Research Article | Clinical Care/Education/Nutrition/Psychosocial Research

Hypothyroidism Is a Risk Factor for New-Onset Diabetes: A Cohort Study

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Abstract

OBJECTIVE To identify risk factors for the development of statin-associated diabetes mellitus (DM).

RESEARCH DESIGN AND METHODS The study was conducted in two phases. Phase one involved high-throughput in silico processing of a large amount of biomedical data to identify risk factors for the development of statin-associated DM. In phase two, the most prominent risk factor identified was confirmed in an observational cohort study at Clalit, the largest health care organization in Israel. Time-dependent Poisson regression multivariable models were performed to assess rate ratios (RRs) with 95% CIs for DM occurrence.

RESULTS A total of 39,263 statin nonusers were matched by propensity score to 20,334 highly compliant statin initiators in 2004–2005 and followed until the end of 2010. Within 59,597 statin users and nonusers in a multivariable model, hypothyroidism and subclinical hypothyroidism carried an increased risk for DM (RR 1.53 [95% CI 1.31–1.79] and 1.75 [1.40–2.18], respectively). Hypothyroidism increased DM risk irrespective of statin treatment (RR 2.06 [1.42–2.99] and 1.66 [1.05–2.64] in statin users and nonusers, respectively). Subclinical hypothyroidism risk for DM was prominent only upon statin use (RR 1.94 [1.13–3.34] and 1.20 [0.52–2.75] in statin users and nonusers, respectively). Patients with hypothyroidism treated with thyroid hormone replacement therapy were not at increased risk for DM.

CONCLUSIONS Hypothyroidism is a risk factor for DM. Subclinical hypothyroidism-associated risk for DM is prominent only upon statin use. Identifying and treating hypothyroidism and subclinical hypothyroidism might reduce DM risk. Future clinical studies are needed to confirm the findings.

Introduction

Thyroid disease is common in the general population. Hypothyroidism and subclinical hypothyroidism are more prevalent in patients with type 2 diabetes mellitus (DM), and it is possible that hypothyroidism is a risk factor for the development of DM. Women with subclinical hypothyroidism are more likely to develop gestational diabetes (1). After restoration of thyroid function, reduction of glucose-stimulated insulin secretion has been shown in patients with hypothyroidism as well as in those with subclinical hypothyroidism (2).

Hypothyroidism is a known risk factor for the development of myopathy following statin (3-hydroxy-3-methyl glutaryl CoA reductase inhibitor) treatment (3–6). Statins may lead to the development of de novo DM (7). The cardiovascular preventive effects of statins outweigh the risk of developing DM (8), but the benefit/risk ratio can be less obvious in specific subpopulations (9). Epidemiological studies have identified the elderly, women, and people of Asian origin as more prone to develop statin-associated DM (7). In phase one of the current study, we identified through a mechanism of action (MoA)–based analysis that hypothyroidism and subclinical hypothyroidism are probable risk factors for statin-associated DM (Supplementary Data). We next aimed to confirm this finding in a large cohort and to evaluate whether hypothyroidism and subclinical hypothyroidism are associated with an increased risk for developing DM and statin-associated DM.

Research Design and Methods

Clinical Outcome Search Space MoA-Based Analysis

MoA-based analysis relies on the high-throughput in silico processing of large biomedical corpora, namely the biomedical and patent literature. Clinical Outcome Search Space (COSS), a proprietary platform for MoA-based analysis (10–12), creates and compares multidimensional data profiles of biomedical concepts of interest, including drugs, diseases, genes, proteins, biological pathways, and clinical outcomes.

COSS comprises three separate software modules: information extraction, ranking, and outcome analysis. These modules are used sequentially in the context of an MoA-based analysis. Each analytical step involves domain experts defining the input parameters and curating the output of each module; the curated output of each step serves as input for the next step (the method is outlined in detail in the Supplementary Data).

Epidemiological Methods

Study Population

Clalit Health Services (CHS) is the largest health services provider in Israel, providing medical care to more than one-half of the Israeli population (13). All clinical and administrative data of CHS is centrally computerized to produce an electronic record of all patient diagnoses (ICD-9 codes) and anthropometric and lifestyle variables, such as BMI and smoking, as well as full hospitalization records and radiology, laboratory, and pharmacy data. This database has been described previously and is considered valid and reliable (14,15). Patient informed consent was not necessary because the data were anonymized for research purposes. The study was approved by the CHS Chief Physician's Office.

