RESEARCH ARTICLE

Retrospective study on the impact of statins on glycemic levels in hospitalized Lebanese diabetic patients

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Abstract

Objective: The American Food and Drug Administration have warned about a possible association between statins and the development of new-onset diabetes. Lebanese studies lack sufficient data about this correlation. This study was conducted to evaluate the clinical implication of statins on blood glucose levels among diabetic Lebanese hospitalized patients.

Methods: A four-month retrospective observational study was conducted from February till May 2017. It included 131 type II diabetic patients stabilized on statins for a minimum of one year. In addition to statin type, strength, and duration, fasting blood glucose (FBG), glycosylated hemoglobin (Hba1c), body mass index (BMI), and lipid profiles were recorded.

Results: The mean baseline FBG levels before the initiation of statins and post-statin intake were 115.25 mg/dL and 175.81 mg/dL for atorvastatin 10mg, 110.63 mg/dL and 183.16 mg/dL for atorvastatin 20mg, 119.25 mg/dL and 189.11mg/dl for atorvastatin 40mg, 123.21mg/dL and 202.05mg/dL for rosuvastatin 10mg, 114.53 mg/dL and 169.50 mg/dL for rosuvastatin 20mg, and 118.56 mg/dL and 174.64mg/dL for simvastatin 20mg. The association between statins at different doses and mean FBG levels was statistically significant ($p<0.05$). The mean baseline glycosylated hemoglobin before statin prescription was 5.63% and significantly increased to 7.5% three months after statin intake (p-value of 0.03).

Conclusion: In view of the evidence, it is difficult to refute that an association exists between statin use and elevated blood glucose levels. Patients on statins should carefully monitor their glucose levels to assess the risk and benefit of statin use.

Keywords: Statins; Fasting Blood Glucose, Diabetes

INTRODUCTION

Atherogenic dyslipidemia represents the most important modifiable risk factor that contributes to cardiovascular diseases (CVDs) [1] and is frequently present in patients affected by type II diabetes mellitus (T2DM). Over the past years, the frequency of prescribing statins has risen, which in turn has increased the incidence of their adverse effects such as an increase in liver enzymes and myopathy [2]. In 2012, the American Food and Drug Administration updated its label requirements for statins, mandating that they warn about the possibility of new-onset diabetes mellitus and poor glycemic control in patients maintained on statins, in addition to monitoring liver function and alerts about memory loss [3].

The two landmark trials that reported conflicting results regarding new-onset diabetes with statins were Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) and West of Scotland Coronary Prevention Study (WOSCOPS). JUPITER, a double-blind randomized study that allocated 17,802 subjects either to rosuvastatin 20 mg or a placebo, reported an overall 27% increase in T2DM and a significant increase in median hemoglobin A1c levels in the rosuvastatin compared to the control group [4]. The WOSCOPS suggested that the incidence of diabetes was 30% lower in patients taking pravastatin 40mg/day than with those taking a placebo [5]. In the HPS (Heart Protection Study), 335 subjects developed diabetes mellitus in the simvastatin group versus 293 subjects in the placebo group (hazard ratio: 1.15, 95% confidence interval [CI]: 0.98 to 1.35, p = 0.10) [6]. In the ASCOT (Anglo Scandinavian Cardiac Outcomes Trial), the atorvastatin group developed diabetes with a hazard ratio of 1.15 (95% CI: 0.91 to 1.44) [7]. In both studies, there were no significant differences between the treatment group and placebo group; however, both studies showed a trend toward an increase in new onset diabetes.

Many explanations for the influence of statins on glucose metabolism and insulin sensitivity have been proposed. In theory, statins carry an anti-inflammatory effect that improves insulin sensitivity since inflammatory markers and pro-inflammatory cytokines are linked with insulin resistance. However, statins have been associated with increased secretion of the pro-inflammatory cytokine interleukin-1β (IL-1β) from macrophages through activation of the NOD-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome [8]. The NLRP3 inflammasome is causally linked to the development of insulin resistance in rodents [9]. It has been proposed that the altered gut microbiome, in the presence of obesity or other dysmetabolic states, might provide the

endotoxin lipopolysaccharide (LPS) that may mediate the paradoxical pro-inflammatory effect of statins by activation of inflammasomes [10]. This concept requires further explanation in human subjects. In addition, some statins affect insulin secretion through direct, indirect, or combined effects on calcium channels in pancreatic β-cells [11]. Also, the reduced translocation of glucose transporter type 4 in response to treatment results in hyperglycemia and hyperinsulinemia [12]. Another reason is that statin therapy decreases important downstream products, such as coenzyme Q10,[13] farnesyl pyrophosphate,[14] geranylgeranyl pyrophosphate, and dolichol [15] which reduces the intracellular signaling. Other possible implicated mechanisms are the inhibition of adipocyte differentiation leading to decreased peroxisome proliferator activated receptor gamma and CCAAT /enhancer-binding protein Cytosine-Cytosine-Adenosine-Adenosine-Thymidine), which are important pathways for glucose homeostasis [12]. Leptin is decreased as well, which inhibits β cells proliferation and insulin secretion [16, 17].

