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Review

The statins effects on HbA1c control among diabetic patients: An umbrella review of systematic reviews and meta-analyses of observational studies and clinical trials

Mohamed Anwar Hammad [a,*], Mahmoud Saeed Abdo [a], Abdalla Mohamed Mashaly [a], Syed Azhar Syed Sulaiman [a], Saleh Alghamdi [b,c], Altaf A. Mangi [c], Dzul Azri Mohamed Noor [a]

[a] Department of Clinical Pharmacy, Pharmacy School, Universiti Sains Malaysia, Penang, Malaysia
[b] Department of Clinical Pharmacy, Faculty of Clinical Pharmacy, Al Baha University, Al Baha, Saudi Arabia
[c] Faculty of Pharmacy, Gomal University, DI-Khan KPK, Pakistan

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ABSTRACT

Statins have impacts on the metabolism of glucose that might influence the progress of diabetes in non-diabetics or affect glycemic control in patients with existing diabetes. Experimental proof has been contradictory about whether some statins display beneficial properties while others indicate harmful impressions. Some systematic reviews of statins had stated conflicting findings on the concern of glucose metabolism. The current study investigates the published systematic reviews and meta-analyses to combine their results and give a clear situation regarding the influence of statins therapy on glycated hemoglobin (HbA1c). This study has valuable strength points; long follow-up period and big sample size.

1. Introduction

Statin treatment is the foundation stone of primary and secondary prevention of cardiovascular disease [1]. As diabetes is a significant hazard feature for cardiovascular disease and is estimated as a cardiovascular disease risk equivalent, therapy guidelines stated that most patients with diabetes would benefit from statin therapy [2–4]. Latest clinical standard guidelines from the American College of Cardiology (ACC) and the American Heart Association (AHA) recommended that all patients with diabetes who are 40–75 years of age should be placed on moderate or high-intensity statin remedy to avoid or delay cardiovascular disease [5].

Even though their essential role in the prevention and delay of cardiovascular disease, pieces of evidence are suggesting that statins worsen glycemia and increase the risk of developing Type 2 diabetes [6–9]. However, the effect of statins on glycemic control in patients with pre-existing diabetes is less clear [10]. While further revisions have reported no worsening or even a potential benefit of statins on the glycemic control in patients with diabetes [11–13]. However, utmost studies were observational studies or uncontrolled trials, were under-size and had short follow-up phases restricting the available evidence to delineate the consequence of statins on glycemic control in diabetes [14].

Investigational proof has been inconsistent about whether statins as a group improve glucose metabolism or whether some statins show beneficial impact while others show injurious properties [15–20]. Statins mainly are prescribed among elderly patients with many co-morbidities and polypharmacy [21–34]. Some clinical trials of statins had described incompatible outcomes on the matter of glucose metabolism [35–37]. Therefore, this study

* Corresponding author. Egypt - Qena Governorate, Farshot City, Eizbat Haroun, 83651, Egypt.
E-mail addresses: m_anwaaar@hotmail.com (M.A. Hammad), ma7moudsa3ed@hotmail.com (M.S. Abdo), a.mashaly3@gmail.com (A.M. Mashaly), sazhar@usm.my (S.A. Syed Sulaiman), saleh.alghamdi@bu.edu.sa (S. Alghamdi), dzulazri@usm.my (D.A. Mohamed Noor).

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was intended to explore the effects of statins therapy on glycated hemoglobin control.

2. Materials and methods

2.1. Literature search

The published systematic reviews and meta-analysis from January 2008 to February 2019 were discussed and examined for the impacts of statins utilization on HbA1c. The present umbrella study is based on the "*Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines*" retrieved from www.prisma-statement.org/. Google Scholar Medline, EMBASE, and PubMed databank was used to examine for the articles of concern by keywords "diabetes AND HbA1c AND statin". A systematic search methodology was tracked. Qualified studies were primary studies of every design(systematic reviews and meta-analysis) published in English until February/2019 (date of the last search). Secondary studies (observational studies, cross-sectional, cohort, case studies, case series, clinical trials, letters), as well as revisions published in languages other than English, were omitted. Three reviewers independently did the literature search.

