Al-Sayegh T, Toubasi A. The Effect of Statin Use on the Prevention and Progression of Diabetic Kidney Disease: A Systematic Review and Meta-analysis. *High Yield Medical Reviews*. Published online December 1, 2024. doi:10.59707/hymrOHUG7074

Online first

The Effect of Statin Use on the Prevention and Progression of Diabetic Kidney Disease: A Systematic Review and Meta-analysis

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Keywords: Statin, Diabetic Kidney Disease, Diabetic Nephropathy.

https://doi.org/10.59707/hymrOHUG7074

High Yield Medical Reviews

Introduction

This systematic review and meta-analysis aim to investigate the effect of statin on the prevention and progression of Diabetic Kidney Disease (DKD) hypothesizing that statin would elicit beneficial effects on patients with DKD.

Methods

PubMed, Scopus, CENTRAL, and Web of Sciences were searched. The studies were included if they investigated the impact of statin on the development or progression of DKD. DKD development was defined as the occurrence of proteinuria or albuminuria due to type 2 diabetes. DKD progression was defined as the change in proteinuria, albuminuria, and GFR over time.

Results

The total number of the included patients was 36,938 from 27 studies. Statin use was significantly associated with reduction in DKD risk (HR=0.66; 95%CI: 0.58-00.76). Moreover, patients on statin had significantly lower deterioration in albuminuria (WMD=-21.81; 95%CI: -36.91- -6.70), proteinuria (WMD= -0.12; 95%CI: -0.12- -0.03) and GFR (WMD=-1.21; 95%CI: -2.20- -0.23).

Conclusion

Our study demonstrated that statin has beneficial effect on DKD by reducing albuminuria, proteinuria and GFR. These findings were reproducible among patients with microalbuminuria, patients on low intensity statins and patients on different treatment durations. Future larger high-quality trials are needed to investigate this topic and make more fine and reliable conclusions in the view of the encouraging findings we found in our analysis.

INTRODUCTION

Diabetic Kidney Disease (DKD) is defined as persistent albuminuria, decline in kidney functions and is always associated with increased blood pressure.[1] DKD is the leading cause of nephrotic syndrome and end-stage kidney disease.[2] This disease is associated with a large morbidity and mortality.[2] The estimated statistics indicate that around 40% of patients with diabetes will develop DKD and the incidence is growing over years worldwide.[3] The current guidelines recommend tight and strict control of blood pressure and glucose to prevent and halt the progression of the disease.[4,5] Despite the advancement in research and reforming the guidelines continuously to include the most recent evidence, DKD is often progressive and poses a huge impact on patient's quality of life.

Statins are a class of medications that are used to manage hyperlipidemia.[6] Statins are well known for their efficacy in lowering cholesterol levels and significantly reducing cardiovascular events, thus they are used for primary and secondary prevention. These effects were found in patients regardless of age, sex, cholesterol level, and the pres-

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ence of other comorbidities.[7] Different statins provide different powers in lowering cholesterol.[8] The potential applications of statin increased to include various diseases beyond the cardiovascular ones, such as chronic obstructive lung disease, acute respiratory distress syndrome, pneumonia, and cancer.[9]

Several studies hypothesized that an important relationship exists between DKD and dyslipidemia as they proposed that dyslipidemia might contribute to more rapid kidney function loss in populations with preexisting renal impairment.[10] In addition, patients with DKD have high rates of dyslipidemia.[11] Accordingly, it was reasonable to think of therapeutic options like statins that aim to lower lipid profile among patients with DKD to reduce the progression of the disease.[12]

Several observational studies, clinical trials, and meta-analyses studied the effect of statin on the progression of DKD. However, the results were hugely inconsistent and controversial and mainly limited to the low sample size.[13] The last meta-analysis conducted about this topic was done in 2016 [13]. This necessitates conducting a systematic review and meta-analysis that accounts for the previous limitations and accommodates the largely growing literature about the topic. Thus, we decided to conduct a systematic review and meta-analysis about the effect of statin on the prevention and progression of DKD hypothesizing that statin would elicit beneficial effects on patients with DKD.

