Statins and Risk of Diabetes Mellitus Type 2

A Systematic Review of the Literature

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Abstract

Objective: Several historical studies have indicated a relationship between statin use and the occurrence of new-onset diabetes mellitus type II (NODM). The aim of this study is to review the data in order to determine how significant this risk is, and whether there are any underlying factors that should be considered when prescribing statins. This will add to the current body of knowledge and potentially provide valuable clinical guidance in terms of whether careful monitoring or screening of patients taking statin medication is warranted, in order to mitigate the risk of incident diabetes.

Methods: A systematic literature search of MEDLINE, google scholar, and JSTOR was conducted. Studies were included if they examined the association of statin exposure with the risk of NODM or insulin resistance (IR) in a non-diabetic or non-pre-diabetic population of participants taking statin therapy for at least two months; amongst excluded were systematic reviews or literature reviews. Of the selected studies, data on the association between statin use and the risk of NODM/IR were presented and discussed.

Results: The majority of the chosen investigations found a statistically significant association between statin drug therapy and risk of development of NODM or IR. Six of seven studies used for sub-analysis of gender-specific effects showed an increased risk of NODM/IR in females. Nine of ten studies used for investigations examining dosage found an increased risk of NODM in higher dosage statin regimens. While studies examining classification-specific effects had variable findings, the majority found an increased risk in lipophilic statins.

Conclusions: Statistically significant associations were found between statin exposure and incident diabetes, indicating it may be advisable to incorporate initial risk screening and individualized statin therapies into practice.

Introduction

For decades, statins have been used as a first-line treatment for elevated LDL-C. However, in 2012 the FDA, based on its review of several meta-analyses and other published data, modified statin warning labels to include information related to the connection between statins and incident diabetes, elevated HbA1C, and elevated fasting plasma glucose. The goal of this systematic review is to assess the association between statins and the potential adverse effect of NODM.

Statins (such as rosuvastatin and lovastatin) work by inhibiting HMG-CoA reductase, thus preventing the conversion of HMG-CoA (3-hydroxy-3-methyl-glutaryl-coenzyme A) to its metabolite mevalonate, an essential precursor to cholesterol synthesis. One of the reasons that this yields a powerful blockade of cholesterol synthesis is because HMG-CoA reductase is the rate limiting step in this reaction. Another mechanism of action that is exhibited by statins is the upregulation of LDL receptors in the liver, thus, increasing the clearance of plasma LDL.

Previous literature has proposed several different mechanisms through which statins may exert their diabetogenic effects, although a precise mechanism of action has yet to be ascertained. The major mechanisms elucidated include the impairment of insulin secretion, reduced translocation of glucose transporter 4 (GLUT4), and the downregulation of other important downstream products such as coenzyme Q10 (CoQ10), farnesyl pyrophosphate, geranylgeranyl pyrophosphate, and dolichol, which normally play an important role in intracellular signaling and transduction (Brault et al., 2014). Other potential mechanisms include the involvement of statins in inhibition of adipocyte differentiation which affects glucose homeostasis; decreased leptin, and decreased adiponectin levels (Brault et al., 2014). See figure 1 for a summary of the various proposed mechanisms.

Diabetes mellitus type II (T2DM) results from an increase in resistance to insulin. Under normal circumstances, insulin functions to transport plasma glucose into cells for a source of energy. When the body exhibits resistance to insulin, this can result in hyperglycemia and its associated side effects. In practice, the most reliable methods of measuring insulin resistance are the hyperinsulinemic euglycemic clamp and the intravenous glucose tolerance test, both of which are considered reference standards (Gutch et al., 2015). The clamp in particular is a more difficult and complicated method to use in large-scale investigations and clinical practice, and thus simple indices have been developed for the measurement of insulin resistance (Chen et al., 2005). The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) is a simple computation which serves to evaluate the function of beta cells and insulin resistance via fasting steady-state glucose and insulin levels (Gutch et al., 2015; Wallace et al., 2004). Originally defined by Katz et al. (2000), the quantitative insulin-sensitivity check index (QUICKI) is another index for measurement of insulin resistance and is determined by a mathematical transformation utilizing fasting glucose and fasting insulin levels (Chen et al., 2005). During its initial development, QUICKI showed a better correlation with the reference standard (glucose clamp) than other indices, thus making it an accurate and useful tool for use in larger investigations (Katz et al., 2000).

In regard to the diagnostic criteria for T2DM, both the American Diabetes Association and Diabetes Canada adhere to equivalent biochemical reference values. According to the American Diabetes Association, in order to meet the diagnostic criteria for T2DM, the fasting plasma glucose levels must be ≥126 mg/dl (or ≥7.0 mmol/L in Canada); the oral glucose tolerance test levels must be ≥200 mg/dl (or ≥11.1 mmol/L in Canada); the random plasma

glucose levels (taken at any time of the day) must be ≥200 mg/dl (or ≥ 11.1 mmol/L in Canada); HbA1C must be ≥6.5% (American Diabetes Association, 2018; Punthakee et al., 2018).

The Canadian Cardiovascular Society's Dyslipidemia Guidelines indicates statin treatment in the risk management of various conditions (refer to table 1). These high-risk conditions necessitate statin therapy in order to lower the risk of cardiovascular disease (CVD) events and mortality (Anderson et al., 2016). Risk assessment for primary prevention of CVD is quantified through the Framingham Risk Score (FRS), which is commonly used to estimate the 10-year cardiovascular disease risk, or the Cardiovascular Life Expectancy Model (CLEM) (Anderson et al., 2016). The FRS allocates points separately according to gender, and considers risk factors such as: age, HDL-C levels, total cholesterol, systolic blood pressure, smoker status, as well as diabetes status. As per table 1, statins are not indicated in an FRS<10%. Recommended are lifestyle interventions such as smoking cessation, exercise, and a Mediterranean diet (Allan et al., 2015). This risk estimation is to be retested every 5 years or when the individual's risk is anticipated to change, as per Canadian Cardiovascular Society recommendations (Allan et al., 2015; Anderson et al., 2016).

The American College of Cardiology/American Heart Association (ACC/AHA) task force provides guidelines on the management of blood cholesterol, the most recent of which was published in 2018 (Grundy et al., 2019). These guidelines take into consideration the risk level of patients for atherosclerotic cardiovascular disease (ASCVD), using the ASCVD risk estimator web application 10-year risk score to determine the recommended treatment protocols. This score is calculated based on age, sex, race, systolic and diastolic blood pressure, cholesterol markers, and healthy history including diabetes, smoking, and hypertension medications. As can

be seen in figure 2, the corresponding protocols range from the discussion of lifestyle modifications to the maximal tolerated statin (Grundy et al., 2019).