We carried out a cohort study of statin initiators without DM and a matched cohort of patients who were not statin users and did not have DM and followed them for 5–7 years to study DM occurrence within these cohorts. We had detailed clinical data on each patient, including thyroid status, comorbidities, and laboratory results, and we performed a time-dependent multivariable analysis with thyroid status as one of the variables.

Within the CHS population, we selected all patients 40–80 years of age who had started statin treatment between 1 January 2004 and 31 December 2005 and did not have a diagnosis of DM in their medical record, prescribed DM drugs, or serum glucose ≥200 mg/dL or HbA_{1c} ≥6.5% (48 mmol/mol) before and at the time of statin initiation and 6 months after initiating a statin. We used drug

dispensing data from the CHS pharmacies database to restrict the study population to patients who had been filling statin prescriptions ≥80% of the time from the beginning to the end of the study period (highly compliant patients) to see the effect of the drug.

For each statin user, we randomly chose from among the total CHS population three to four subjects who were unexposed to statins until the end of the study period and without DM 6 months from recruitment and matched them to each statin user by age, sex, and ethnicity (Jewish/Arab) in 2004 and in 2005 separately. We followed this cohort with propensity score matching.

Clinical Variables

Data gathered for each subject included obesity (BMI ≥30 kg/m^2), smoking status, and history of hypertension and ischemic heart disease at the beginning of the study period (until 3 months from study entry); levels of serum glucose, total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides at the beginning of the study period (the closest reading to enrollment date in the period between 6 months before to 3 months after enrollment [baseline]); fibrate use at the beginning of the study period until 3 months from enrollment; and medications with a potential to increase DM risk, and medications for the same indications but not known to increase DM risk, prescribed until 1 year after enrollment. Following high-throughput in silico processing of a large amount of biomedical data using COSS, the cohorts were evaluated for thyroid disease as a risk factor for development of DM. Thus, each individual in the two cohorts was assigned a thyroid status. Hypothyroidism was identified by at least one of three different diagnostic sources (a national database of chronic diseases, primary care diagnosis as written by general practitioners at time of visit, and diagnosis from hospitalization), treatment with thyroid hormone replacement therapy, or serum thyroid-stimulating hormone (TSH) >10 IU/mL. Patients treated with thyroid hormone replacement therapy for reasons other than hypothyroidism (e.g., after thyroid cancer) were sorted by diagnosis and excluded. Patients with hypothyroidism were divided into those who were treated with thyroid hormone replacement and those who were not throughout the study period. Subclinical hypothyroidism was defined as a serum TSH ≥5.5 and ≤10 IU/mL and no thyroid hormone replacement therapy throughout the study period. Patients with hyperthyroidism were identified as having one of the hyperthyroid diseases. All other individuals were classified as patients with euthyroidism.

Follow-up

Individuals were followed until 31 December 2010. Time from 1 January 2004 for the 2004 statin users cohort and from 1 January 2005 for the 2005 statin users cohort until start of statin treatment throughout the year was added to the nonuser cohort time analysis to prevent immortal time bias (**16**). Follow-up time was calculated for the patients with thyroid disease using the time when both statin use and thyroid disease were present.

End points were new-onset DM by physician diagnosis (extracted from at least one of three diagnostic sources as mentioned previously), DM drug prescription, or serum glucose ≥200 mg/dL or HbA_{1c} ≥6.5% (48 mmol/mol) at least 6 months after initiating a statin. The 6-month period was chosen to reduce the risk of detection bias and to allow reasonable time for a biological process to develop. All patients were followed until DM occurrence, death, end of the study period, or date lost to follow-up, whichever came first.

Statistical Methods

Imputation analysis was performed for missing variables. A logistic regression model including age; sex; ethnicity; obesity; smoking status; history of hypertension and ischemic heart disease; euthyroid, hyperthyroid, hypothyroid, and subclinical hypothyroid states; levels of serum glucose, total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides; and medications was used to calculate the propensity score for receiving statins. Using SAS version 9.2 software and the criterion of a propensity score difference <0.01, one to four statin nonusers were matched to each statin user for the 2004 and 2005 cohorts. To assess unbalanced confounders, the standardized mean difference was calculated for each variable.

