Effect of Fibrates on Albuminuria: A Systematic Review and Meta-analysis

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Abstract

Background: Diabetes is a global problem with huge implications. The efforts aim to reduce the burden of diabetes through investigating therapeutic agents targeting cardiovascular and diabetic nephropathy complications. Fibrates are gaining momentum as one of these agents that can play a significant role in diabetic nephropathy prevention.

Objectives: This systematic review and meta-analysis aimed to evaluate the clinical benefits and harms of fibrates versus placebo or standard care or fibrates plus other lipid-lowering drugs versus other lipid-lowering drugs alone on the progression or regression of albuminuria.

Methods: The search process included the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (Ovid), Embase (Ovid), ClinicalTrial.gov, and ISRCTN (all from 1990 to 10 July 2017). We searched two clinical trial registers (last searched on 10 July 2017). We searched the databases to identify randomized controlled trials evaluating the clinical effects of fibrate therapy on albuminuria for diabetic patients. We

searched the grey literature using Google and Google Scholar. Only studies in the English language were considered.

Results: The systematic review of the current evidence indicates favourable results in the studies included. The Meta-analysis results show that the pooled Risk Ratio of the studies suggest a protective effect of fibrates in delaying the albuminuria when compared to either placebo arms or statin without fibrates. The overall Risk Ratio 0.89 (0.85, 0.94) suggests a decrease in albuminuria risk in the fibrates group by an average of 11%.

Conclusion: Evidence suggests that fibrates lower the risk of developing albuminuria moderately. The pooled Risk Ratio proposes an overall reduction of risk by 11%.

Keywords: Fenofibrate, fibrates, diabetes, cardiovascular, albuminuria

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Introduction

When the protein albumin is present in urine in significant levels, then this condition is called Albuminuria.[1] Albuminuria is a type of proteinuria. Albumin is an essential plasma protein circulating in blood in normal circumstances, only trace amounts of it are present in urine. Larger amounts occur in the urine of patients with kidney disease. Clinical terminology is changing to focus on albuminuria more than proteinuria.[1] Albuminuria is an insensitive biomarker for kidney disease. That means it is usually asymptomatic until the kidney experienced considerable deterioration. Microalbuminuria is when the level of albumin is ≥ 30 mg/g.[3] The symptoms that may occur at the later stage of albuminuria are swelling of ankles, hands, abdominal area, or in the face, if the loss of albumin is high and produce low serum protein levels.[3] Chronic Kidney Disease (CKD) is an increasingly leading cause of mortality and loss of disability-adjusted life-years worldwide.[6] Diabetic nephropathy remains the single largest cause of CKD and end-stage renal disease (ESRD) in many countries and one of the most causes of ESRD worldwide.[2, 7] It is estimated that 20% of diabetic patients develop ESRD within 20 years of showing the first signs of diabetic nephropathy.[3] Cardiovascular complications start early in renal disease. Current therapies may not stop renal function deterioration. Therefore, there is an urgent need for new targets and interventions, since renal failure and associated cardiovascular disease increase mortality rates.[8]

Fibrates are classified pharmacologically as a class of amphipathic carboxylic acids. They are used for different metabolic disorders, such as Hyperlipidemia, and are therefore hypolipidemic agents.[9, 10] Fibrates has been shown to decrease

albuminuria in a mouse model of type 2 diabetes, and in humans.[11] Although there is a potential renal benefit, there are possible safety concerns arising from the rise in plasma creatinine.[12] Currently available fibrates in North America and/or Europe include gemfibrozil, fenofibrate, fenofibric acid, bezafibrate, etofibrate, and ciprofibrate. Clofibrate is no longer in use due to excess mortality.[13] Potential side effects or adverse effects from fibrate therapy are “increased venous thrombotic events, pancreatitis, reversible rise in creatinine (described with all fibrates except gemfibrozil), rise in homocysteine, and elevations in transaminases, gallbladder disease (since fibrates increase the cholesterol content of bile), and myositis/rhabdomyolysis, in particular for combinations of gemfibrozil with statins”.[14, 15]