Common risk factors for the onset of T2DM include age (typically occurs in later years), genetics (strong association with family history), and obesity. As previously stated, the aim of this research paper is to assess the extent to which statins can be added to the list of associated risk factors. Previous studies have shown that the benefits of statins potentially outweigh the risk of incident diabetes due to its powerful effects of decreasing and preventing the incidence of CVD. However, along with the administration of statins there should be advised guidelines of appropriate exercise and diet (Zigmont et al., 2019). The following results are to the researchers' best ability as medical students, and to stay in accordance with the proposed timeline and resources approved by Saint James School of Medicine.

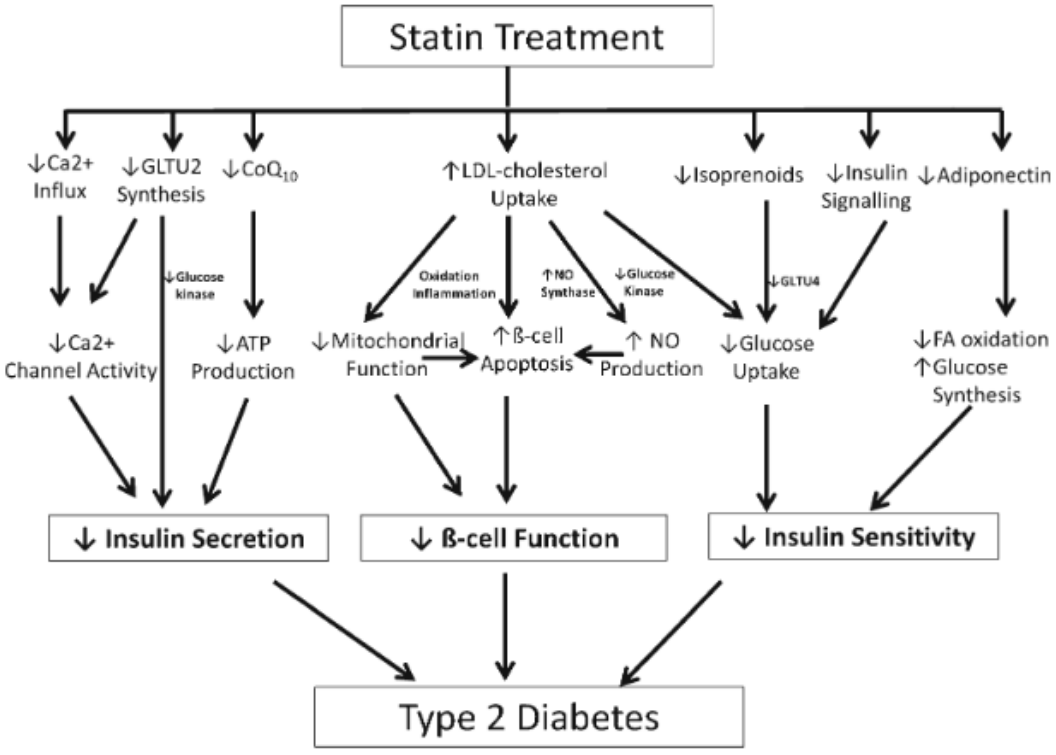

Figure 1. Potential mechanisms of action in the development of diabetes mellitus type II (Chan et al., 2015).

Table 1. Risk stratification according to Framingham Risk Score.

Using 10-year CVD risk from Step 2, determine if patient is Low, Moderate or High risk.† Indicate Lipid and/or Apo B targets

Risk Level†	Initiate Treatment If:	Primary Target (LDL-C)	Alternate Target
High FRS ≥20%	• Consider treatment in all *(Strong, High)*	• ≤2 mmol/L or ≥50% decrease in LDL-C *(Strong, Moderate)*	• Apo B ≤0.8 g/L or • Non-HDL-C ≤2.6 mmol/L *(Strong, High)*
Intermediate FRS 10-19%	• LDL-C ≥3.5 mmol/L *(Strong, Moderate)* • For LDL-C <3.5 mmol/L consider if: • Apo B ≥1.2 g/L • OR Non-HDL-C ≥4.3 mmol/L *(Strong, Moderate)* • *Men ≥50 and women ≥60 with 1 risk factor: low HDL-C, impaired fasting glucose, high waist circumference, smoker, hypertension*	• ≤2 mmol/L or ≥50% decrease in LDL-C *(Strong, Moderate)*	• Apo B ≤0.8 g/L or • Non-HDL-C ≤2.6 mmol/L *(Strong, Moderate)*
Low FRS <10%	• statins generally not indicated	• statins generally not indicated	• statins generally not indicated
Statin-indicated conditions**	• *Clinical atherosclerosis** • *Abdominal aortic aneurysm* • *Diabetes mellitus* *Age ≥ 40 years* *15-Year duration for age ≥ 30 years (DM1) Microvascular* ***disease*** • *Chronic kidney disease* *(age ≥ 50 years)* *eGFR <60 mL/min/1.73 m2 or ACR > 3 mg/mmol*		

Lipid targets LDL-C:_____ or Apo B:_____

Note: Data is adapted from Genest et al. (2009) and Anderson et al. (2013), for the Canadian Cardiovascular Society.