A study showed that 55.9% of statin-treated patients (mean age 60.3 years, 47% female) in Lebanon and Jordan did not achieve goal levels for low-density lipoprotein cholesterol that were dependent on Systematic Coronary Risk Evaluation (SCORE) risk, and 70% of patients (76% men and 63.3% of women) were at a very high cardiovascular risk [18].

To date, the association between statins and diabetes has not been evaluated in the Lebanese population. Therefore, it is vital to assess the impact of statins on blood glucose levels in Lebanon. This study aims at assessing the effect of different statin types and doses on mean fasting blood glucose levels and glycosylated hemoglobin in hospitalized Lebanese type II diabetic patients.

MATERIALS AND METHODS

Study design and setting

This was a retrospective observational study conducted in three Lebanese hospitals. Patients were recruited from different hospital settings chosen randomly from the list of hospitals provided from the Lebanese Ministry of Health. Patient's information was obtained from the medical records of each site. The study design was approved by the Institutional Review Board of the three hospitals and by the ethics committee at the Lebanese International University. Informed consent was not obtained, as this was a retrospective study and did not pose any risk to the patients. However, data were stripped of any personal identifying information.

Patient selection criteria

All adult type II diabetic patients admitted to the hospitals and maintained on statins for at least one year were enrolled in the study during the period from December 2015 till December 2016. Patients enrolled in the study were stabilized and controlled for their diabetes and excluded if; they had diseases that impair blood glucose levels such as thyroid, adrenal, pituitary, or pancreatic abnormalities; or severe infections (sepsis, meningitis); or a brain tumor, or medications that may impair blood glucose levels such as glucocorticoids, barbiturates, atypical antipsychotics, thyroid products, and niacin.

Data collection

Medical records review was performed on site by the principal investigator, without interference or bias, using a structured data collection sheet which was divided into two parts. The first part included demographic characteristics of the patients, co-morbidities, allergies, social habits, and assessment of BMI, baseline FBG and second reading post statin intake and HBa1c. It incorporated also the lipid panel including triglycerides, Low Density Lipoprotein (LDL), High Density Lipoprotein (HDL), and total cholesterol levels. The second part assessed the past and present medical history including the previous and current medications intake and documented the statin type, dosage strength, and duration of intake.

Statistical analysis

The statistical analysis was performed using IBM Statistical Package for the Social Science software (SPSS version 22.0). Descriptive statistics were used to describe patient characteristics, with frequencies and percentages for categorical variables and mean ± standard deviation for continuous variables. The two groups of patients were compared for statistically significant differences using Paired Sample T test for continuous variables as appropriate. Analysis of variance (ANOVA) was used to assess the association between statins and FBG levels with confidence interval of 95% to compare the different means. All reported p-values are two-sided, with alpha set at a significance level of 0.05.

RESULTS

Patients' characteristics

From a total of 1500 screened patients' profiles, 131 were enrolled in the study. Baseline demographic characteristics of all participants are shown in Table 1.

Table 1: Baseline demographic characteristics of type II diabetic participants according to hospital data

Characteristics	Number (Percentage)
Gender	
Male	80 (61.1)
Female	51 (38.9)
BMI (mean Kg/m^2 ± SD)	27.44± 7.61
Past medical history	
Kidney	26 (19.8)
Hypertension	109 (83.2)
Cognitive	8 (6.2)
Cardiovascular	92 (70.2)
State of hypertension	
Prehypertension	25 (19.08)
Hypertension (stages I, II or III)	99 (75.6)
Dyslipidemia	54 (41.2)
Anti-diabetic medications	
Insulin	56 (42.7)
PO anti-diabetic	48 (36.6)
Insulin + PO anti-diabetic	16 (12.2)
Not mentioned	11 (8.5)

SD: Standard Deviation; BMI: Body Mass Index; PO: Per Os (Oral)

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Patients had a mean age of 63.34 ± 11.43 years. Among the participants, 61.1% were males and the mean BMI of the study subjects was 27.44 ± 7.61 Kg/m^2. Of the patients enrolled in the study, 83.2% were hypertensive, 70.2 % had cardiovascular diseases, 41.2 % were dyslipidemic, and 19.8 % had kidney diseases. Insulin was used by 42.7% of the patients, 36.6% of the patients were on oral anti-diabetic medications, and 16% received combination therapy of both agents.