2.2. Data collection and synthesis

Revisions were designated for retrieval after three independent investigators had collected titles and abstracts, which were identified in the electronic searches. The extracted titles of articles were documented and categorized according to the exclusion and inclusion search record. All these extracted topics were examined for the eligibility. All the unmatched or inappropriate topics were rejected. A two independent reviewer compared the results of the three reviewers, and any differences of opinion were resolved by discussion as described in Fig. 1. The encompassed revisions were collected and presented in a summary table featuring the fundamental points of each revision; the following data were collected: first author surname, year of publication, study type, number of the total population, trials number, quantitative results (OR, RR, and CI) of the study findings.

3. - Results

The umbrella study includes 12 systematic reviews and meta-analysis, which encompass 184 observational studies and randomized controlled trials (RCTs). The current study involved 2,752,990 patients as demonstrated in Table 1.

4. Discussions

In 2008, Coleman et al., determined the ability of statins to prevent the development of new-onset type 2 diabetes mellitus through a meta-analysis of randomized, controlled trials. A systematic literature search through November 6, 2007, was conducted to identify randomized, placebo-controlled trials of statins that reported data on the incidence of new-onset diabetes mellitus. Incidence of new-onset type 2 diabetes mellitus was treated as a dichotomous variable. Weighted averages were documented as relative risk (RR) with accompanying 95% CI. A random-effects model was used. Five prospective, RCTs (n = 39,791) were recognized. Upon meta-analysis, the use of a statin did not significantly alter a patient's risk of developing new-onset type 2 diabetes mellitus (relative risk [RR], 1.03; 95% confidence interval 0.89–1.19). Subgroup and sensitivity analyses did not significantly change the results. There was statistical heterogeneity that stemmed from pravastatin's tendency towards a reduction in risk and the other statins showing an increase in risk. The funnel plot could not rule out publication bias. Statins, as a class, do not demonstrate a statistically significant positive or negative impact on a patient's risk of developing new-onset type 2 diabetes mellitus [38].

In 2009, a meta-analysis by Rajpathak et al., searched for randomized statin trials that reported data on diabetes through February 2009 was conducted using specific search terms [40]. In addition to the hypothesis-generating data from the West of Scotland Coronary Prevention Study (WOSCOPS) [35], hypothesis-testing data were available from the Heart Protection Study (HPS) [49], the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) Study [50], the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) [51], the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) [36], and the Controlled Rosuvastatin Multinational Study in Heart Failure (CORONA) [52], together including 57,593 patients with mean follow-up of 3.9 years during which 2082 incident diabetes cases accrued. Weighted averages were documented as risk ratios (RRs) with 95% confidence intervals (CIs) using a random-effects model. The scores of statistical heterogeneity were estimated with the Q and I^2 statistic. In the meta-analysis of the hypothesis-testing trials, they observed a small growth in diabetes risk (RR 1.13 [95% CI: 1.03–1.23]) with no proof of heterogeneity through trials. On the other hand, this evaluation was weakened and no longer significant when the hypothesis-generating trial WOSCOPS was encompassed (1.06 [0.93–1.25]) and resulted in significant heterogeneity (Q 11.8 [5 d.f.], *P*: 0.03, I^2: 57.7%). Although statin therapy significantly lowers vascular risk, including among those with and at risk for diabetes, the relationship of statin therapy to incident diabetes remains uncertain. Future statin trials should be designed to address this issue formally.

Certain limitations of (Rajpathak et al., 2009) meta-analysis warrant consideration. First, their investigation was constrained to the little RCTs that described data on diabetes occurrence in statin trials; other statin trials may have data on diabetes available that can expand their outcomes. Second, none of these clinical trials was conducted with diabetes as the major outcome and therefore was not statistically powered to assess this finding. Their data are restricted in that the diagnostic benchmark for diabetes differs between the RCTs and frequently was based on physician sketch rather than systematic investigation. Lastly, they cannot rule out the probability that the augmented hazard of diabetes amongst statin-users may be due to survival bias linked to better survival in the intervention cluster [40].