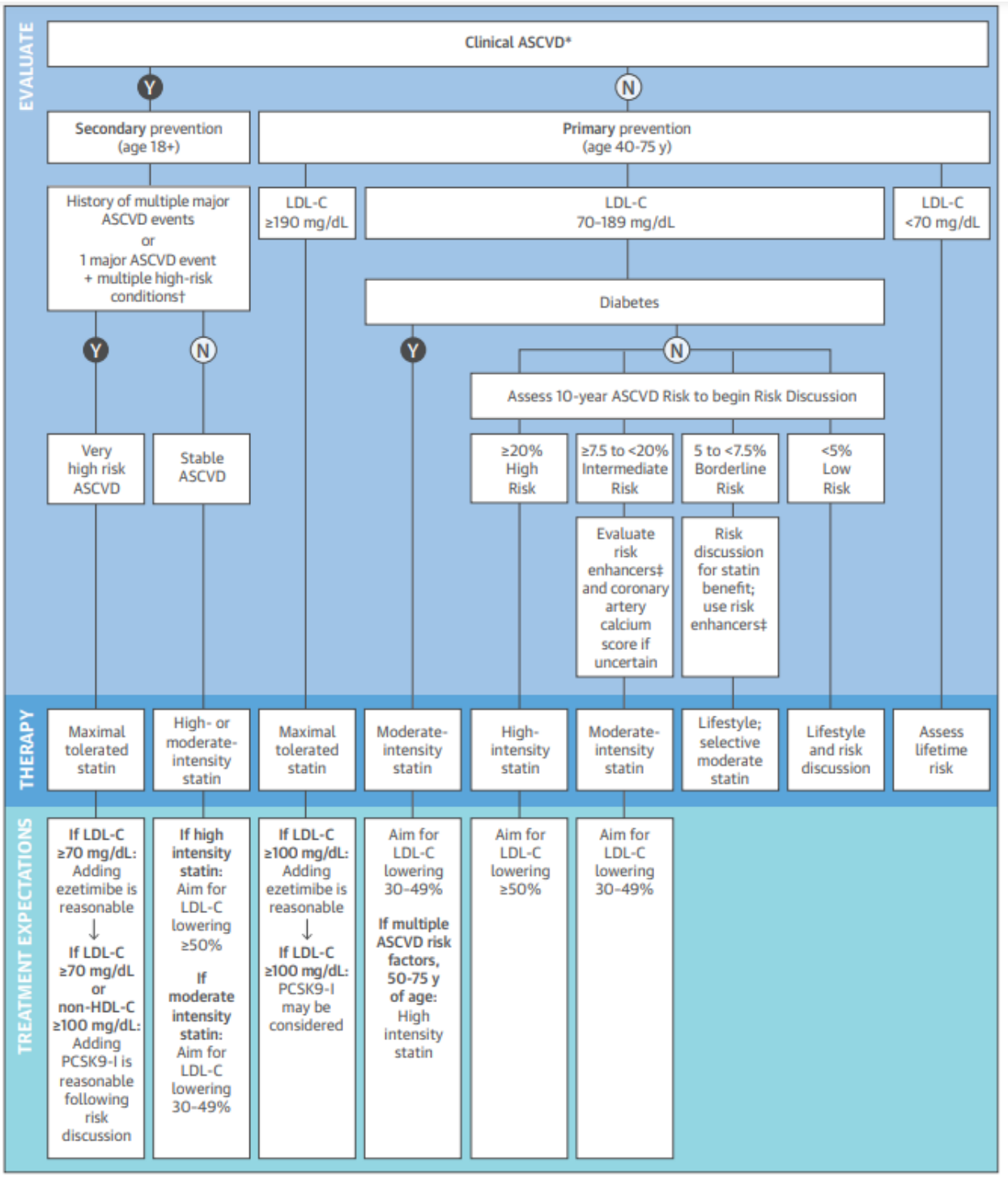

Figure 2. ACC/AHA 2018 Cholesterol Guideline: Overview of Primary and Secondary Prevention (Grundy et al., 2019).

Methods

The aim of this research was to perform a comprehensive systematic literature review search through a variety of resources including: MEDLINE, Google Scholar, and JSTOR. Search terms “insulin”, “hyperinsulinemia”, “type II diabetes”, “diabetes”, “statin”, “HMG-CoA reductase inhibitor”, “hyperglycemia”, “insulin resistance” were used to identify relevant studies discussing the role of statin drug therapy and IR/NODM. Citations were screened and assessed for quality via Rayyan, a web application. If an article met the below listed exclusion criteria, it was excluded from the analysis. Two review authors assessed study eligibility and risk of bias, with a third reviewer settling any discrepancies. Data screening and extraction were completed independently by each reviewer.

The inclusion criteria for this research were as follows: scholarly or peer-reviewed studies, relevant articles published within the last 15 years, articles published in the English language, and studies in which participants had taken statin therapy for the duration of at least two months. Chosen articles were those examining the possible association between statin drug therapy and the development of NODM or IR. Excluded were publications potentially used for marketing purposes, articles in foreign languages, articles dated prior to 2005, literature reviews, systematic reviews, and duplicate articles. Studies examining a previously diagnosed pre-diabetic population or a population with previously diagnosed type 1 or 2 diabetes mellitus were also excluded.

The primary outcome was NODM, defined as a record of diagnosis of T2DM or prescription for insulin or an oral antidiabetic agent. Other outcome measures included an elevation in fasting serum insulin levels (indicator of IR) or elevated blood glucose/HbA1C levels as defined by Diabetes Canada and the American Diabetes Association diagnostic

biochemical criteria. Additionally, a qualitative sub analysis was performed for the following secondary outcomes: to examine any gender-specific effects, statin classification, and statin dosage on the development of T2DM.