We performed three Poisson regression multivariable models to assess DM risk: for the statin user and nonuser cohorts separately to evaluate the contribution of thyroid disease to DM occurrence under statin exposure and irrespective of statin exposure and for both cohorts together to evaluate the magnitude of statin use as a risk factor for developing DM. We also performed two sensitivity analyses. First, we repeated the analysis using median TSH values obtained throughout the follow-up time to define thyroid subgroups. Second, to assess the independent effect of statin use over hypercholesterolemia on DM risk in patients with hypothyroidism (**17**), we performed an analysis in patients with hypothyroidism and subclinical hypothyroidism stratified by two levels of LDL (≤130 and >130 mg/dL). All analyses were two-sided, and $P \leq 0.05$ was considered significant.

Kaplan-Meier estimates were used to calculate the proportion free of DM to examine the unadjusted association between thyroid disease and DM event rate within statin use groups. Log-rank tests were used for between-group comparisons. All analyses were conducted with SPSS version 19 software.

Results

A total of 94,855 statin nonusers were randomly chosen from the CHS population and matched by age, sex, and ethnicity to 23,788 highly compliant statin users. Eight hundred sixty subjects from the statin user cohort and 3,258 from the statin nonuser cohort with no serum TSH laboratory test results were excluded. Subjects with missing clinical and laboratory variables after imputation were excluded, leaving 22,909 statin users and 90,558 statin nonusers (Supplementary Fig. 1). By propensity scoring, 39,263 statin nonusers were matched to 20,334 statin users.

The demographic and clinical characteristics of the cohorts are shown in **Table 1**. A total of 3,666 new-onset DM cases were identified during 235,944 person-years of follow-up in the statin nonuser cohort (crude incidence rate 155/10,000 person-years), and 4,410 new-onset DM cases were identified during 106,265 person-years of follow-up in the statin user cohort (crude incidence rate 415/10,000 person-years). In the Poisson regression model, the rate ratio (RR) to develop DM in highly compliant statin users was 2.57 (95% CI 2.45–2.70) (**Table 2**). Within 59,597 statin users and nonusers, a multivariable model showed that hypothyroidism and subclinical hypothyroidism carried an increased risk for DM (RR 1.53 [1.31–1.79] and 1.75 [1.40–2.18], respectively).

Table 1

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Characteristics of statin users and propensity score–matched cohort of statin nonusers

Characteristic	Statin users (*n* = 20,334)	Statin nonusers (*n* = 39,263)	Standardized mean difference (%)
Age (years)	63.02 (9.65)	64.17 (11.17)	10.99
Male sex	8,502 (41.81)	14,079 (35.86)	12.24
Jewish ethnicity	18,882 (92.86)	36,934 (94.07)	4.89
Obesity	9,007 (44.30)	17,132 (43.63)	1.33
Smoking	6,035 (29.68)	10,168 (25.90)	8.45
Hypertension	11,634 (57.21)	20,589 (52.44)	9.61
Ischemic heart disease	5,167 (25.41)	6,424 (16.36)	22.40
Serum total cholesterol (mg/dL)	189.25 (39.49)	184.94 (34.73)	11.59
Serum LDL (mg/dL)	112.21 (33.17)	110.50 (28.83)	5.52
Serum HDL (mg/dL)	45.99 (11.73)	48.23 (13.11)	18.00
Serum triglycerides (mg/dL)	117.41 (54.83)	109.85 (54.11)	13.88
Serum glucose (mg/dL)	95.50 (17.14)	93.59 (19.60)	10.35
Medications			
Fibrates	761 (3.74)	858 (2.19)	9.19