Recently, integrative therapies have been introduced using intensive glucose-lowering treatment and advanced therapies for cardiovascular risk factors. However, despite these efforts diabetes mellitus with the accompanying macro- and microvascular complications remains a major, health problem. Diabetic nephropathy is a dominant cause of morbidity and mortality with increasing prevalence globally.[1, 6] Peroxisome proliferator-activated receptor-α (PPAR-α) manifests in several tissues including the kidney.[9, 16] The recent evidence from experimental data have indicated PPAR-α activation has a critical role in the modulation of fatty acid oxidation, lipid metabolism, inflammatory and vascular responses, and potentially modulate various metabolic and intracellular signaling pathways that lead to diabetic microvascular complications, Fibrates activate PPAR-α.[9, 16, 17] This review examines the role of fibrates in diabetic nephropathy and summarizes data from experimental and clinical studies on the

therapeutic potential of fibrates in diabetic nephropathy using the effect of albuminuria as a manifestation.

This systematic review and meta-analysis aimed to evaluate the clinical benefits and harms of fibrates class drugs on albuminuria versus placebo or standard care among diabetic patients in randomized control trials.

Materials and Methods

The search protocol initiated in the first week of February 2017 and ended on the 10th of July 2017. Last search was conducted on February 2019. The search process was restricted to English language only. The search protocol used a searching strategy that is recognized for excellent performance, a strategy that minimizes the difference between sensitivity and specificity in the search for treatment studies according to Wong.[18] In other words, we used a strategy reduces the duplication of results within the same databases and grant

The following sources were targeted in the search process: Medline; EMBASE; Cochrane central register of controlled trials (central); clinical trials registration databases (clinicaltrial.gov); and ISRCTN. The search process used the following search protocol in all article database.

The following words solely or as part of combination(s) were used in the searching process: fibrate or “fibric acid” or fibrates or “fibric acid derivatives” or fenofibrate or clofibrate or bezafibrate or gemfibrozil or ciprofibrate or etofibrate. Study types used were randomized controlled trial, or randomized controlled trial, or random or random

allocation, or placebo, or placebos. Grey literature searching was done using Google and Google Scholar.

We just included randomized controlled trials and parallel or cross-over design. We excluded the Non-randomized trials, and all types of Observational studies. Patients with Albuminuria, microalbuminuria, macro-albuminuria, kidney disease, and end-stage kidney disease. In adult humans with or without diabetes according to the study design.

Studies with uncommon conditions: e.g. familial dyslipidemias, kidney disease, liver disease, HIV infection or other condition that could potentially confound the outcome of interest. Or pediatric trials were excluded. We in duplicate chose studies that discussed the Fibrates class or similar compared with a non-exposed control group, including placebo, or fibrates and active comparator for at least one year of follow up. The main outcome is the incidents of developing albuminuria, risk ratio, hazard ratio, odds ratio, incidence rate, or the data is sufficient to estimate risk or odds ratios. A random effect meta-analysis for the aggregated study-level data was used. The quality assessment were done using Cochrane method on the proper used of randomization, blinding and concealment of allocation, completeness of follow up and other biases[i].

Results

Our literature search for articles, editorials, and reviews on the topic yielded 953 without duplication hits (Figure 1). After exclusion of articles based on titles and abstracts, we reviewed 11 publications in full-text. We identified a total of 5 primary prevention trials which fulfilled our inclusion criteria, but only 3 studies included sufficient data for the quantitative analysis. Therefore, the final dataset included the

following studies (Nagai 2000[19], Gaede 2003[20], DAIS 2005[21], Davis 2011[8], ACCORD 2010[22]). The 3 studies that are included in the quantitative part are DAIS (2005), Davis (2011), and ACCORD (2010).