METHODS

STANDARD PROTOCOL APPROVALS, REGISTRATIONS, AND PATIENT CONSENT

The preferred Items of Reporting Systematic Reviews and Meta-analyses (PRISMA) and the Cochrane Collaboration Handbook were used to conduct this study. This study was registered in the International Prospective Register of Systematic Reviews (PROSPERO)(CRD42023438878). The Institutional Review Board (IRB) at the University of Jordan exempted our study protocol from review. The IRB waived the need for patient consent.

SEARCH STRATEGY

The search was done using PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, and Web of Sciences. The search was conducted using terms about DKD and statins. The terms used in the search were selected through the Medical Subject Headings (MeSH). The detailed search strategy is described in eMethods. The search was done by TNA and AAT and any discrepancy was solved by discussion until a consensus was reached.

The studies were included if they were:

- Observational studies assessed the impact of statin use on the development or progression of DKD.
- Interventional studies investigated the impact of statin on the development or progression of DKD.

The studies were excluded if they were reviews, editorials, and animal studies. Also, the studies were excluded if they investigated the impact of statin on inflammatory mediators in the kidney. Moreover, we excluded studies that evaluated the impact of hyperlipidemia on DKD. The search results were imported on Rayyan (https://rayyan.ai/), an artificial intelligence tool for systematic reviews, where the study selection was done. The study selection was done by AAT and TNA independently and any discrepancy was solved by discussion.

MAIN OUTCOMES

The exposure of interest was statin use while the outcome of interest was DKD development and progression. DKD development was defined as the occurrence of proteinuria or albuminuria due to type 2 diabetes. DKD progression was defined as the change in proteinuria, albuminuria, and GFR over time. Albuminuria was measured using Urine Albumin to Creatinine Ratio (UACR) whereas proteinuria was measured using Urine Protein to Creatinine Ratio (UPCR) or 24-hour protein in urine collection. UACR and UPCR used units were milligram/gram (mg/g).

DATA EXTRACTION AND QUALITY ASSESSMENT

For data extraction, a spreadsheet was formed to collect the following variables: title, year of publication, study design, country of origin (referring to the location of the study), primary outcome measure, statin exposure, statistical analysis of the primary outcome, and any other noteworthy results. The data extraction process was conducted by the same two independent researchers (AAT and TNA), and any disagreements were resolved through discussion until a consensus was reached. To assess the risk of bias in the included observational studies, the Newcastle-Ottawa scale for observational studies was utilized. This scale provides a framework for evaluating the quality and potential biases in observational study designs by assessing 3 components; selection, comparability, and outcome. The Cochrane Risk of Bias Assessment for Randomized Clinical Trials (RoB2) was used to assess the risk of bias among the included randomized clinical trials.

STATISTICAL ANALYSIS

The effect measure for binary outcomes was Hazard Ratio (HR) and its 95% Confidence Interval (95%CI), while it was the mean and standard deviation for continuous outcomes. The difference between the exposed and non-exposed patients was assessed using Weighted Mean Difference (WMD) and its 95%CI. The analysis was done by creating a model for each outcome. In addition, we performed subgroup analysis across statin dose (low vs moderate), baseline albuminuria (<300mg/g vs >300mg/g), and statin treatment duration (<12 months vs ⩾12 months). The heterogeneity was assessed using I^2 and Cochrane Q statistics. Funnel plot and doi plot were used to test for publication bias. Meta XL, version 5.3 (EpiGear International, Queensland, Australia) was used to conduct the analysis.