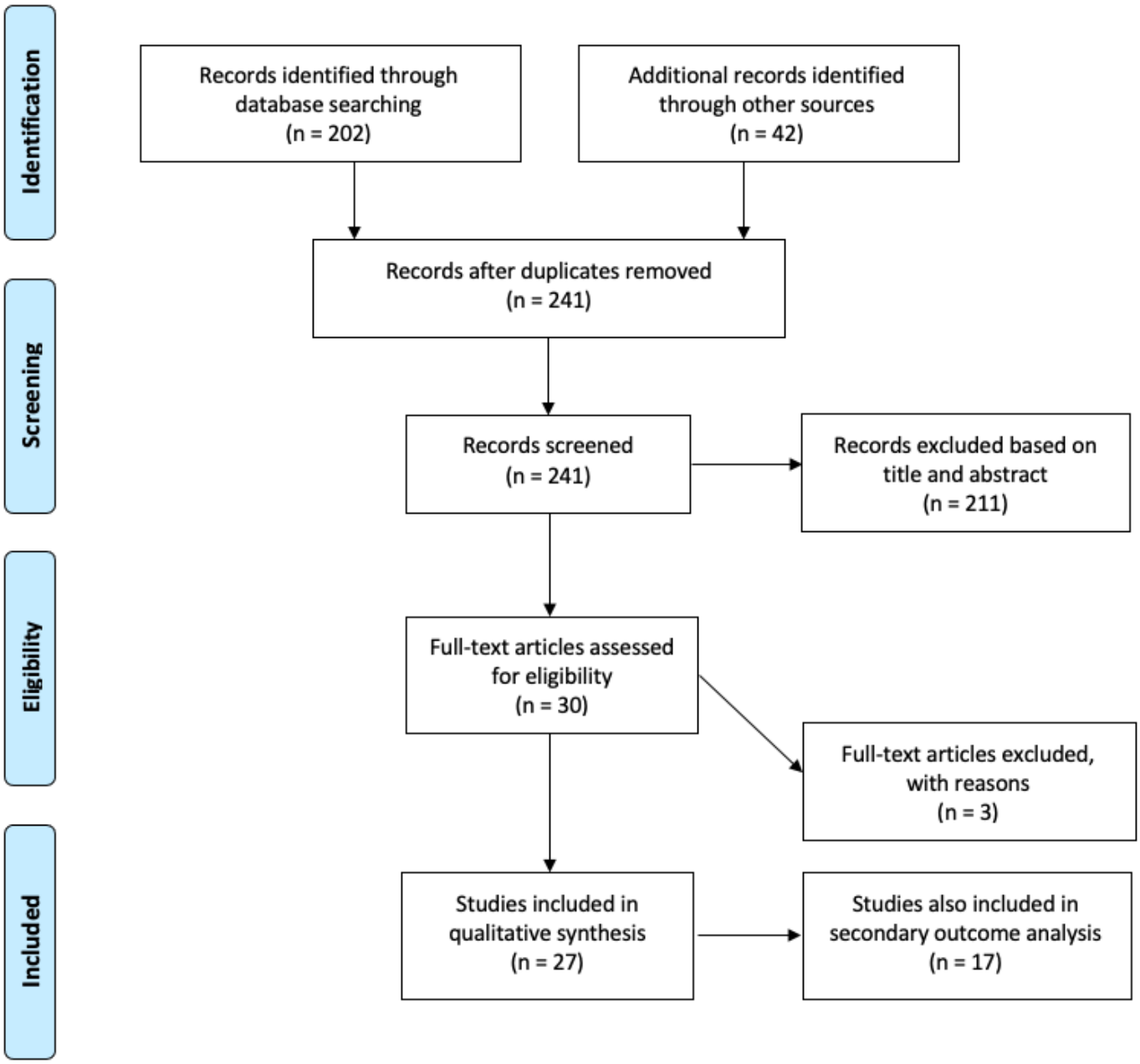

Figure 3. Flow-chart for the selection and review of eligible studies

Results

Table 2. Summary of Primary Outcome Findings

First author (Year)	Design	NODM definition (where applicable)	Mean age (Year)	Findings
Association of statin users with the diagnosis of diabetes mellitus type II				
Carter AA (2013)	Retrospective cohort (n=471,250)	Diagnosis of diabetes in the Ontario Diabetes Database	Reported by statin class used; ranged 72.83 ± 5.49 to 73.97 ± 6.34	Crude event rates for incident DM ranged from 21.52 outcomes/1000 PY for fluvastatin to 34.21 outcomes/1000 PY for rosuvastatin. Atorvastatin use was associated with a 22% increase in NODM (adjusted HR 1.22; 1.15-1.29). Increased risk was also associated with rosuvastatin (1.18; 1.10-1.26) and simvastatin (1.10; 1.04-1.17).
Castro MR (2016)	Retrospective cohort (n=18,071)	Diagnosis of NOD via Rochester Epidemiology Project resources	53.52 ± 17.10 (no statin exposure) 60.12 ± 13.60 (statin exposure)	At the end of follow-up, the normoglycemic group saw 1182 (10%) new diagnoses of diabetes. A higher risk was found in patients with pre-existing IFG, compared to normoglycemic patients. As a predictor of diabetes, statin use showed the following: in normoglycemic patients HR 1.191; 1.05-1.35 and in IFG patients 1.24; 1.1l-1.38.
Casula M (2017)	Meta-analysis of 20 studies	Varied: diagnosis, prescription for antidiabetic drugs, self-report, biochemical measures	Ranged from 40.0-65.4	Statin therapy was found to have a significantly higher risk of NODM, compared with no therapy (RR 1.44; 1.31-1.58). Single statins, rosuvastatin and atorvastatin, produced the greatest increase in risk, RR 1.61 (1.30-1.98), and RR 1.49 (1.31-1.70), respectively.
Cederberg H (2015)	Prospective cohort (n=8749)	FPG ≥7.0 mmol/L, 2hPG ≥11.1 mmol/L in an OGTT, or HbA1C ≥6.5%, or use of antihyperglycemic medication started during follow-up		A greater percentage of statin users (11.2%) developed diabetes, compared with non-users (5.8%), p<0.001. During follow-up, statin treatment resulted in a twofold increased risk of diabetes (HR 2.01; 1.71-2.36). After adjustment for baseline confounders, the risk was 1.46; 1.22-1.74.
Culver AL (2012)	Randomized controlled trial (n=153,840)	Self-report of a new physician diagnosis of treated DM	63.2 ± 7.3	The event rate was 10,242 incident cases of DM/1,004,466 PY of follow-up. Statin use at baseline showed a statistically significant association with increased DM risk (HR 1.71; 1.61-1.83), compared to non-users.
Izzo R (2012)	Prospective cohort (n=4750)	Prescriptions of oral antihyperglycemic drugs or insulin. Diagnosis confirmed by biochemical measures: FPG ≥7.0 mmol/L, 2hPG ≥11.1 mmol/L in an OGTT, HbA1C ≥6.5%, or non-fasting serum glucose ≥11.1 mmol/L	57.91 ± 9.1 (no statin exposure) 62.54 ± 7.3 (statin exposure)	At the end of follow-up, patients under statin therapy saw an 18.1% prevalence of diabetes, and a prevalence of 7.2% in non-statin users (RR 2.85; 2.28-3.56; p<0.0001). The unadjusted risk of incident diabetes did not show a significant difference as statin users saw a 10.2% incidence and 8.7% in non-users (RR 1.02; p=0.192).
Jones M (2017)	Prospective cohort (n=8372)	Prescription for insulin or analogues or other antihyperglycemic medications	72.7 ± 1.5 (no statin exposure) 72.4 ± 1.5 (statin exposure)	383 study participants (5%) were given new prescriptions for insulin/analogues/other antihyperglycemic medications. Cox regression indicated an association between statin drug therapy and treatment for NOD (HR 1.33; 1.04-1.79; p=0.024).