Statin type and dose

Patients had been treated with different statin types and strengths. Atorvastatin (10, 20, 40mg), Rosuvastatin (10, 20 mg) and Simvastatin 20 mg were mainly used. The most commonly prescribed statin was Atorvastatin

20 mg (54.2%). The distribution of remaining statin types in descending order was as follows: 16% on atorvastatin 40 mg, 9.9% on rosuvastatin 10 mg, 7.6% on simvastatin 20 mg, 6.9% on atorvastatin 10 mg, and only 5.4% on rosuvastatin 20 mg.

Effects of different statins and statin doses on FBG levels

The highest mean FBG (202.05 mg/dl) was detected in patients receiving rosuvastatin 10 mg. These patients had a mean baseline FBG of 123.21 mg/dL, before rosuvastatin initiation. Patients taking the higher dose of rosuvastatin (20mg) had a mean FBG of 169.5 mg/dL, with baseline level of 114.53 mg/dL. The remaining baseline and post-statin intake FBG levels were, respectively: 110.63 mg/dL and 183.16 mg/dL for patients on atorvastatin 20 mg, 119.25 mg/dL and 189.11 mg/dL for atorvastatin 40 mg, 118.56 mg/dL and 174.64 mg/dL for simvastatin 20 mg, and 115.25 mg/dL and 175.81 mg/dL for atorvastatin 10 mg. The association between statins at different doses and mean FBG levels was statistically significant ($p<0.05$) as shown in Table 2.

Table 2: Fasting Blood Glucose readings both baseline and post-statin intake

Statin	Baseline FBG (mg/dL)	Post-Statin FBG (mg/dL)	P-value
Rosuvastatin 10 mg	123.21 ± 9.56	202.05 ± 10.54	0.03
Rosuvastatin 20 mg	114.53 ± 11.21	169.50 ± 14.56	0.05
Atorvastatin 10 mg	115.25 ± 10.15	175.81 ± 13.86	0.03
Atorvastatin 20 mg	110.63 ± 9.53	183.16 ± 12.65	0.02
Atorvastatin 40 mg	119.25 ± 11.24	189.11 ± 11.85	0.02
Simvastatin 20 mg	118.56 ± 11.12	174.64 ± 12.43	0.01

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Effects of statin on HbA1c levels

Glycosylated haemoglobin was recorded for all patients receiving statin therapy, both at baseline and post-treatment. Mean HbA1c prior to statin therapy was 5.63%. Three months later, after statin intake, this level increased to 7.5% (p-value= 0.03).

Discussion

This study is a retrospective, observational study aiming to detect the clinical implication of statin use (according to its type and strength) on blood glucose levels of type II diabetic hospitalized Lebanese patients. The results indicated that there was a significant

association between the different statins at different doses with the mean FBG levels and HbA1c of participants at different sites. It also showed that moderate-dose atorvastatin is the most commonly used statin among diabetic patients in Lebanese hospitals.

Statin Prescription Patterns

The results of the present study demonstrated that the most commonly prescribed statin therapy was atorvastatin, followed by simvastatin and rosuvastatin. This finding is consistent with a Lebanese study conducted by Azar, S. et al (2014) [18] which found that the most commonly prescribed statins were atorvastatin (44.6%), followed by simvastatin (27.7%), rosuvastatin (21.2%), fluvastatin (3.3%), pravastatin (3%), and lovastatin (0.2%). Similarly, another study showed that the most widely used statins in Lebanon were atorvastatin 10 & 20mg, simavstatin 10, 20& 40mg and rosuvastatin 10mg [19].