However, Sattar et al., 2010 meta-analysis of 13 trials (N = 91,140) found little evidence of heterogeneity among large-scale chronic treatment trials. For inclusion, trials were required to have more than 1000 patients and duration of follow-up of more than one year. This meta-analysis found an overall small increased risk for diabetes in patients treated with statins (odds ratio [OR] for incident diabetes 1.09, 95% CI 1.02–1.17). Subgroup analyses found very similar diabetes risks in trials of hydrophilic or lipophilic statins, and no apparent differences among individual statins. The results were also similar after the exclusion of the JUPITER trial. Since JUPITER had raised much of the concern about diabetes and statins [36], the stability of the result without JUPITER lowers the likelihood that the glucose findings in the meta-analysis were due to chance [41].

A meta-analysis (Preiss et al., 2011) of five randomized trials (N = 32,752) also found an increased risk of incident diabetes with intensive statin therapy compared with moderate statin therapy (OR: 1.12, CI: 1.04–1.22) with little or no heterogeneity across trials [8]. This translates into approximately one additional case of diabetes for every 500 patients treated with intensive rather than moderate statin therapy. Similarly, a large observational study

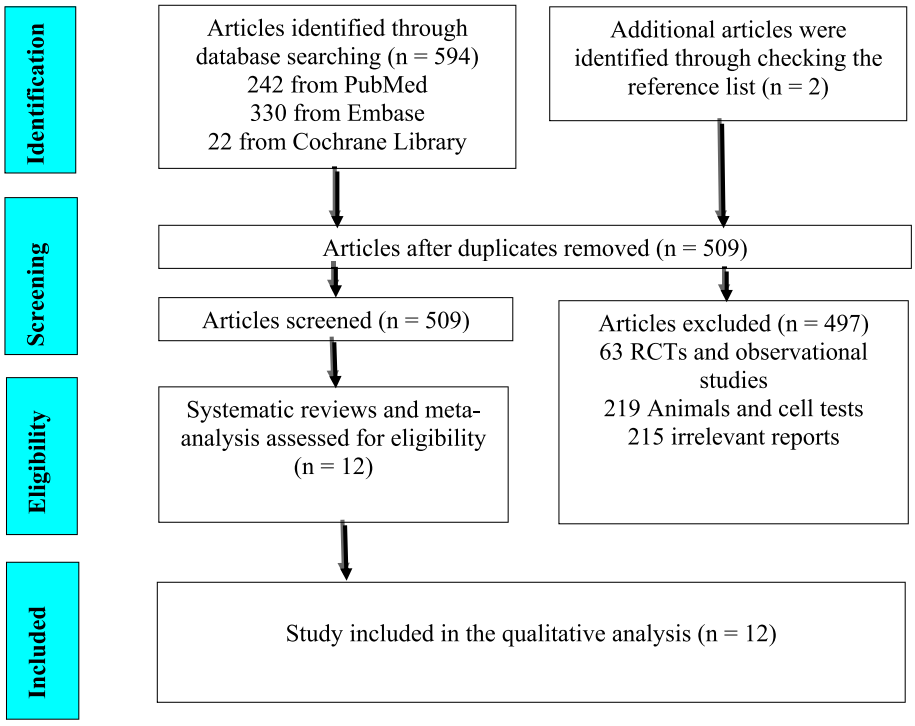

Fig. 1. Flowchart of the umbrella review process.

Table 1
Details of the studies were included in the umbrella review.