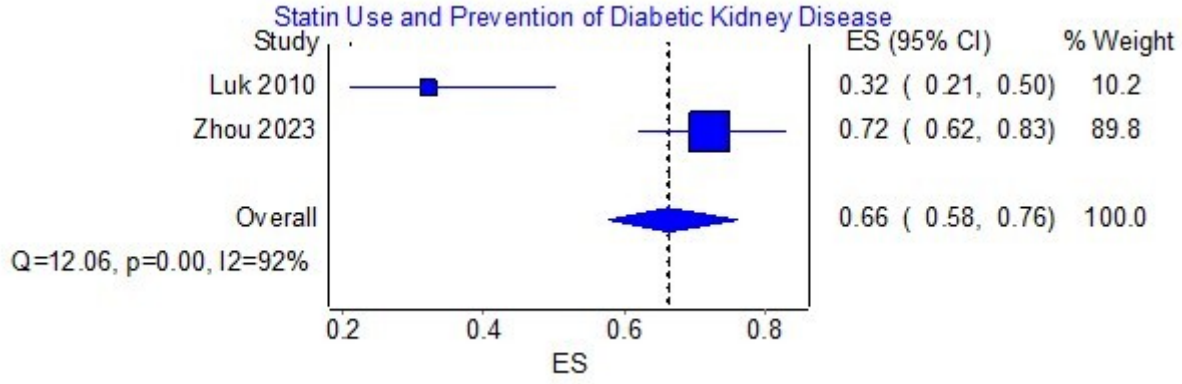

Figure 1. The Impact of Statin Use on the Prevention of Diabetic Kidney Disease.

RESULTS

The search yielded 1,463 articles, of which 460 articles were duplicates. The remaining 1,003 articles were screened using their titles and abstracts and 879 articles were excluded because they were reviews, editorials, and animal studies. The remaining 124 articles were screened using their full-text form and 97 articles were excluded because they did not report data about the outcomes of interest. Finally, 27 articles were included in this systematic review and meta-analysis.[14-40] Supplementary Figure 1 shows the detailed selection process of the included studies.

MAIN ANALYSIS

Two studies investigated the association between statin use and DKD prevention. The model that pooled these studies showed that statin use was significantly associated with a reduction in DKD risk (Figure 1: HR=0.66; 95%CI: 0.58-00.76); the model had significant heterogeneity (I^2=92%, P-value=0.00).

The model that investigated the difference in albuminuria between statin and control groups showed that patients on statin had significantly lower deterioration in albuminuria (Supplementary Figure 2: WMD=-21.81; 95%CI: -36.91- -6.70); the model had significant heterogeneity (I^2=100%, P-value=0.00). Moreover, 5 studies evaluated the difference in proteinuria between statin and control groups. The model showed that statin use was significantly associated with lower deterioration in proteinuria (Supplementary Figure 3: WMD= -0.12; 95%CI: -0.12- -0.03); the model had insignificant heterogeneity (I^2=0%, P-value=0.46).

Sixteen studies investigated the difference in GFR between statin and control groups. The model that pooled these studies demonstrated that the statin group had a significantly lower reduction in GFR compared to the control group (Supplementary Figure 4: WMD=-1.21; 95%CI: -2.20- -0.23); the model had significant heterogeneity (I^2=100%, P-value=0.00).

Two studies evaluated the difference in 24-hour urine protein collection. The model that investigated these studies demonstrated that statin use was significantly associated with lower deterioration in 24-hour protein in the urine (Supplementary Figure 5: WMD=-0.33; 95%CI: -0.61- -0.06).

SUB-GROUP ANALYSIS

Sub-group analysis showed that low-intensity statin was significantly associated with a reduction in albuminuria but not proteinuria progression among patients with DKD (Supplementary Figure 6: WMD=-23.37; 95%CI: -39.29- -7.45, Supplementary Figure 7: WMD=0.00; 95%CI: -0.17-0.17). Zhang et al demonstrated that moderate-intensity statin was associated with reduction in albuminuria progression. In addition, de Zeeuw et al showed that moderate-intensity statin was associated with a reduction in the proteinuria progression. Moreover, sub-group analysis for patients with baseline albuminuria<300mg/g showed that statin was associated with a reduction in the albuminuria but not proteinuria progression (Supplementary Figure 8: WMD=-23.37; 95%CI: -39.29- -7.45, Supplementary Figure 9: WMD=0.00; 95%CI: -0.17-0.17). In addition, analysis for patients who received statin for <12 months or ⩾12 months demonstrated that both treatment durations were associated with a reduction in albuminuria but not proteinuria progression (Supplementary Figure 10-13).