Statin type as a risk factor

Questions have been raised as to whether the type of statin used hydrophilic: pravastatin and rosuvastatin, versus lipophilic: atorvastatin, lovastatin, and simvastatin that influences the relationship between statins and diabetes. Some studies found similar results to our study, while others found the relationship between statin type and blood glucose level as significant. The effect of atorvastatin 10 mg/day, pravastatin 10 mg/day, and pitavastatin 2 mg/day on glycemic control were examined over three months in a retrospective analysis. Random blood glucose and hemoglobin A_1C levels were increased in the atorvastatin group but not in the others [20]. A prospective comparison of atorvastatin 20 mg versus pitavastatin 4 mg in patients with type II diabetes were presented at the American College of Cardiology's 2011 annual meeting. They reported a significant increase in FBG levels with atorvastatin, particularly in women, but not with pitavastatin [21]. In the Compare the Effect of Rosuvastatin with Atorvastatin on Apo B/Apo A-1 Ratio in Patients with Type 2 Diabetes Mellitus and Dyslipidemia (CORALL) study, both high-dose rosuvastatin (40 mg) and high-dose atorvastatin (80 mg) were associated with significant increases in hemoglobin A_1C, although the mean fasting glucose levels were not significantly different at 18 weeks of therapy [22]. Similarly, Angelidi. et al. conducted a review using data from 1.9 million patients included in 33 articles, 20 focusing on DM dysregulation and 13 on new-onset diabetes. Among the later, majority of articles found high-dose atorvastatin to be associated with new-onset diabetes; and among the earlier, some studies linked FBG and HbA1c increases to atorvastatin [23].

Statin dose as a risk factor

Intensive statin therapy has been shown to reduce cardiovascular risk more than low-dose or moderate-dose therapy, thus supporting more aggressive treatment of LDL-C in higher-risk patients. However, some controlled studies comparing more-potent with less-potent statin regimens suggest that there may also be a higher risk of incident diabetes at higher doses.

In the large METSIM observational study of more than 8000 men, simvastatin and atorvastatin were associated with a dose-dependent increase in post-glucose load, an increase in glycemia, a mean decrease in insulin sensitivity by 24%, and a decline in insulin secretion by 12% [24]. Preiss et al (2015),[25] performed a meta-analysis on the impact of statin intensity on diabetes risk. Data was examined from 32,752 participants without diabetes at baseline in five randomized controlled trials with more than 1,000 participants and more than a year of follow-up. Intensive therapy (atorvastatin 80 mg and simvastatin 40 and 80 mg) was compared to moderate-dose statin therapy (pravastatin 40 mg and simvastatin 20 mg). There was a 0.8% absolute increase in diabetes cases on intensive therapy and a 2.6% absolute reduction in adverse cardiovascular events. In contrast, a review by Yousef et al (2012),[26] of the data from the Enhanced Feedback for Effective Cardiac Treatment (EFFECT) study did not find a higher diabetes risk with more intensive statin therapy based on the magnitude of LDL-C reduction. The risk of diabetes was in fact lower (but the difference was not statistically significant) in the high-dose groups. The risk of myocardial infarction or death was numerically different in the high-dose groups, but the difference again was not statistically significant.

Other Risk Factors

Hashiguchi et al. conducted a retrospective, cohort, time-matched case-control study using post-marketing surveillance database in Japan, to investigate possible risk factors for DM and hyperglycemia associated with statins' use [27]. Seven studied risk factors were examined: sex, age, BMI, statin use duration, complications (hypertension, hyperuricemia, fatty liver…), concomitant medications, and clinical laboratory test values. Both BMI and hypertension were not significantly associated with DM, though BMI showed high OR values (2.7). However, multivariate analysis extracted new possible risk factors as fatty liver and hyperuricemia were significant risk factors for DM or hyperglycemia development.

Limitations

The outcome of diabetes was partially based on non-standardized, physician reporting which

may overstate an adverse effect. Also, in this study, some parameters were not obtained such as HbA1C (glycated hemoglobin) and OGTT (oral glucose tolerance test) as they were not regularly performed in the included hospitals. In addition, important diabetes risk factors that were not taken into consideration such as: metabolic syndrome; family history; treatment adherence; severity of hypertension and dyslipidemia; dietary information; obesity; and impaired fasting glucose before the prescription of statins. Also, some confounding factors (such as duration of statin intake) were not able to be controlled, as the study design was retrospective.

CONCLUSION

In view of the evidence, it is difficult to refute that an association exists between statin use and new-onset diabetes, at least in some subgroups. The dose response noted in some studies further reinforces the conclusion that this association is real.

However, many questions remain unanswered regarding the mechanism of effect, whether there are differences depending on the statin or dose used, or differential effects in the population treated (such as patients with metabolic syndrome or the elderly).

Until the contradictory observations can be resolved and plausible mechanisms of action elucidated, causality cannot be established. From a clinical standpoint there is no current evidence suggesting that the elevations in blood glucose seen while on lipid-lowering are associated with an increased risk of cardiovascular events, or that they attenuate the beneficial effects of the therapy. The association between statin use and impaired FBG level is not statistically significant. Accordingly, statins should continue to be used based on a careful assessment of risk and benefit.

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