Authors/year	Study type	Population (n)	Trials No.	OR/RR of DM and CI
Coleman et al., 2008 [38]	Meta-analysis	39,791	5	RR: 1.03, 95% CI: 0.89–1.19
Rajpathak et al., 2009 [39]	Meta-analysis	57,593	6	RR: 1.13, 95% CI: 1.03–1.23
Sattar et al., 2010 [40]	Meta-analysis	91,140	13	OR:1.09, 95% CI: 1.02–1.17
Preiss et al., 2011 [8]	Meta-analysis	32,752	5	OR: 1.12, 95% CI: 1.04–1.22
Waters et al., 2011 [41]	Meta-analysis	18,859	3	RR: 1.02, 95% CI: 0.77–1.35
Zhou et al., 2013 [42]	Meta-analysis	3232	26	RR: 1.04, 95% CI: 0.08 to 0.16
Erqou, Lee and Adler 2014 [43]	Meta-analysis	9696	9	RR:1.12, 95% CI: 0.04–0.20
Vallejo-Vaz et al., 2015 [44]	Meta-analysis	1600	15	RR: 1.13, 95% CI: 1.03–1.23
Swerdlow et al., 2015 [45]	Meta-analysis	223,463	43	OR: 1.11, 95% CI: 1.03–1.20
Lotta et al., 2016 [46]	Meta-analysis	321,044	3	RR: 1.26, 95% CI: 1.07–1.47
Cui et al., 2018 [47]	Meta-analysis	2707	23	RR: 1.11, 95% CI: 1.01–1.21
Angelidi et al., 2018 [48]	Systematic review	1,951,113	33	Δ HbA1c 2–5%
Total	**12 Reviews**	**2,752,990 pts**	**184 studies**	**RR: 1.11, 95% CI: 1.04–1.27**

CI: Confidence interval, DM: Diabetes mellitus, HbA1c: Glycated haemoglobin, OR: Odds ratio, pts: Patients, RR: Relative risk.

using administrative data found a higher risk of diabetes with high-potency statins, a moderate risk with moderate-potency statins, and lower risk with low-potency statins [10].

Waters et al., 2011, inspected the occurrence and clinical predictors of new-onset type 2 diabetes mellitus (NOT2DM) within three large randomized trials with atorvastatin. They used a standard definition of diabetes and excluded patients with prevalent diabetes at baseline. They identified baseline predictors of NOT2DM and compared the event rates in patients with and without NOT2DM. In the Treating to New Targets (TNT) trial, 351 of 3798 patients randomized to 80 mg of atorvastatin and 308 of 3797 randomized to 10 mg developed NOT2DM (9.24% vs. 8.11%, adjusted hazard ratio (aHR): 1.10, 95% CI: 0.94 to 1.29, *P*: 0.226). In the IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering) trial, 239 of 3737 patients randomized to atorvastatin 80 mg/day and 208 of 3724 patients randomized to simvastatin 20 mg/day developed NOT2DM (6.40% vs. 5.59%, aHR: 1.19, 95% CI: 0.98 to 1.43, *P*: 0.072). In the "*Stroke Prevention by Aggressive Reduction in Cholesterol Levels*" (SPARCL) trial, NOT2DM occurred in 166 of 1905 persons randomized to atorvastatin 80 mg per day and in 115 of 1898 individuals in the placebo cohort (8.71% vs. 6.06%, aHR: 1.37, 95% CI: 1.08 to 1.75, *P*: 0.011). In each of the three trials, baseline fasting blood glucose, body mass index, hypertension, and fasting triglycerides were independent predictors of NOT2DM. Across the three trials, major cardiovascular events occurred in 11.3% of patients with and 10.8% of patients without NOT2DM (aHR: 1.02, 95% CI: 0.77 to 1.35, *P*: 0.69). High-dose atorvastatin treatment compared with placebo in the SPARCL trial is associated with a slightly increased risk of NOT2DM. Baseline fasting glucose level and features of the metabolic syndrome are predictive of NOT2DM across the three trials [41].

In 2013, Zhou et al., conducted a meta-analysis to investigate whether statins deteriorate glycemic control in type 2 diabetes. Cochrane Central Register of Controlled Trials, Medline, and EMBASE from 1966 to 2012 were searched for randomized controlled trials (RCTs) of statins. Included were only trials with

type 2 diabetes. The $I^{(2)}$ statistic was used to measure heterogeneity between trials and calculated mean differences for glycemic parameters with random-effect meta-analysis. A total of 26 eligible studies were identified with 3232 participants. Statin therapy had no remarkable influence on HbA1c (WMD 0.04%, 95% CI -0.08 to 0.16, $I^2 = 45.7\%$, n = 3070), FPG (2.25 mg/dl, 95% CI: 3.50 to 7.99, $I^2 = 46\%$, n = 1176), BMI, fasting insulin or HOMA-IR. However, subgroup analysis showed a significant, detrimental effect of atorvastatin on HbA1c, whereas simvastatin presented an ameliorative effect. Statin therapy showed a non-significant effect on glycemic control in type 2 diabetes. Statin therapy need not change among them with moderate or high cardiovascular risk or existing cardiovascular disease [42].