Ezetimibe	31 (0.15)	11 (0.03)	4.15
Aspirin	9,305 (45.76)	13,472 (34.31)	23.53
Clopidogrel	1,065 (5.24)	304 (0.77)	26.37
ACE inhibitors	7,142 (35.12)	10,705 (27.26)	17.02
Angiotensin II receptor blockers	488 (2.40)	649 (1.65)	5.30
β-Adrenergic antagonists	8,483 (41.72)	13,120 (33.42)	17.21
Thiazides and thiazide-like agents	5,376 (26.44)	8,896 (22.66)	8.79
ACE inhibitors with hydrochlorothiazide	1,615 (7.94)	2,519 (6.42)	5.92
Calcium channel blockers	5,658 (27.83)	9,499 (24.19)	8.29
α-Adrenergic antagonists	1,487 (7.31)	2,437 (6.21)	4.41
Sympatholytics, centrally acting	226 (1.11)	357 (0.91)	2.02
Arterial vasodilators	32 (0.16)	56 (0.14)	0.38
Glucocorticoids	4,092 (20.12)	8,108 (20.65)	1.31
Calcineurin inhibitors	37 (0.18)	45 (0.11)	1.75
Antipsychotics, typical	565 (2.78)	1,252 (3.19)	2.41
Antipsychotics, atypical	849 (4.18)	1,752 (4.46)	1.41
Thyroid disease			
Euthyroidism	18,377 (90.38)	35,764 (91.09)	
Subclinical hypothyroidism	118 (0.58)	74 (0.19)	6.34
Hypothyroidism untreated with thyroid hormone replacement	174 (0.86)	344 (0.88)	0.22
Hypothyroidism treated with thyroid hormone replacement	1,514 (7.45)	2,748 (7.00)	1.73
Hyperthyroidism	151 (0.74)	333 (0.85)	1.19

Data are *n* (%) or mean (SD). Statin users were prescribed simvastatin (96.6%), pravastatin (2.9%), or atorvastatin (0.5%).

Table 2

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Risk to develop DM associated with statin use and thyroid disease (*n* = 59,597): multivariable model results

Variable	RR (95% CI)
Statin use	2.57 (2.45–2.70)
Thyroid status	
Euthyroidism	Reference
Subclinical hypothyroidism	1.75 (1.40–2.18)
Hypothyroidism not treated with thyroid hormone replacement	1.53 (1.31–1.79)
Hypothyroidism treated with thyroid hormone replacement	0.90 (0.83–0.98)
Hyperthyroidism	0.95 (0.77–1.17)
Female sex	0.99 (0.94–1.05)
Arab ethnicity	1.50 (1.40–1.62)
Obesity	1.42 (1.35–1.49)
Smoking	1.11 (1.05–1.18)
Age	1.01 (1.01–1.01)
Serum triglycerides (mg/dL)	1.002 (1.002–1.003)
Serum HDL (mg/dL)	0.99 (0.99–0.99)
Serum LDL (mg/dL)	1.00 (1.00–1.001)
Serum glucose at baseline (mg/dL)	1.012 (1.011–1.014)

Hypertension	1.24 (1.14–1.34)
Ischemic heart disease	1.27 (1.19–1.34)

Adjusted also for use of aspirin, clopidogrel, ACE inhibitors, angiotensin II receptor blockers, β-adrenergic antagonists, thiazides, ACE inhibitors with hydrochlorothiazide, calcium channel blockers, α-adrenergic antagonists, centrally acting sympatholytics, arterial vasodilators, ezetimibe, glucocorticoids, calcineurin inhibitors, and antipsychotics.

Propensity score matching did not ideally match the highly compliant statin user and statin nonuser cohorts. Eleven clinical and laboratory characteristics carried >10% of the standardized difference (**Table 1**), and we assumed that the analysis of the two separate cohort models would compare populations with different characteristics, such as health behavior, and thus carry other unidentified biases. Therefore, we repeated the analysis in a selected subpopulation with no ischemic heart disease and drug treatment that had a high standardized mean difference (**Table 3**), including 14,856 statin nonusers and 5,264 statin users. DM developed after a mean follow-up time of 6.78 ± 0.08 years in statin nonusers and 6.22 ± 0.02 years in statin users. Subclinical hypothyroidism was found to be a significant risk factor for developing DM within the statin user cohort (RR 1.94 [95% CI 1.13–3.34]) and not within the statin nonuser cohort (RR 1.20 [0.52–2.75]). Hypothyroidism carried an increased risk for new-onset DM in both cohorts (RR 2.06 [1.42–2.99] and 1.66 [1.05–2.64] in statin users and nonusers, respectively). Patients with hypothyroidism treated with thyroid hormone replacement were not at risk for new-onset DM (**Table 4** and **Fig. 1**).