First author (Year)	Design	NODM definition (where applicable)	Mean age (Year)	Findings
Association of statin users with the diagnosis of diabetes mellitus type II (cont.)				
Kim DW (2019)	Case-control (n=6417)	FSG ≥126 mg/dl or as a record of T2DM diagnosis according to ICD-9 diagnosis codes, and prescription of antidiabetic agents	51.1 ± 13.2	Risk of NODM for age- and sex- adjusted data was 1.44 (1.31-1.59). When adjusted for drinking, smoking, exercise, BMI, hypertension, HDL-C, LDL-C, TG, and WC, no significant difference was noted (OR 1.03, 0.93-1.14).
Ko MJ (2019)	Prospective cohort (n=1,034,982)	ICD-10 codes E11-14 and new prescription of insulin or oral antidiabetic drugs	55.0 ± 8.6	Statin ever-use showed a significant association with DM risk compared with statin never-use (13.4 vs 6.9 events / 1000 PY, respectively; adjusted HR 1.88; 1.85-1.93). A proportional increase in the risk of DM was reported with an increasing duration of statin use (HR 1.25 < 1 yr, 2.22 1-2 yrs, 2.62 > 2 yrs).
Lee J (2016)	Retrospective cohort (n=94,370)	Record of T2DM diagnosis and prescription of antidiabetic agents	60.84 ± 11.63	The incidence rates of NODM were 7.8% and 4.8% in the statin users and non-statin users, respectively. The risk of NODM was higher among statin users (crude HR 2.01, 1.93-2.10; covariate-adjusted HR 1.84, 1.63-2.09), compared with non-users.
Lee SE (2018)	Prospective cohort (n=40,164)	ICD-10 codes E11-14, with prescription of diabetic drugs	55.1 ± 9.0	Statin use was associated with the development of NODM (HR 1.66, 1.49-1.85, p<0.001). The risk of NODM in relation to statin use was significantly increased in normotensive patients (HR 1.31, 1.09-1.58, p=0.0069) and not in hypertensive patients (HR 1.18, 0.96-1.46, p=0.114).
Macedo AF (2014)	Prospective cohort (n=2,016,094)	Diagnosis via CRPD record using Read codes	63.77 ± 10.81	A positive association between statin use and increased risk of T2DM was reported (HR 1.57; 1.54-1.59) - this risk increased with longer duration of statin use.
Porath A (2018)	Retrospective cohort (n=265,414)	DM registry (MHS EMR) - contains hospitalization records, prescribed medication, laboratory tests, physician diagnoses	50.8 ± 7.6	From 2010-2014, 11,637 (4.4%) new cases of DM were observed (RR 3.8).
Preiss D (2011)	Meta-analysis of 5 trials (n=32,752)	FPG ≥ 126 mg/dL on two occasions, adverse event report of NODM, or prescription for antihyperglycemic medication	Ranged from 58 ± 11 to 64 ± 9	8.4% of the 32,752 participants without diabetes at baseline developed diabetes after statin exposure (OR 1.12, 1.04-1.22; I^2 = 0%).
Rajpathak SN (2009)	Meta-analysis of 6 trials (n=57,593)	Varied: FSG ≥ 126 mg/dL on two occasions, initiation of antidiabetic medication, or physician diagnosis	Ranged from 55.2-73.0	The summary RR reported for NODM was 1.13 (1.03-1.23; p=0.007). Collectively, all six studies reported a total of 2082 cases of NODM during follow-up.
Roy R (2019)	Retrospective cohort (n=270)	FSG of 100-125 mg/dL were categorized as prediabetic and FSG ≥ 126 mg/dL as diabetic		Among 270 dyslipidemic patients, 7.03% developed statin-induced NODM and 25.56% were classified as pre-diabetic.

First author (Year)	Design	NODM definition (where applicable)	Mean age (Year)	Findings
Association of statin users with the diagnosis of diabetes mellitus type II (cont.)				
Sattar N (2010)	Meta-analysis of 13 trials (n=91,140)	Varied by trial, mainly one or two FSG ≥ 7 mmol/L	Ranged from 55.0 to 76.0	4727 participants, 2226 of whom were on statins, developed diabetes during a mean of 4 years. Statin treatment was associated with a 9% increased risk (OR 1.09; 95% CI 1.02-1.17) for NODM. In 2 large trials of patients with heart failure, statin therapy did *not* show cardiovascular benefit yet risk of NODM was increased.
Thakker D (2016)	Meta-analysis of 29 trials (n=141,863)	Varied by trial, mainly one or two FSG ≥ 7 mmol/L	Ranged from 54.1 ± 10.8 to 75.4 ± 3.3	Statins increased the risk of NODM by 12% (pooled OR 1.12, 1.05-1.21; I^2 36%; p=0.002; 18 RCTs). Atorvastatin 80 mg had the highest risk of NODM (OR 1.34, 1.14-1.57) followed by rosuvastatin (OR 1.17, 1.02-1.35).
Thomson SR (2018)	Cross-sectional (n=104)	FSG, FSI, and HOMA scores	62.26 ± 10.02	Of the 104 patients who were exposed to statins, 7.7% (n=8) developed NODM and 3.8% (n=4) developed prediabetes.
Wang S (2017)	Meta-analysis of 14 trials (n=60,287)	Varied by trial, but mainly one or two FSG ≥ 126 mg/dL	Ranged from 55.2 to 76.0 depending on the trial	Of the initial non-diabetic patients, 4559 developed diabetes (OR 1.11, 1.03-1.20). LDL reductions of 40-50% were associated with a 29% increase in NODM (OR 1.29, 1.13-1.47), and reductions of 30-40% were associated with a 13% increase (OR 1.13, 1.01-1.26), but LDL reductions of less than 30% had no statistical significance of NODM.
Waters DD (2011)	Meta-analysis of 8 trials (n=7595)	≥2 post-baseline FSG ≥7.0 mmol/L and at least 1 post-baseline FSG > 2 mmol/L above baseline; also, NODM identified via adverse event reporting	Ranged from 60.6 ± 8.9 to 62.5 ± 11.6 depending on the trial	In the TNT trial, there was an 8.11% - 9.24% incidence of NODM depending on dose (HR 1.10, 0.94 to 1.29; p=0.226). In the IDEAL trial, there was a 5.59% - 6.40% incidence of NODM depending on drug/dose (HR 1.19, 0.98 to 1.43; p=0.072). In the SPARCL trial, 6.06% of placebo and 8.71% of statin use resulted in NODM (HR 1.37, 1.08 to 1.75; p=0.011).
Yoon D (2016)	Prospective cohort (n=14,067)	ICD-10 codes, or patients receiving antidiabetic medications or having abnormal glucose/HbA1c results	54.1 ± 14.0 (no statin exposure) 54.3 ± 12.3 (statin exposure)	The statin-exposed group had a higher incidence of NODM (6.000/1000 PY) than the non-exposed group (3.244/1000 PY). Statin exposure resulted in a higher risk of developing NODM (HR 1.872; 1.432-2.445; p<0.001).
Zigmont VA (2019)	Retrospective cohort (n=7064)	ICD-9 diagnosis codes present on an inpatient medical claim/claim with a CPT code	45.83 ± 10.53 (no statin exposure) 49.17 ± 9.58 (statin exposure)	Over the course of the study period, statin users saw an incidence rate of 6.6% for NODM, with a greater proportion of cases among statin users (n=112; 14.8%) compared with no exposure to statins (n=198; 5.0%). Statin users had a higher risk of developing NODM (AHR 2.14; 1.35-3.58; p=0.002).