In a systematic review and meta-analysis, (Erqou, Lee and Adler 2014) recognized articles between from January 1970 to November 2013 by examining reference lists and electronic databanks. They comprised randomized controlled trials (RCTs) in which the interference cluster received statins, and the control cohort was given placebo or standard therapy, with >200 persons joined, with the intervention lasting more than three months and with pre and post-intervention glycated haemoglobin was stated. They pooled study-particular evaluations based on random-effects model meta-analysis. A combined investigation of nine trials encompassing 9696 individuals (4716 control and 4980 statins) and an average tracking-up of 3.6 years, the mean glycated haemoglobin (HbA1c) of persons randomized to statins was higher than those randomized to the control cohort: mean difference (95% CI: 0.04−0.20) was 0.12% or 1.3 mmol/mol (95% CI: 0.4−2.2); *P:* 0.003. There was modest heterogeneity through the studies (I^2: 54%, *P:* 0.014) not illuminated by presented study-level characteristics [43].

Erqou and his colleague's study have some strengths worth mentioning. Primary, they carried out a wide spread criticism by mined the bibliography list and corresponding databases of related studies. Moreover, merging data from RCTs permit them to achieve interpretations about causation that statins in itself deteriorate glycemic control. Furthermore, they used firm, well-defined standards to guarantee the excellence of the clinical studies incorporated and to confirm their applicability to answering the intended clinical query. For illustration, they excepted most of the RCTs with a period less than three months' tracking-up, because glycated haemoglobin enumerates the mean plasma glucose level over the duration of a three-months. Additionally, although significant variances between the trials, they did not detect considerable heterogeneity in the meta-analysis or statistical proof of bias in the publication. Finally, and utmost significant, it is the earliest considerable clarification of a dysglycemia influence of statin therapy among persons with present diabetes [53].

At hand are some of the boundaries that limit the generalization that can be done from the study of Erqou, Lee, and Adler (2014). First, there were a minor number of studies (Nine studies), and two of them had sample size less than one-hundred fifty subjects of each (About seventy-five patients for arm) [54,55]. The other three studies of them with a sample size less than three-hundred forty participants/study available for the review [56−58]. Second, they had data only on pravastatin and atorvastatin besides one trial on simvastatin [52]. Therefore extrapolations concerning the consequence of various members of statins are restricted. Third, the designated trials did not generally document the variations in the utilization of antidiabetic drugs, which might influence the impact of statins on glycated hemoglobin level. Fourth, for glycated hemoglobin difference (95% CI), three studies [49,53,56] included patients with type 1 diabetes with statically insignificant findings. While in nine studies, include type 2 diabetes, only four studies [52,54,59,60] with significant findings, which give controversy data. Fifth, the main outcomes of the nine studies were the incidence of CVD or other endpoints, for example, the LDL-C level. Finally, most of the patients' ethnicity was white and older age, which give limited data about younger patients and the other ethnicities. In addition, the follow-up of patients was less than three months, in three studies and less than six months in another two studies, which limited the data about the effect of the prolonged use of statin on HbA1c.

As the review study of Erqou, Lee, and Adler (2014) is a collected work established on meta-analysis, they did not have entrance to the personal data of contributor, and could not find out detailed heterogeneity. Even though friction of statins trials encompassed diabetic persons, a little number of studies only described glycated hemoglobin level. A cooperative meta-analysis that ponds together the available results and recent data, permitting extra comprehensive, reliable and potent investigation, would aid to deliver an additional convinced response than has been probably in the future, therefore that an extra strong deduction can be considered [53].