Table 3

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Characteristics and standardized mean difference of statin users and propensity score–matched statin nonusers after exclusion for history of coronary artery disease and use of aspirin, clopidogrel, ACE inhibitors, and β-adrenergic receptor antagonists

Characteristic	Statin users(*n* = 5,264)	Statin nonusers(*n* = 14,856)	Standardized mean difference (%)
Age (years)	59.79 (9.21)	58.16 (10.69)	16.36
Male sex	1,672 (31.76)	5,050 (33.99)	4.75
Jewish ethnicity	4,876 (92.63)	13,709 (92.28)	1.33
Obesity	1,878 (35.6S)	5,224 (35.16)	1.07
Smoking	1,440 (27.36)	4,265 (28.71)	3.01
Hypertension	1,107 (21.03)	2,866 (19.29)	4.33
Serum LDL (mg/dL)	121.61 (33.91)	117.88 (29.55)	11.71
Serum HDL (mg/dL)	48.64 (11.92)	49.66 (13.10)	8.08
Serum triglycerides (mg/dL)	119.14 (58.24)	115.06 (59.38)	6.94
Serum glucose (mg/dL)	93.14 (16.24)	92.11 (20.07)	5.64
Medications			
Fibrates	227 (4.31)	230 (1.55)	16.44
Ezetimibe	12 (0.2)	4 (0.03)	5.64
Angiotensin II receptor blockers	27 (0.51)	35 (0.24)	4.54
Thiazides and thiazide-like agents	440 (8.36)	920 (6.19)	8.35
ACE inhibitors with hydrochlorothiazide	151 (2.87)	252 (1.70)	7.86
Calcium channel blockers	493 (9.37)	920 (6.19)	11.87
α-Adrenergic antagonists	155 (2.94)	255 (1.72)	8.15
Sympatholytics, centrally acting	12 (0.23)	20 (0.13)	2.19
Arterial vasodilators	1 (0.02)	2 (0.01)	0.43
Glucocorticoids	1,022 (19.41)	2,520 (16.96)	6.36
Calcineurin inhibitors	7 (0.13)	6 (0.04)	3.15

Antipsychotics, typical	219 (4.16)	289 (1.95)	12.9
Antipsychotics, atypical	268 (5.09)	478 (3.22)	9.4

Data are *n* (%) or mean (SD).

Table 4

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Risk of developing DM in association with thyroid disease: multivariable model results

Cohort	Euthyroidism	Subclinical hypothyroidism	Hypothyroidism not treated with thyroid hormone replacement	Hypothyroidism treated with thyroid hormone replacement	Hyperthyroidism
Statin users (*n* = 5,264)	Reference	1.94 (1.13–3.34)	2.06 (1.42–2.99)	0.84 (0.68–1.03)	1.27 (0.75–2.13)
Statin nonusers (*n* = 14,856)	Reference	1.20 (0.52–2.75)	1.66 (1.05–2.64)	0.86 (0.67–1.09)	0.52 (0.19–1.40)

Data are RR (95% CI). Statin users cohort included all CHS highly compliant statin initiators in 2004–2005. Statin nonusers cohort included CHS propensity score–matched subjects. Patients with a history of coronary artery disease and use of aspirin, clopidogrel, ACE inhibitors, and β-adrenergic receptor antagonists were excluded. Each model was also adjusted for age; sex; ethnicity; obesity; smoking; serum glucose; LDL, HDL, and triglyceride levels at baseline; history of hypertension; and medication use, including fibrates, ezetimibe, angiotensin II receptor blockers, thiazides, ACE inhibitors with hydrochlorothiazide, calcium channel blockers, α-adrenergic antagonists, centrally acting sympatholytics, arterial vasodilators, glucocorticoids, calcineurin inhibitors, and antipsychotics.

Figure 1

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Kaplan-Meier estimates. Unadjusted association between thyroid disease and DM event rate within statin use groups. *A*: Statin users. *B*: Statin nonusers. *$P \leq 0.005$. ref, reference group (patients treated for hypothyroidism).