First author (Year)	Design	NODM definition (where applicable)	Mean age (Year)	Findings
Association of statin users and elevated blood glucose and HbA1C levels				
Kim J (2018)	Prospective cohort (n=379,865)		51.9 ± 9.2	High PDC by statins was associated with an increase in fasting glucose (β=0.093; SE 0.007; p<0.001).
Association of statin users and elevated serum fasting insulin levels				
Rees-Milton KJ (2020)	Prospective cohort (n=609)			A positive association between statin use and higher levels of HOMA-IR was reported (β=1.52, 1.18-1.95, P<0.01).
Combined primary outcomes				
Ahmadizar F (2019)	Cross-sectional (n=9535) Longitudinal follow-up (n=8567)	FSG ≥7.0 mmol/L or non-fasting serum glucose ≥11.1 mmol/L, or use of antihyperglycemic medication	54.3 ± 10.1	A statistically significant association was found between baseline statin use and increased serum fasting insulin levels (β = 0.07; 95% CI 0.02-0.13) and HOMA-IR index (β = 0.09; 95% CI 0.03-0.14). At the end of follow-up, ever-statin use was associated with incident type 2 diabetes, compared with never-users (crude HR 1.64; 95% CI 1.37-1.97).
Kim W (2013)	Randomized, prospective, single blind (n=53)	Fasting glucose, insulin, HbA1C, HOMA and QUICKI indices for insulin sensitivity	60.7 ± 6.8	The results for the control and rosuvastatin treatment groups were the following: HbA1C (3.0 ± 10.1% vs. -1.3 ± 12.7%; p=0.33), fasting glucose (-1.3 ± 18.0% vs. 2.5 ± 24.1%; p=0.69), fasting insulin levels (5.2 ± 70.5% vs. 22.6 ± 133.2%; p=0.27), QUICKI index: mean change, 2.2 ± 11.6% vs. 3.6 ± 11.9%; p=0.64), and the HOMA index (11.6 ± 94.9% vs. 32.4 ± 176.7%; p=0.44).

FSG, fasting serum glucose; FSI, fasting serum insulin; HOMA-IR, homeostatic model assessment of insulin resistance; PY, person years; IFG, impaired fasting glucose; OGTT, oral glucose tolerance test; 2hPG, 2-hour plasma glucose; WC, waist circumference; PDC, proportion of days covered by statins; QUICKIE, Quantitative Insulin-Sensitivity Check Index; EMR, electronic medical records

Secondary outcome sub analyses:

Table 3. Associations of New-Onset Diabetes Mellitus Risk According to Gender

Author	Year	Findings
Culver, et al.	2012	There is an association between NODM and postmenopausal women. Of the 153,840 patients included in the study, 10,834 were receiving statin therapy with a total of 1076 reporting NODM (9.93%); of the remaining 143,006 patients not receiving statin therapy, 9166 self-reported NODM (6.41%).
Izzo, et al.	2012	Statin therapy is associated with NODM, especially amongst older females who had high initial total cholesterol levels.
Lee, et al.	2018	Amongst female statin users, there was an increased risk in the development of NODM in patients with normal blood pressure (HR 1.76; 95% CI 1.48-2.10, p<0.001) as well as patients with hypertension (HR 1.32, 1.21-1.70, p=0.030).
Rajpathak, et al.	2009	Female sex is significantly associated with increased risk of NODM.
Roy, et al.	2019	Out of the 270 patients enrolled in the study, 19 developed NODM. Of the patients who developed NODM, 11 (57.8%) were female
Yoon, et al.	2016	Among patients receiving statin therapy, males were at a statistically significant increased risk of developing NODM (HR 1.944; 1.497–2.523).

Table 4. Associations of New-Onset Diabetes Mellitus Risk According to Statin Classification

Author	Year	Findings
Carter, et al.	2013	Of the 471,250 patients followed throughout the study (receiving statin therapy for either primary or secondary prevention of CAD), NODM was highly associated with the lipophilic statin, atorvastatin. There was a total of 30 patients diagnosed with NODM per 1000 patients receiving atorvastatin. In addition, there were no statistically significant differences between patients taking statin therapy for primary prevention compared to those taking statin therapy for secondary prevention.
Rees-Milton, et al.	2020	Insulin resistance amongst patients taking statin therapy was statistically significantly higher amongst patients receiving hydrophilic statins compared to lipophilic statins ($\beta = 1.79$; 1.15-2.79; $P < 0.05$).
Roy, et al.	2019	Lipophilic statins have an increased likelihood NODM due to their ability to enter extra-hepatic cells (such as pancreatic beta islet cells) and impair beta cell function.
Sattar, et al.	2010	Lipophilic (OR 1.10; 0.99–1.22; I^2=0%) and hydrophilic (OR 1.08; 0.98–1.20; I^2=36%) statins were both associated with very similar risks for the development of NODM. However, atorvastatin (a lipophilic statin) exhibited the greatest diabetogenic effects due to its negative effects on GLUT4.