In meta-analysis 2015, Vallejo-Vaz and his colleagues searched Medline, Cochrane, Embase and clinical trials registries websites until November-2014 for more than or equals three months' follow-up placebo or statin-controlled RCT of pitavastatin that included participants without diabetes and reported on fasting blood glucose (FBG), HbA1c or new-onset diabetes (NOD). Random-effects meta-analyses estimated the association of pitavastatin with the outcomes. About fifteen studies (Approximately, one-thousand and six-hundred individual-years) were involved. No significant variances associated with pitavastatin (vs. control) were observed for FBG mean differences (MD). Sensitivity and subgroup analyses (including the type of control [placebo or another statin], pitavastatin dose or follow-up) did not yield significant results. Potential publication bias may occur for the NOD. In this study, pitavastatin did not harmfully influence the metabolism of glucose or progress new cases of diabetes in matching with other statins or placebo [44].

While, the meta-analysis of Vallejo-Vaz et al. (2015) is the largest study up to date assessing pitavastatin and its effects on glucose metabolism and diabetes incidence. Several limitations must be acknowledged; for instance, the limited number of studies for some subgroup analyses (e.g., to compare with placebo) or those above relatively short follow-up time from most trials. Most of the participants were non-diabetic. Additionally, the differences in the populations included may have attenuated possible differences that may or may not exist; nonetheless, sensitivity and subgroup analyses were materially consistent with the overall results. Heterogeneity was assessed by the I2 test and was observed concerning effects on HbA1c. Thus influence evaluates for glycated hemoglobin would be explained with carefulness. The results of Vallejo-Vaz et al. (2015) analysis must also be interpreted considering the characteristics of the population included: on average sixty years old, non-obese and FBG within the normal level. However, some studies have suggested that certain conditions such as older age, higher BMI or pre-diabetes are potential risk factors for the NOD. While on statin therapy, they, unfortunately, could not perform sub-analyses considering these characteristics. The small number of NOD events (twenty-nine cases overall) and the absence of any cases in eight studies undoubtedly mean this particular analysis is underpowered. Potential publication bias may also exist for NOD (Asymmetry in funnel plots related to three studies with a sample size less than forty subjects per arm) [61−63]. The perceived missing studies dropped in areas of low statistical significance [suggesting publication bias as a potential cause of this asymmetry]. However, they need to note that these studies were not primarily designed to assess NOD risk and, therefore, their glucose findings would not have influenced the decisions to publish

the results. Finally, in common with previous meta-analysis and individual RCT, it should be remembered that their results are mostly based on post-hoc analyses from trials not specifically designed to evaluate effects on measures of glycemia or diabetes risk.

A 2015 meta-analysis (Swerdlow et al., 2015) supported the findings both for the incidence of diabetes with statins against placebo (OR 1.11, CI 1.03–1.20) and for high-intensity against moderate-intensity statin treatment (OR 1.12, 1.04–1.22) [45]. This meta-analysis also incorporated the Mendelian randomization study that establish that decreased genetic HMG-CoA reductase activity is connected with a higher danger of type 2 diabetes, such that at slightest some of the hazard noted with statin treatment seems to be related to its on-target impact of inhibiting HMG-CoA reductase. This is important because it means that this adverse effect of statins cannot likely be avoided while maintaining the main effectiveness of statin treatment [64]. A 2016 analysis approximate that high-dose intensity statin treatment (Atorvastatin 40 mg per day) would result in fifty to one-hundred new cases of diabetes in ten thousands treated persons [65].