Sub-group analysis according to statin dose showed that low and moderate intensity statin were significantly associated with a reduction in GFR deterioration (Supplementary Figure 14: WMD=-4.11; 95%CI: -7.41- -0.81, Supplementary Figure 15: WMD=-1.04; 95%CI: -2.06- -0.02). Analysis according to baseline albuminuria showed that patients with baseline albuminuria <300mg/g and >300mg/g were significantly associated with a lower reduction in GFR (Supplementary Figure 16: WMD=-1.49; 95%CI: -2.55- -0.43, Supplementary Figure 17: WMD=-3.41; 95%CI: -5.40- -1.41). Additionally, sub-group analysis based on treatment duration showed that both durations were associated with a lower reduction in GFR among the statin group (Supplementary Figure 18: WMD=-0.16; 95%CI: -0.25- -0.06, Supplementary Figure 19: WMD=-1.80; 95%CI: -1.85- -1.75).

CHARACTERISTICS OF THE INCLUDED STUDIES

The total number of the included patients was 36,938 from 27 studies.[14-40] Of them, 47.2% were on statin while the rest were off it. The majority of the studies were clinical trials (81.5%) while the rest were observational in design (18.5%). The overall male-to-female ratio among the included patients was 2.22 while the mean age was 57.76. Moreover, 55.6% followed patients for 12 months or more whereas only 11.1% had baseline albuminuria >300mg/g. In addition, only 4 studies assessed the impact of moderate-intensity statin on DKD while the rest assessed the impact of low-intensity statin. eTable 1 describes the characteristics of the included studies.

QUALITY ASSESSMENT

RoB2 showed that 57.1% had a high overall risk of bias while the rest 42.9% had a low overall risk of bias. The majority of the studies had a high risk of bias in the blinding of the participants and blinding of outcome assessment (38.1% for each). The rest of the studies mainly had a high risk of bias in the allocation concealment (19.0%) and incomplete reporting of the data (33.3%). Most of the studies were of high quality (NOS ⩾7) and only 1 study was of low quality. The studies mainly lost points for not adjusting for confounding bias (50.0%) (eTable 2).

PUBLICATION BIAS

Funnel and doi plots showed a significant asymmetry indicating a high possibility of publication bias (Supplementary Figure 20&21).

DISCUSSION

Kidney Disease is a common complication among patients with diabetes with a significant impact on mortality and quality of life. Our study analyzed data from 36,938 patients with DKD from 27 articles and showed several findings. First, Statin use was significantly associated with a reduction in the risk of developing kidney disease among patients with diabetes. Moreover, statin use was associated with protective and beneficial effects on kidney disease progression as it reduced the deterioration in albuminuria and proteinuria. In addition, statin use significantly halted the deterioration in GFR among patients with DKD.

Our results demonstrated the beneficial effects of statin use on many DKD measures including albuminuria, proteinuria, and GFR. These results were reproducible in GFR and albuminuria outcomes when a sub-group analysis was done among patients on low-intensity statin and patients with albuminuria<300. In addition, the findings were reproducible among patients on statin for <12 months and ⩾12 months. However, the sub-group analyses in the proteinuria outcome according to statin intensity, baseline albuminuria, and duration of treatment showed no significant results. This can be explained by the low number of studies included in the analysis after sub-grouping. In addition, it is important to note that analysis among patients on moderate-intensity statin was limited by the low number of studies. Thus, we recommend future clinical trials to investigate the impact of moderate-intensity statin on DKD.

A previous meta-analysis done in 2009 demonstrated that statin reduced the level of pathologic albuminuria.[41] Also, previous meta-analyses showed similar findings with a lower sample size.[42] Moreover, another two meta-analyses showed that statin reduced proteinuria and GFR deterioration.[43,44] The latest meta-analysis done in this regard showed that statin reduced albuminuria but not proteinuria or GFR, which is different from our findings as we showed that statin use reduced all 3 measures of DKD progression.[13] The difference between our meta-analysis and the previous one is the fact that we included a higher number of studies and patients in the analysis as we included 36,938 patients while the previous study only included 543 participants. Thus, our results are considered more valid and reliable. Another difference is that the previous meta-analysis did not investigate the impact of statin use on DKD prevention while we showed that statin use significantly reduced the risk of developing DKD. Pathak et al[45] showed that a main limitation of investigating the impact of statin on DKD is that the majority of the patients included in the trials have multiple comorbidities and are on multiple medications that can lower kidney disease progression such as anti-hypertensive medications. Thus, these effects might be confounded by the use of multiple medications that are known to be protective of kidney functions.

