Journal of Clinical Lipidology (2014) 8, 401–407

Journal of Clinical Lipidology

Hypothyroidism as a risk factor for statin intolerance

Craig D. Robison, MD*, Tami L. Bair, BS, Benjamin D. Horne, PhD, MPH, Ray O. McCubrey, MS, Donald L. Lappe, MD, Joseph B. Muhlestein, MD, Jeffrey L. Anderson, MD

Department of Internal Medicine, University of Utah School of Medicine, Salt Lake City, UT, USA (Dr Robison); Intermountain Heart Institute, Intermountain Medical Center, Salt Lake City, UT, USA (Drs Bair, Horne, McCubrey, Lappe, Muhlestein, and Anderson); and Division of Cardiology, University of Utah School of Medicine, Salt Lake City, UT, USA (Drs Horne, Muhlestein, and Anderson)

KEYWORDS:
HMG-COA reductase inhibitors;
Statins Hypothyroidism;
Statin intolerance;
Dyslipidemia;
Subclinical hypothyroidism;
Statin rechallenge;
Epidemiology

BACKGROUND: Three-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) are one of the most commonly prescribed classes of medications because of their proven cardiovascular benefits. However, statin intolerance occurs in 5% to 20% of patients. Understanding the basis for statin intolerance remains a key issue in preventive medicine.

OBJECTIVES: To evaluate the association of statin intolerance with hypothyroidism in a large integrated health care system, including its sex-specific relationship and subsequent statin rechallenge and prescription history.

METHODS: The Intermountain Healthcare electronic medical record database identified patients (n = 2686; males = 1276, females = 1410) with a documentation of intolerance ("allergy") to at least 1 statin. Age and sex similar controls (n = 8103; males = 3892, females = 4211) were identified among patients prescribed statins without documented intolerance. Patients were evaluated for a history of hypothyroidism, development of hypothyroidism, and statin prescription history up to 5 years of follow-up.

RESULTS: A total of 30.2% patients (210 males, 16.5%; 602 females, 42.7%) with statin intolerance had a history of hypothyroidism compared with 21.5% of statin-tolerant patients (475 males, 12.2%; 1266 females, 30.1%), for an odds ratio (OR) in the total population of 1.49 (95% confidence interval [CI] 1.34–1.65; $P < .0001$); in males, OR was 1.29 (CI 1.07–1.55; $P = .001$); in females, OR was 1.60 (CI 1.41–1.82; $P < .0001$). During follow-up, patients with statin intolerance and hypothyroidism were less likely to be on a statin than their statin-intolerant counterparts without hypothyroidism (hazard ratio 0.84; 95% CI 0.75–0.94; $P = .002$).

CONCLUSIONS: Hypothyroidism is more prevalent in those with statin intolerance, both in males and, especially, in females. People with hypothyroidism are less likely to have a prescription for a statin at follow-up than those without hypothyroidism.

Financial Disclosures: None.
Conflicts of Interests: None.

* Corresponding author. Department of Internal Medicine, University of Utah School of Medicine, 30 N 1900 E, Rm 4C104, Salt Lake City, UT 84132.
E-mail address: Craig.Robison@hsc.utah.edu

Submitted November 27, 2013. Accepted for publication May 18, 2014.

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http://dx.doi.org/10.1016/j.jacl.2014.05.005

Dyslipidemia is one of the most common cardiovascular disorders, affecting 29.3% of the middle-aged population who do not have existing cardiovascular disease and a higher percentage among those who do.[1] This has led to the rise in use of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors (statins), and statins have become one of the most commonly prescribed classes of medications. Thyroid disease, particularly hypothyroidism, is one of the most common endocrine disorders.[2] With a prevalence of 9.5% in the general population and more in elderly individuals, the prevalence of abnormal biochemical thyroid function is substantial.[3] Hypothyroidism is commonly treated with thyroxine replacement therapy in the form of levothyroxine.

Despite the high prevalence of dyslipidemia and hypothyroidism in the general population, very little is known about the interaction between these 2 diseases. The majority of knowledge resides within case reports and small cohort studies. To date, only 1 large cohort, the PRIMO Study, and no randomized controlled trials, have evaluated the interaction of treatment for both dyslipidemia and hypothyroidism.[4] The PRIMO cohort did not provide sex-specific analysis or statin rechallenge data.