Lotta et al., 2016 exmined whether LDL-lowering alleles in or near Niemann-Pick C1-like 1 (NPC1L1) - the LDL cholesterol transporter - and other genes encoding current or prospective molecular targets of lipid-lowering therapy (i.e., 3-Hydroxy-3-Methylglutaryl-CoA Reductase (HMGCR), Proprotein convertase subtilisin/kexin type 9 (PCSK9), ATP-cassette binding proteins G5 (ABCG5) and G8 (ABCG8), low density lipoprotein receptor (LDLR)) are connected with the hazard of type 2 diabetes mellitus (T2DM). The correlations with T2DM and coronary artery disease (CAD) of LDL-lowering genetic variants were exmined in meta-analyses of genetic association studies. Meta-analyses incorporated 50,775 persons with T2DM and 270,269 controls including three studies and 60,801 individuals with CAD and 123,504 controls from a published meta-analysis. Data collection took place in Europe and the United States between 1991 and 2016. The odds ratio of T2DM and CAD was measured. LDL-lowering genetic variants at NPC1L1 were inversely associated with CAD (OR for a genetically-predicted reduction of 1 mmol/L in LDL cholesterol, 0.61; 95% CI: 0.42–0.88; $P < 0.008$) and directly associated with T2DM (OR: 2.42, CI: 1.70–3.43; $P < 0.001$). The OR of T2DM for PCSK9 genetic variants was 1.19 (95% CI: 1.02–1.38, $P < 0.03$). For a given reduction in LDL cholesterol, genetic variants were linked with a similar reduction in CAD risk (I^2 for heterogeneity in genetic associations = 0.0%; $P < 0.93$). However, associations with T2DM were heterogeneous (I^2: 77.2%; $P < 0.002$), indicating gene-specific associations with metabolic hazard for LDL-lowering alleles. In this meta-analysis, exposure to LDL-cholesterol lowering genetic variants in or near NPC1L1 and other genes was connected with a higher danger of T2DM. These data give insights into the potential adverse effects of LDL cholesterol-lowering treatment [46].

In 2018, a review by Cui et al. was conducted to match the associations of individual statins with their adversely impact on controlling glycemia in diabetic patients. They envolved twenty-three RCTs matching statin therapy with placebo in diabetic persons. The primary outcomes were HbA1c and FBG; besides that, the standard mean differences (SMD) and 95% CI were estimated. Statins therapy was associated with a higher level of HbA1c in matching with placebo. The moderate-dose strength of pitavastatin depressed HbA1c matched with the moderate-dose strength of atorvastatin, high-dose strength of atorvastatin, the moderate-dose strength of rosuvastatin and low-dose strength of pravastatin. The moderate-dose strength of simvastatin dropped glycated hemoglobin matched with the high-dose strength of rosuvastatin and high-dose strength of atorvastatin. The high-dose strength of atorvastatin linked with the high level of HbA1c matched with placebo, moderate-dose strength of rosuvastatin, low-dose strength of pravastatin and moderate-dose strength of atorvastatin [47].

Moreover, the moderate-dose strength of pitavastatin has pulled down FBG paralleled with placebo, moderate-dose strength of rosuvastatin, moderate-dose strength of atorvastatin and high-dose strength of atorvastatin. Furthermore, the high-dose strength of atorvastatin has high FBG matched with placebo, moderate-dose strength of atorvastatin, moderate-dose strength of rosuvastatin and moderate-dose strength of simvastatin. Statins were concomitant with an escalation in HbA1c matched with placebo. In diabetic persons, the moderate-dose strength of pitavastatin result in an improvement of the glycemic control; however, high-dose strength of atorvastatin deteriorated it. Suitable member of statin should be prescribed for diabetic people.

Cui et al. (2018) revision had some restrictions such as first of all, the available information for each statin were comparatively restricted and incomplete, which may result in the unclear assessment of the consequence for some matching. Moreover, the interference times of comprised RCTs were a somewhat short period (the mainstream of RCTs continued from three-months to one-year), which may not mirror the longstanding therapy outcome. Furthermore, the bulk of the covered studies were not intended to estimate the effect of statin on controlling of glycemia and at hand was no explanation of whether the antidiabetic treatment was identical through the therapy period in some RCTs.

Angelidi et al., 2018 review was to discover the influence of atorvastatin in causing new-onset diabetes or HbA1c control in patients with diabetes mellitus (DM). Two independent reviewers did the literature search, throughout the PubMed database search for papers until April 2015. About thirty-three studies with 1,951,113 subjects were included in the analysis. Twenty articles examined the dys-regulation of DM result from atorvastatin therapy. About 50% of them indicated that there was non significant modification in HbA1c control in patients treated with atorvastatin. Other studies revealed that fasting plasma glucose (FBG) and HbA1c levels were augmented by atorvastatin. Thirteen articles investigated if atorvastatin causes new-onset diabetes. Most of these articles stated that persons who used atorvastatin had a higher dose-dependent danger of developing new onset diabetes. This systematic review recommends that there is an relationship between atorvastatin therapy and new-onset diabetes. Furthermore, it stated that atorvastatin in high-dose intensity results in deterioration of the HbA1c control in patients with DM [48].