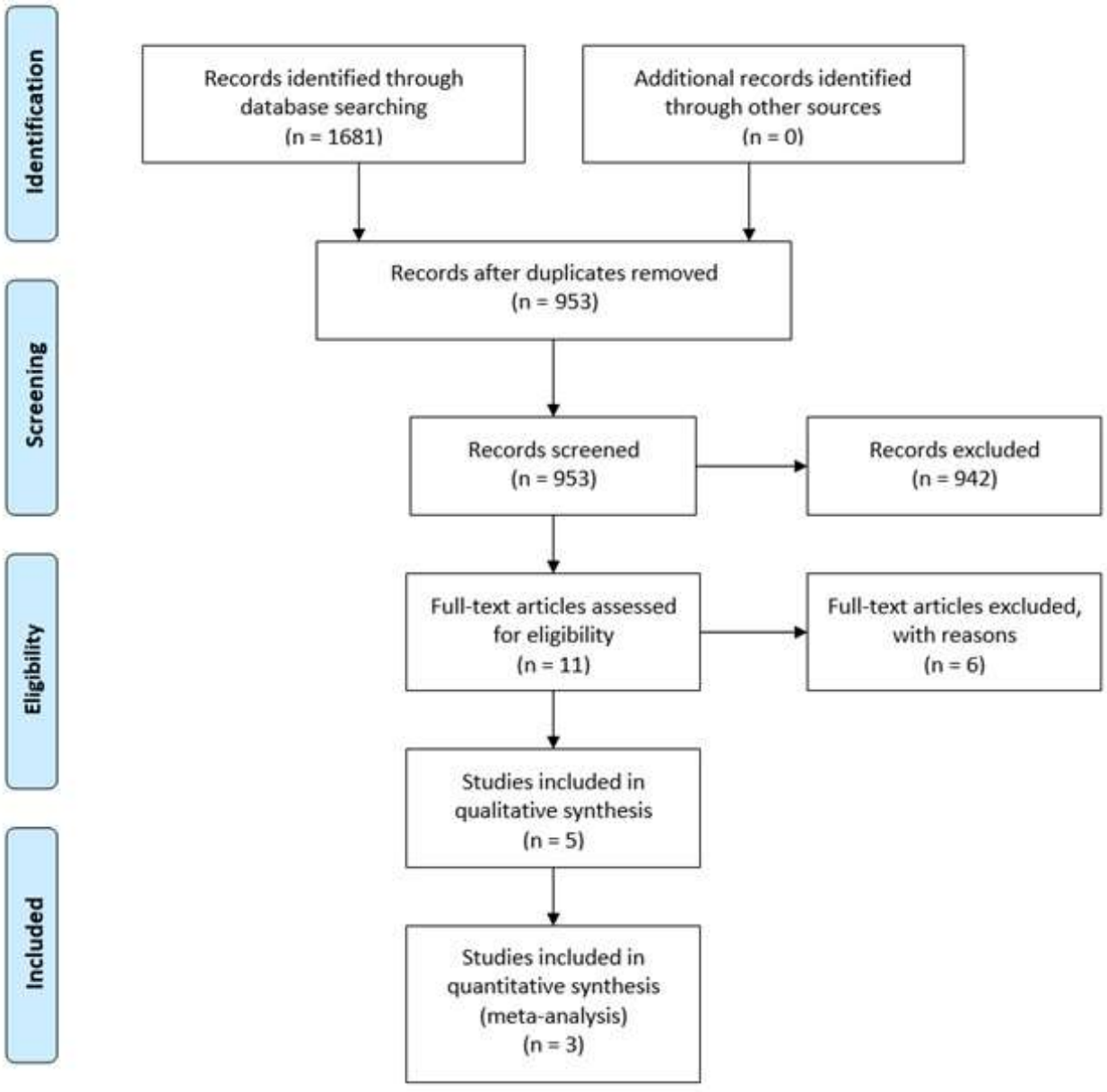

Fig 1: Identification of Eligible Studies.

The characteristics of the included studies are provided in Table 1. The studies included a total of 15848 participants. The average age varied from 55.1 – 66.4 years in the primary studies included in systematic review part, and 56.7 – 62.3 years in the quantitative part. The percentages of male participants ranged from 61.5% – 100% in the systematic review part, and 61.5% – 77.6% in the quantitative part. All studies recruited patients with type 2 diabetes mellitus (T2DM).