These accumulating reports have led to the suggestion that hypothyroidism may be a risk factor for statin-induced myopathy and statin intolerance, potentially through unmasking undiagnosed or undertreated hypothyroidism.[5,6] We aimed to further evaluate these claims by investigating statin use and statin intolerance in those with and without hypothyroidism in a large health care systems database.

Methods

Data from the electronic medical record database of the Intermountain Healthcare system (Murray, UT) were studied to address 4 objectives in a general health care population: (1) to determine the prevalence of hypothyroidism in patients with documented intolerance to at least 1 statin; (2) to provide sex-specific analysis of the relationship between statin intolerance and hypothyroidism; (3) to evaluate the development of hypothyroidism in persons with and without statin intolerance; and (4) to evaluate subsequent statin use, as documented by a prescription of any statin at follow-up. The present study was approved by the Intermountain Institutional Review Board.

The Intermountain database was searched to identify subjects with a documented history of an "allergy" (i.e., intolerance) to at least 1 statin between January 1994 and January 2013. Age- and sex-similar controls of people with a prescription for a statin but without history of stain intolerance were identified and included in a 3:1 ratio. Neither a minimum duration of statin therapy nor attempting therapy with more than 1 statin was required for inclusion.

The incidence of statin intolerance, hypothyroidism, myalgias, and other diagnoses were determined by *International Classification of Diseases*, version 9, code entries documented in electronic medical records at baseline and during follow-up. The prospectively defined variables of interest and available to study were age, sex, race, statin intolerance, and hypothyroidism. Creatine kinase (CK), thyroid stimulating hormone (TSH), and lipid panels including total cholesterol (CHOL), high-density lipoproteins (HDL), low-density lipoproteins, very low-density lipoproteins, triglycerides, and total CHOL/high-density lipoprotein ratios were evaluated for each patient when available. Patients were followed after the initial event for an average of 3.6 years (maximum, 18.5). The presence of an active prescription for a statin at follow-up in those with a history of statin intolerance was evaluated as a surrogate for statin rechallenge.

For statistical comparisons, the 2-tailed Student t-test with unequal variance and Wilcoxon signed-rank test were used for comparing continuous variables. The chi-square statistic was used to assess statistically significant differences in the categorical variables. Odds ratios (OR), hazard ratios (HR), and 95% confidence intervals (CI) are provided where appropriate. All ORs and HRs were adjusted for comorbidities (hypertension, diabetes, coronary artery disease, tobacco history, and chronic kidney disease). Cox proportional models and logistic regression was used to estimate HRs and ORs. In this study, a significance level of alpha = 0.05 was used.

Results

Demographics are presented in Table 1. A study population of n = 10,789 subjects was identified with 47.9% males and 52.1% females. The mean age of all subjects was 67.2 ± 11.4 years. Males were older than females ($P < .0001$). Overall, 2686 subjects had statin intolerance matched 3:1 to 8103 controls with no history of statin intolerance. Persons with statin intolerance were more likely to have hypertension ($P < .0001$), diabetes ($P < .0001$), coronary artery disease ($P = .0001$), a history of tobacco use ($P = .01$), and chronic kidney disease ($P < .001$).

During follow-up, 39,024 cumulative patient-years (males 19,568 years, females 19,456 years) were included, with 5839 patient-years for those with statin intolerance (males 2817 years, females 3021 years) and 33,185 patient-years (males 16,750 years, females 16,435 years) for those with no history of statin intolerance.

Hypothyroidism

A total of 30.2% people with statin intolerance had a history of hypothyroidism compared with 21.5% people without a history of statin intolerance having a history of hypothyroidism (OR 1.49; 95% CI 1.34–1.65; $P < .0001$). In males, 16.4% with statin intolerance had a history of hypothyroidism and 12.2% males without a history of statin intolerance had a history of hypothyroidism (OR 1.29; 95% CI 1.07–1.55; $P = .001$). In females, 42.7% with statin intolerance had a history of hypothyroidism and 30.1%