In 2019, Ward et al. review the incidence of new-onset type 2 diabetes mellitus with statin treatment appears to be more common in patients with preexisting risk factors, including elevated body massive index and glycated hemoglobin or impaired fasting glucose. It has been observed for both hydrophilic and lipophilic statins and appears to occur more frequently in older patients and those on high-dose statin therapy [66]. Mechanistically, the incidence of new-onset type 2 diabetes mellitus is not known but may be related to both on-target and off-target action, including effects on body weight, body mass index, adipocyte differentiation, blood glucose homeostasis via gluconeogenesis and the insulin signaling cascade, changes in circulating free fatty acids or hormones such as adiponectin and leptin, as well as impaired β-cell function [67].

As reviewed by Betteridge and Carmena (2016) [68] of Mendelian randomization studies suggest that the effect of statins on glucose homeostasis reflects reduced 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase activity, while there is in-vitro and in vivo evidence that reduced synthesis of mevalonate pathway products and increased cholesterol loading impairs pancreatic β-cell function and decreases tissue insulin sensitivity. These effects are probably quantitative, consistent with the graded

increase in HbA1c by the intensity of statin therapy. Clinicians should, therefore, be aware that introduction of simvastatin/atorvastatin >40 mg/d or rosuvastatin >10 mg/d may lead to the need for more intensive treatment for diabetes, depending on the current level of control and individualized glycemic targets. In FDS2, high-intensity statin therapy was associated with a change in median HbA1c from 6.6% to 8.0% (49–64 mmol/mol), implying that a substantial proportion of patients went from adequate to suboptimal control [69]. Given the tendency to therapeutic procrastination in Type 2 diabetes, this effect may have adverse consequences for chronic vascular complications [70].

In 2018, to quantitatively assess the evidence for potential side effects of longstanding statin treatment on the homeostasis of glucose, cognitive, and risk for cataract. A review mining cover from 2000 to 2017 was achieved. The Panel analytically evaluated the information and decided by agreement on the classification of described adverse reaction. RCTs and genetic research indicated that statin treatment is concomitant with moderate growth in the hazard of new cases of diabetes, usually well-defined by laboratory outcomes (HbA1c $\geq$ 6.5); this threat is meaningfully effective in the prediabetes or metabolic disorder. Therapy of statin does not harmfully effect on cognitive function, even at the very low LDL-C level and is not connected with the significant development of cataract. Extended therapy of statin has a remarkable safety with a little hazard of clinically related side effects as described above, the established CV benefits of statin therapy far outweigh the risk of adverse effects [71].

In 2018, the European Atherosclerosis Society (EAS) Consensus Panel stated that the medical advantages of statin therapy faraway compensate for the possible hazard of new cases of diabetes, particularly in persons with elevated glycated hemoglobin. The overpowering inference of this Consensus Panel is that the recognized CV aids of statin treatment far overshadow the hazard of some such side effects. Healthcare providers should be relieved about the statin safety and non-cardiovascular influences of statins [72–75] founded on this comprehensive evidence-grounded analysis [76].

5. Conclusions

In lipid-lowering reviews in patients with diabetes, limited data suggest that there is no consistent relationship between statin therapy and alterations in glycosylated hemoglobin or other glycemic parameters. In the current study, small differences in HbA1c concentrations were observed over time in the treatment groups, with a slightly more significant difference in the atorvastatin group. Some studies have also shown small increases in HbA1c following long-term treatment with statins.

IRB approval

The institution's IRB has approved the research.

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Conflicts of interest

All the authors do not have any possible conflicts of interest.

Authors' Contributions

- MAH contributed in the conception of the work, data collection, data analysis, manuscript drafting, manuscript revising, and approval of manuscript final, all aspects of the work and agreed for all aspects of the work.
- MSA contributed in the data collection, the manuscript drafting, manuscript revising, manuscript final approval and agreed for all aspects of the work.
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