In an analysis using median TSH values obtained throughout follow-up, we observed a higher risk for DM in patients with median TSH values within the upper portion of the subclinical hypothyroid range (TSH 8 to <10 IU/mL) than in patients with TSH levels of 5.5 to <8 IU/mL, but due to smaller groups, these differences were not statistically significant. A statistically significant higher risk was associated within the hypothyroid TSH range of ≥10 IU/mL (RR 2.69 [95% CI 1.45–4.99] and 1.79 [1.04–3.07] for statin users and

nonusers, respectively) (Supplementary Table 1).

In a multivariate model of the association among new-onset DM, hypothyroidism, and statin use, risk of developing DM increased (RR 1.77 [95% CI 1.12–2.80], 3.56 [3.22–3.93], and 6.55 [4.46–9.64] for patients with hypothyroidism not exposed to statins, patients with euthyroidism exposed to statins, and patients with hypothyroidism exposed to statins, respectively) (Supplementary Table 2). Similarly, in a model comprising patients with subclinical hypothyroidism, RRs to develop DM were 1.31 (0.57–3.02), 3.55 (3.22–3.92), and 6.41 (3.69–11.14) in those with subclinical hypothyroidism not using statins, those with euthyroidism using statins, and those with subclinical hypothyroidism using statins, respectively (Supplementary Table 3). In stratification analysis of only patients with hypothyroidism and subclinical hypothyroidism by serum LDL levels, statin use was associated with DM risk at both normal and hypercholesterolemic levels (RR 3.71 [95% CI 1.70–8.09] and 3.35 [1.45–7.72] for LDL ≤130 and >130 mg/dL, respectively), demonstrating that DM risk in patients with hypothyroidism was not the result of hypercholesterolemia (Supplementary Table 4).

To confirm that there was no early detection (surveillance) bias as a result of the subclinical nature of early DM, we evaluated HbA_{1c} values at time of DM diagnosis in the various thyroid disease subgroups. If patients with hypothyroidism were diagnosed with DM earlier because they were in closer clinical follow-up as a result of their condition, they were expected to be diagnosed with a lower HbA_{1c}. Mean HbA_{1c} levels at diagnosis were 6.81 in patients with euthyroidism, 6.92 in patients with hypothyroidism not treated with thyroid hormone replacement, and 6.71 in patients with hypothyroidism treated with thyroid hormone replacement, showing that the observed higher risk for DM in untreated patients with hypothyroidism was not a result of early detection bias. Additionally, if patients with hypothyroidism were diagnosed with DM earlier due to closer surveillance, then the same could have occurred in patients with hypothyroidism treated and not treated with thyroid hormone replacement. Patients with hypothyroidism treated with thyroid hormone replacement were in the lowest risk group for DM and had the longest time to DM occurrence (**Fig. 1*A*** and **Table 4**), implying that diagnosis was not due to earlier detection but probably to thyroxine levels. We also evaluated the number of laboratory serum glucose measurements in the 2-year period before DM diagnosis as a measure of frequency and intensity of medical care received. If there were more frequent laboratory tests in any of the thyroid disease subgroups, then there could have been earlier detection of DM in this subgroup. We found a median of four laboratory glucose measurements in the euthyroid, subclinical hypothyroid, and hypothyroid not treated with thyroid hormone replacement subgroups and a median of five laboratory glucose measurements in the hypothyroid treated with thyroid hormone replacement subgroup. Thus, no difference in this measure of frequency of medical care was observed between the euthyroid and hypothyroid not treated with thyroid hormone replacement subgroups, and it is unlikely that DM excess risk in the patients with hypothyroidism was a result of an early detection bias.