The relationship between dyslipidemia and kidney disease is considered bidirectional. Studies showed that dyslipidemia increases the risk of atherosclerosis, which impacts kidney disease progression and leads to more deterioration in kidney function.[46] Moreover, several studies showed that kidney diseases are strongly associated with dyslipidemia, including high triglyceride, low high-density lipoprotein, and high low-density lipoprotein.[12,47] These lipid panel abnormalities develop at very early stages of kidney disease even before the clinical detection of dyslipidemia.[12,47] As a result, the international guidelines for patients with kidney disease made several recommendations on managing dyslipidemia among patients with CKD,[48] especially since over half of deaths among patients with kidney disease are attributed to cardiovascular events.[46] However, it is important to note that clinicians should pay attention to statin dose used among kidney disease patients[49] as studies showed that statin use is associated with an increase in renal injury, especially in the first 4 months of use. However, the current evidence supports that statins do not induce any harm to the kidney, yet dose restrictions should be taken into consideration among patients with kidney disease.[50] The literature suggests that various statin types can be used among patients with kidney disease with minimal dose adjustment in the early stages of CKD. However, dose adjustment is needed at the end stage of renal disease (GFR<30).[50] Furthermore, using statin among patients with diabetes poses another risk to these patients by raising normal fasting glucose and dysregulating glucose control.[51] The current US guidelines rec-

ommend using statins among patients with kidney disease on intermediate to high risk of cardiovascular disease.[51]

Several limitations should be acknowledged. First, the low sample size in several sub-groups in the analysis limits the power of these models to detect significant results. Second, several studies were assessed as high risk of bias according to RoB2 and low quality according to NOS. As we showed in the results, the studies were mainly limited due to blinding and not adjusting for confounding bias. Thus, we recommend future studies to account for these limitations as additional evidence from high quality randomized clinical trials is needed to confirm the effect of statins. Third, the low number of studies limited our ability to conduct analysis for the effect of moderate-intensity statins among patients with albuminuria>300. Thus, future studies are needed to fill these gaps in the literature by including more patients with overt albuminuria and participants on moderate-intensity statins. Moreover, the high heterogeneity across several models is another limitation that might affect the validity of our results. This heterogeneity might be a result of differences in the included studies in baseline kidney measures, type of statin along with its dose and duration, and the differences in the included populations in the comorbidities and used medications. Although we tried to lower this heterogeneity by using a random effect model and sub-group analysis, the heterogeneity persisted in some of the models. Finally, funnel and doi plots showed significant publication bias, which might limit our findings.

In conclusion, our study demonstrated that statin has a beneficial effect on DKD by reducing albuminuria, proteinuria, and GFR. These findings were reproducible among patients with microalbuminuria, patients on low-intensity statins, and patients on different treatment durations. However, the analysis was limited by sample size among patients with macroalbuminuria and patients on moderate-intensity statin. Thus, future studies are needed to fill these gaps in the literature and account for previous studies' limitations. In addition, future larger high-quality trials are needed to investigate this topic and make more fine and reliable conclusions in view of the encouraging findings we found in our analysis.

CONTRIBUTION

TNA and AAT were involved in Conceptualization; AAT and TNA were involved in Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, and Writing the original draft; TNA and AAT were involved in Supervision and Reviewing & Editing the manuscript.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

ACKNOWLEDGMENT

None.

FUNDING

The authors have no funding to declare.

Submitted: August 05, 2024 AST, Accepted: November 20, 2024 AST

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SUPPLEMENTARY MATERIALS

Supplementary Material

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