Table 5. Associations of New-Onset Diabetes Mellitus Risk According to Statin Dosage

Author	Year	Findings
Carter, et al.	2013	High dose statins were associated with NODM (adjusted hazard ratio 1.22, 95% confidence interval 1.19 to 1.26). Specifically, amongst patients receiving atorvastatin and simvastatin. However, this finding was not the same for patients receiving rosuvastatin (NODM did not differ between high and low dosage of rosuvastatin). Rosuvastatin (34.21 cases per 1000 persons) and atorvastatin (30.70 cases per 1000 persons) both had the greatest association with NODM (even after dose was adjusted).
Cederberg, et al.	2015	NODM was significantly associated with high dose atorvastatin as well as both high and low dose simvastatin. High and low dose simvastatin administration led to decreased insulin sensitivity.
Kim, et al.	2018	High dosages of atorvastatin (80 mg) were positively associated with increased risk of NODM. However, all statins measured carried some risk for the development of NODM, with the exception of pitavastatin (a new statin therapy that decreases the risk of NODM).
Ko, et al.	2019	Both dosage of statin and length of treatment were associated with NODM. Patients receiving high dosages of statins (40-80 mg) and receiving statin therapy for 2 or more years were at an increased risk for NODM.
Porath, et al.	2018	Patients who were receiving low dose statins and had an adherence over 50% were at the highest risk of developing NODM (43.92 cases per 1000 persons). No relationships were studied between high doses and adherence.
Preiss, et al.	2011	Patients receiving high dose statins were at a greater increased risk of NODM (18.9 cases per 1000 persons) compared to patients receiving moderate dose statins (16.9 cases per 1000 persons).
Roy, et al.	2019	In Western countries, higher dosage statins were associated with the greatest increased risk of NODM, compared to South-Asian countries where statins were associated with NODM (dose-independent). In addition, patients receiving statins for more than 1 year were more likely to develop NODM, compared to those who were receiving statins for less than 1 year.
Thakker, et al.	2016	High dose statins were associated with increased risk of NODM. There were no differences between different types of high dose statins (40-80 mg) and their risk of NODM.
Thomson, et al.	2018	Atorvastatin (80mg) had the highest incidence of NODM compared to atorvastatin (40 mg) and atorvastatin (20 mg). 25% of patients taking atorvastatin 80 mg developed diabetes. The total patients enrolled in the study was 104; 8 of which were prescribed atorvastatin 80 mg and 2 of those patients were later diagnosed with NODM.
Waters, et al.	2011	Compared to the placebo group, patients receiving atorvastatin (80 mg) were more likely to be diagnosed with NODM.

Discussion

Statin Use and Risk of New-Onset Diabetes Mellitus / Insulin Resistance

The majority of the studies included for primary outcome analysis reported an association between statin drug therapy and risk of NODM or IR. Findings from Ahmadizar et al. (2019) and Rees-Milton et al. (2020) suggested an association between statin drug therapy and increased IR, as measured via FSI levels and HOMA-IR indices, respectively (see table 2). The majority of studies which examined the primary outcome of NODM found that ever-use of statins significantly increased the risk, compared with never-use.

Although statistically significant associations were observed overall in the included studies, many of the study populations chosen had a pre-existing propensity to develop NODM. Predisposing factors include hypertension, hyperglycemia, and excess body fat around the waist, cardiovascular disease, and hyperlipidemia. According to a study by Abbasi et al. (2015), there is an apparent connection between statin-induced IR and factors typically associated with T2DM (see table 2). Participants with elevated TG and LDL-C had a significantly higher HOMA-IR score than those with just elevated LDL-C. However, studies by Thomson et al. (2018) and Castro et al. (2016) started with normoglycemic participants yet still showed elevated risk of NODM, indicating that elevations in glucose levels (a common indicator of predisposition to prediabetes) on outset may not necessarily be present in patients with increased risk for statin-induced IR (table 2).

Many of the chosen investigations focused on whether the mortality benefit of statin drug therapy in patients with cardiovascular risk factors outweighed the risk for development of incident diabetes. In light of the results obtained, it is recommended that patients with these pre-existing risk factors undergo screening and get periodic measurements taken of their blood sugar

and HbA1C (Chrysant et al., 2017). In the event that a patient develops NODM, it is suggested that a switch be made to an alternative, more favorable statin type/class or possibly a change in the dosage regimen (Chrysant et al., 2017). Clinical Practice Guidelines from Canada Family Practice recommend offering a moderate- or low-potency statin if intolerant to a high- or moderate-potency statin, respectively (Allan et al., 2015). Therefore, the use of statins in primary and secondary prevention of CVD events warrants careful monitoring for NODM and glycemic control.

Porath et al. (2018) found that patients with low or moderate risk of CVD, as defined by the European Systematic Coronary Risk Evaluation, experienced no protective benefit from taking low-dose statins regardless of their adherence, and yet even at low doses, the risk of NODM was substantially greater than the risk of new onset CVD, especially when patient adherence was high (table 2). The implication is that screening would be useful in many cases to determine whether a statin should even be prescribed. In low cardiovascular risk instances, patient education regarding supportive lifestyle changes may be the key component of lowering cholesterol. But lifestyle education is extremely important whenever considering adding statin therapy, regardless of the patient's risk levels. Macedo et al. (2014) found that risk of NODM was actually increased the longer the statin was used (table 2). As such, discussing with patients that statins pose a higher risk of adverse effects when used for longer periods of time, and educating them on the impact lifestyle changes can have in affecting cholesterol levels, may encourage patients to take their part in the improvement of their risk more seriously.

Gender Differences

Throughout the compiled research there are multiple studies that suggest an association between gender and the development of NODM. Rajpathak et al. (2009) found that there was a

statistically significant association between statin-induced diabetes and the female gender (see table 3). Females, in contrast with males, are more likely to have an increased amount of overall total body fat (Karastergiou et al., 2012). This may allude to a potential confounding variable, as it has previously been demonstrated in past literature that obesity is strongly associated with T2DM.

However, another contributing factor associated with gender is age. Typically, patients who are prescribed statins are either middle-aged or older, as this is the typical patient population of those affected by CAD. Culver et al. (2012) found an association between NODM and postmenopausal women (table 3). Past research has supported that estrogen acts as a protective factor against T2DM; specifically, the G-protein-coupled estrogen receptor (GPER). Although GPER is expressed on a variety of cells throughout the body, it exhibits diabetic protective properties in pancreatic cells. Sharma et al. (2017) noted that GPER increases insulin secretion from pancreatic beta islet cells and promotes pancreatic cell longevity, in turn decreasing plasma glucose levels. Thus, postmenopausal women taking statin therapy may benefit with the addition of hormone replacement therapy to counteract the statin-induced IR.

Although many of the compiled articles supported the association of the female gender with statin-induced diabetes, there is still a significant risk amongst the male gender. As previously mentioned, females and males differ in the overall distribution of adipose tissue. Females are more likely to exhibit a pear-shaped distribution, while males are more likely to exhibit an apple shaped distribution that is more centrally located. The central accumulation of adipose tissue is highly associated with risk factors that include, but are not limited to, CAD and T2DM (Karastergiou et al., 2012). Thus, these are predisposing risk factors that can contribute to NODM in males.