Conclusions

Hypothyroidism is a risk factor for new-onset DM irrespective of statin treatment. DM risk associated with subclinical hypothyroidism is significant in statin users only. The association among hypothyroidism, subclinical hypothyroidism, and DM is described in the literature but remains to be better established. Insulin resistance is found in patients with hypothyroidism (**18**) and decreased glucose uptake into muscle and adipose tissues exhibited in hypothyroid state in vitro (**19**). Impaired translocation of GLUT4 glucose transporters on the plasma membrane in patients with hypothyroidism and subclinical hypothyroidism (**20**) as well as downregulation of the hepatic glucose transporter GLUT2 (**21**) have been demonstrated. Even low-normal free thyroxin levels in patients with euthyroidism have been associated with insulin resistance (**22**,**23**). Thyroid disease induces mitochondrial dysfunction (**24**–**27**), and statins reduce levels of coenzyme Q10, a component of the electron transport chain involved in the process of ATP generation (**28**), also leading to mitochondrial dysfunction as well as causing reduced insulin release and pancreatic β-cell failure and contributing to the development of DM (**29**–**32**). Downregulation of GLUT4 in adipocytes has also been shown to be a result of statin treatment, an effect that has been explained in terms of reduced isoprenoid biosynthesis (**33**). GLUT4 function, already compromised in patients with hypothyroidism and subclinical hypothyroidism, may be further affected by statin treatment,

thus leading to the development of DM. In the present MoA-based analysis (Supplementary Data), thyroid disease was one of the risk factors identified for statin-associated DM, with mitochondrial dysfunction a common pathophysiological process related to both DM and thyroid dysfunction that can be aggravated by statins.

We found that in highly compliant patients taking at least 80% of their prescribed statin doses in a follow-up of 5–7 years, statin-associated risk for DM was >2.5-fold. In other studies where risk assessments were lower, compliance was not measured. In a meta-analysis of 13 randomized statin trials with a mean follow-up of 4 years (1.9–6 years), a 9% increase in the likelihood of developing DM was identified (**34**). The hazard ratio for statin-associated diabetes was 1.14 (95% CI 1.10–1.19) in a study using electronic medical records that also adjusted for possible differential survival bias (i.e., patients prescribed statins survived longer to develop DM) (**35**). In the Women's Health Initiative, long-term follow-up yielded a propensity score–adjusted hazard ratio of 1.40 (1.31–1.51) to develop DM (**36**). Dose effect was demonstrated in a meta-analysis of five randomized clinical trials with an odds ratio of 1.12 (1.04–1.22) for increasing dose (**37**), and higher-potency statins were associated with increased risk of new-onset DM compared with lower-potency statins (**38**).

Limitations of the current study include residual confounders not introduced into the models and identified unbalanced confounders due to inherent differences between statin users and nonusers. Selection bias might have occurred as a result of the exclusion of subjects with no TSH laboratory tests. However, because the percentage of those excluded from the population studied was low, this would probably not change the results. Misclassification bias might have occurred if patients with DM were not identified by treating physician diagnosis, serum glucose and HbA_{1c} levels, or diabetic drug therapy; however, this misclassification is likely to be nondifferential and thus strengthens the null hypothesis.

In conclusion, this study identifies hypothyroidism as a risk factor for DM irrespective of statin treatment, whereas subclinical hypothyroidism–associated risk is prominent only upon statin treatment. The latter might be a result of an additive effect of the subclinical hypothyroid state and statins on mitochondrial function. This epidemiological exploration was guided by an MoA-based analysis, an approach that allowed us to scrutinize thyroid disease, a formerly unrecognized risk factor for DM. Hypothyroidism and subclinical hypothyroidism are pathological conditions that are easy to monitor and treat. Detecting and correcting hypothyroidism and considering treating subclinical hypothyroidism before initiating a statin are strategies that can potentially decrease DM incidence.

Article Information

Duality of Interest. S.N.D. is the senior vice president of drug discovery at Biovista Inc., which specializes in drug repurposing and adverse drug prediction. A.S.P. is the chief executive officer of Biovista Inc. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. N.G. and S.N.D. contributed to the study concept and design, data acquisition, data analysis and interpretation, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. I.L. contributed to the study concept and design, data acquisition, data analysis and interpretation, statistical analysis, and critical revision of the manuscript for important intellectual content. A.S.P. contributed to the data analysis and interpretation, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. D.R.A. contributed to the study concept and design and critical revision of the manuscript for important intellectual content. G.R. contributed to the study concept and design, study supervision, data analysis and interpretation, and critical revision of the manuscript for important intellectual content. N.G. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Footnotes

- This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc14-2515/-/DC1.

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