children and adolescents is rare, with an estimated incidence of 2.6 new prescriptions per 100,000 person-years.[1] However, the 2008 decision by the American Academy of Pediatrics, followed in 2011 by the National Heart Lung and Blood Institute, to recommend statins as a first-line treatment for hyperlipidemia in children aged 8 or older has intensified a debate over the risks versus benefits of long-term statin use in youth.[2,3] In adults, the adverse effects associated with statin use are low, with approximately 0.1% to 0.2% of all users developing myopathy and less than 1 death due to rhabdomyolysis per 1 million statin prescriptions.[4] Although studied less extensively, reported rates of adverse effects in children and adolescents appear to be similar to those found in adults.[4–7]

Recently a number of studies in adults suggest that statin use is associated with an increased risk of T2DM between 9% and 28%.[8–13] The hypothesized pathways by which statins may increase the risk of diabetes include impairing insulin secretion, increasing weight-dependent or -independent insulin resistance, and potentially enhanced glucose secretion.[14,15] Results from these studies prompted the US Food and Drug Administration to update statin labeling in 2012 to include a warning for the development of T2DM.[16] Although the increased risk of T2DM can be a counterargument to initiating statin therapy in low-risk adults, the benefits in high-risk patients for whom statins are indicated most often outweigh the potential adverse effects, including the risk of T2DM.[11,17] This calculation may differ in children, however, where the short-term risk of T2DM needs to be weighed against the much longer-term risk of cardiovascular disease.

The clearest indication for statin use in children is heterozygous familial hyperlipidemia (heFH), a genetic condition resulting in significantly elevated low-density lipoprotein cholesterol. Children with heFH have an

increased risk of cardiovascular disease, and if left untreated, it is estimated that 50% of male and 30% of female subjects will experience an acute cardiovascular event before the age of 60.[18,19] Complicating the risk assessment in children is a recent study reporting a significantly lower prevalence of T2DM among patients with heFH compared to their unaffected relatives, and a randomized controlled trial reporting no increased risk of T2DM in patients with heFH treated with statins.[20,21] Results from these studies raise the possibility that the gene mutation resulting in heFH may also confer protection from T2DM.

Although there is evidence demonstrating an increased risk of diabetes associated with statin use in adults, to our knowledge, that link has not been evaluated in children. To fully assess the risks versus benefits of statin treatment in childhood, it is necessary to first quantify the risk of T2DM associated with statin treatment in this population. Accordingly, the objective of this study was to estimate the risk of incident T2DM associated with statin use in a commercially insured population of youth ages 8 to 20 with and without diagnosed dyslipidemia between 2003 and 2014. We hypothesized that, similar to adults, statin use in children would be associated with an increased risk of T2DM.

METHODS

DATA SOURCE AND STUDY COHORT

Data for this analysis came from the Marketscan Research Database for calendar years 2003 through 2014. The Marketscan database is a compilation of commercial health insurance claims that includes data on all medical claims for employees and their dependents and thus does not include information on individuals covered under Medicaid or Medicare, or the uninsured. Because data are collected from employers, Marketscan contains information on individuals through the duration of the employment with their employer, or until their employer ceases to participate in providing data. We assessed all patients aged 8 to 20 between 2003 and 2014 for inclusion in the study cohort. Eligibility for inclusion in our analysis was defined as no T2DM diagnosis and no dispensings for a statin in the 12-month period after the first date of enrollment after the age of 7 (Fig. 1, period A).

STATIN EXPOSURE AND FOLLOW-UP TIME

We used a new user study design to estimate the effect of statin use on rates of incident T2DM.[22] Though we chose to exclude individuals with a recorded diagnosis of T2DM, we cannot ensure that we are identifying the first T2DM diagnosis for a patient, only that it was the first diagnosis during the period for which we were able to observe them. New statin use was defined as the first (index) statin dispensing after a minimum 12 months of no recorded dispensings (Fig. 1, period A). In our primary analysis, we limited our exposed group to patients with a minimum of 50 percent of days covered (PDC) in the 12-month lag period after the index dispensing (Fig. 1, period B). The PDC is a commonly used measure of medication adherence in which the total number of days supplied for each prescription are summed and divided by the observation interval, which we defined in our primary analysis as the 12-month lag period. Because we cannot tell if a patient is taking the medication, only that he or she has filled a prescription, our measures may underestimate adherence. However, the PDC has been shown to be a valid measure of adherence in prior studies.[23] All patients with less than 12 months of follow-up or a T2DM diagnosis during the lag period were excluded from the primary analysis.

We chose to use a 12-month lag period for several reasons. First, children who are prescribed statins have a higher prevalence of comorbidities associated with an increased risk of diabetes.[1] Consequently, it is likely that some of the early T2DM diagnoses are due to confounding by indication and unrelated to statin exposure. Second, though there is limited consensus on the mechanism by which statins cause diabetes in adults,[24] results from the reanalysis of clinical trials in adults suggest that 12 months represents a biologically plausible lag time between exposure and outcome.[8,9,25] In sensitivity analyses, however, we varied both the duration of the lag period and the required PDC.

PROPENSITY SCORE MATCHING

We calculated year-specific propensity scores as the probability of initiating statin use in a given year, conditional on a set of measured covariates listed in Table 1. Statin users who did not meet the case criteria of 50 PDC over the 12-month lag period were excluded from the pool of potential unexposed matches, while nonstatin users were eligible to be an unexposed match in each year for which they contributed person-time and

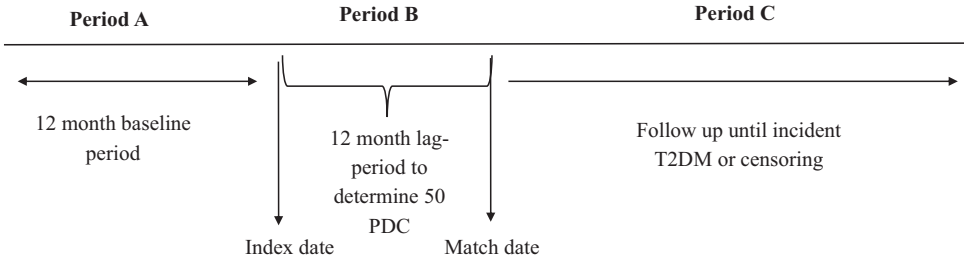

Figure 1. *Study timeline.*