Statin Classification

Differences vary between patients regarding the types of statins and the dosages that are prescribed. Statins can be further classified into either lipophilic (i.e., atorvastatin, simvastatin) or hydrophilic (i.e., pravastatin, rosuvastatin). The majority of studies included have shown a stronger association between lipophilic statins and NODM. However, in contrast to previous studies, Rees-Milton et al. (2020) found that hydrophilic statins have a higher incidence rate of NODM (table 4). One potential reason is that hydrophilic statins work directly on the liver, thus, inhibiting endogenous cholesterol synthesis. In addition, due to their hydrophilic properties, they are more readily excreted in the urine via the kidneys. In contrast, lipophilic proteins have the potential to invade cell membranes and accumulate intracellularly. This mechanism of action associated with lipophilic statins is problematic in pancreatic beta cells due to the interference of calcium entrance into cells which normally allows for insulin secretion (Carter et al., 2013). Another potential mechanism of resistance exhibited by lipophilic statins pertains to decreased GLUT4 expression (Carter et al., 2013). GLUT4 is an essential insulin-dependent transporter that allows for plasma glucose to be taken up into adipocytes. Thus, without these two key components of glucose regulation and uptake, lipophilic statin therapy can increase the risk of NODM. Carter et al. (2013) found that NODM was highly associated with the lipophilic statin, atorvastatin (table 4). In addition, there were no statistically significant differences between lipophilic and hydrophilic statins when they were administered for primary prevention compared to those taking statin therapy for secondary prevention (Carter et al. 2013) (table 4). Due to the conflicting results of the compiled data, further research to explore the differences between classes of statins is advisable.

Statin Dosage

Another important factor to take into consideration is the prescribed dosage of statin therapy. Nine studies demonstrated a positive association between higher dosage statin therapy and increased risk for the development of NODM. Ko et al. (2019) found that individuals taking high dose statins for a period of more than two years were more likely to develop NODM (see table 5). One potential reason for this is patients who are prescribed high dose statins are more likely to exhibit the risk factors associated with the diagnosis of T2DM. There were also differences associated with statin-induced diabetes worldwide. Roy et al. (2019) found that patients in Western countries taking high dose statins are more likely to develop NODM than those taking low dose statins (table 5). In contrast, individuals in South Asian countries are more likely to develop statin-induced diabetes independent of the dosage. However, further research would need to examine these associations to draw a conclusion as to the mechanisms involved with this finding.

Mechanism of Action

While several different mechanisms of action of statin-induced diabetes have been proposed, one particular mechanism is worth further discussion. Inhibition of HMG-CoA reductase not only prevents the synthesis of cholesterol, but also of CoQ10. While the LIPID trial reported that pravastatin reduced CoQ10 concentration by 15%, the more potent statins such as atorvastatin have been shown to decrease plasma CoQ10 concentration by 40%, suggesting these effects are dose related. CoQ10 has varied functions but is a key player in the electron transport chain (ETC). Decreased functionality of the ETC results in lower ATP production, and this in turn results in reduced cellular functionality, including decreased insulin secretion from beta cells. Another important aspect of CoQ10 is its antioxidant properties, making it useful in preventing cellular damage. Initiating CoQ10 supplementation during statin therapy can improve

some of the imbalances associated with insulin resistance such as faulty glycemic control. However, more research is needed to determine whether it can prevent the progression to T2DM (Chan et al., 2015).

Other Considerations

The data presented in this paper confirm there is indeed a strong indication that statins have the ability to induce insulin resistance. According to a mathematical simulation using data from the National Health and Nutrition Examination Survey 1998 –2004, IR has surpassed elevated cholesterol as a risk factor and is likely the most important single cause of CVD. This model predicted that nearly 42% of myocardial infarctions could be prevented by preventing or reversing IR (Eddy et al., 2009). Proposed mechanisms of how IR leads to CVD include cellular oxidative damage caused by hyperglycemia as well as altered lipid metabolism (Ormazabal et al., 2018). Researchers determined that impaired fasting glucose levels up-regulate cholesterol synthesis and downregulate intestinal cholesterol absorption (Gylling et al., 2010). Perhaps IR has always been the underlying cause of the majority of CVD due to its deleterious effects, but hypercholesterolemia was artificially tied to the elevated risk. Further research should be performed to determine whether statin-induced IR can potentially cause an increase in CVD. Such an outcome would stress the importance of determining IR and CVD risk prior to prescribing statins.

Conclusion

From the data presented, it can be concluded that statin drug therapy does indeed increase the risk for development of NODM or IR. This statistically significant association was most pronounced in individuals with a pre-existing propensity for development of NODM, such as in those with metabolic syndrome, obesity, cardiovascular disease, and hyperlipidemia. Although statins are an important pharmacologic intervention in risk management of cardiovascular disease and dyslipidemias, from a clinical standpoint it may be prudent to closely monitor patients for hyperglycemia and NODM risk factors - which could ultimately have the effect of reducing the likelihood of development of statin-induced diabetes. Furthermore, preemptive screening for pre-diabetes or predisposing factors of insulin resistance via glucose clamp or biochemical measures may be of benefit prior to initiation of statin therapy. Individualizing treatment decisions according to patients' risk presentation could also prove to be of value in reducing the risk of incident diabetes. In terms of future directions, quantification of the results obtained via performance of a meta-analysis could serve to increase the robustness of this interpretation.

Statin therapy is associated with the increased risk of NODM amongst a various subset of populations. The majority of the research compiled suggests an association of statin-induced diabetes amongst females, especially those of postmenopausal age. There are various proposals for the mechanism of action of this, such as increased natural adipose tissue as well as decreased estrogen. The second subset of patients that were at an increased risk of NODM were those receiving lipophilic statins. Although both classes of statins (hydrophilic and lipophilic) have an increased risk of NODM, lipophilic statins demonstrated a significantly higher association throughout the majority of the research compiled. Thus, this stresses the importance of physician

knowledge regarding different statin classes to potentially decrease the risk of NODM. The final subset of patients that are at risk for NODM are those who are receiving high dose statins. One of the potential reasons for this association is a higher degree of inflammation of pancreatic beta cells, and thus a further decline of insulin secretion. However, patients who are receiving high dose statins are typically more likely to have pre-diabetic features associated with their elevated cholesterol levels. Thus, this is a potential confounding variable that requires further research in future studies.

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