Table 1: Characteristics of included studies

Study	Design	Sample size & Average age	Intervention:	Control:	Endpoint:	Follow-up	Main Findings
Nagai 2000[19]	RCT	71 T2DM patients with hypercholesterolaemia; 66.4 years Men (%): 100	37 patients Bezafibrate with Pravastatin	34 patients Pravastatin	effect on cholesterol content of apolipoprotein AI, B100 containing particles or remnant-like particles, as well as on urinary albumin excretion	4 years.	No significant change between the two arms in urinary albumin excretion rate after 4 years

Study	Design	Sample size & Average age	Intervention:	Control:	Endpoint:	Follow-up	Main Findings
Gaeda 2003[20]	RCT	160 T2DM patients Average age of participants: 55.1 Men (%): 74.3	80 patients Conventional treatment	80 patients Intensive treatment (behaviour modification, aspirin, angiotensin converting enzyme inhibitor and aggressive treatment for hyperglycaemia, hypertension, dyslipidaemia and microalbuminuria):	effect of intensive treatment on cardiovascular risk	7.8 years.	Intensive treatment: reduced risk of cardiovascular and microvascular events by about 50%. The number of patients treated by Fibrates was 3 in the intensive arm with no effect reported on albuminuria.
DAIS 2005[21]	RCT	304 T2DM patients Average age of participants: 56.7 years Men (%): 77.6	155 T2DM patients Fenofibrate	159 T2DM patients Placebo	Fibrates effect of albuminuria Average	3 years	Fenofibrate: reduced progression of urinary albumin excretion (8% vs. 18% on placebo, $p<0.05$); delayed progression from normoalbuminuria to microalbuminuria: 3/101 patients vs. 20/113 patients on placebo ($p <0.001$)

Study	Design	Sample size & Average age	Intervention:	Control:	Endpoint:	Follow-up	Main Findings
Davis 2011[8]	RCT	9795 T2DM patients Average age of participants: 61.5 years Men (%): 61.5	4895 T2DM patients Fenofibrate.	4900 T2DM patients Placebo,	Fibrates effect on albuminuria nd eGFR	5 years	Fenofibrate: reduced progression of albuminuria in T2DM by 24% vs. 11% with placebo (p<0.001) with a mean difference of 14% (p<0.001); 14% less progression and 18% more regression of albuminuria (p<0.001); improved preservation of estimated GFR (p<0.001)
ACCORD 2010[22]	RCT	5518 T2DM patients Average age of participants: 62.3 years Men (%): 69	155 T2DM patients Fenofibrate.	159 T2DM patients Placebo	Fibrates effect of albumiuria	3 years	Fenofibrate: increase in mean serum creatinine from 0.93 to 1.10 mg/dL at 12 months (p<0.05); reduced development of microalbuminuria (38.2% vs.41.6% with placebo, p= 0.01); reduced development of macroalbuminuria (10.5% vs. 12.3% with placebo, p= 0.04); no difference in end-stage renal disease (fenofibrate: 75 patients, placebo: 77 patients)
* RCT: Randomized Controlled Trial, T2DM: Type 2 Diabetes Mellitus, eGFR: estimated glomerular filtration rate							

Three studies (DAIS 2005, Davis 2011, ACCORD 2010) used fenofibrate as an intervention.[8, 21, 22] Gaede (2003) reported the use of fenofibrate partially of some patients.[20] Nagai (2000) used Bezafibrate as an intervention.[19]

In the first study, Nagai et al. reported no significant change with either Bezafibrate or the placebo in urinary albumin excretion rate after 4 years.[19] The second study by Gaede et al. concluded that intensive treatment reduced the risk of cardiovascular and microvascular events by about 50%. The number of patients treated by Fibrates was 3 in the intensive arm with no effect reported on albuminuria. There is no particular data outcome for fibrates in this study.[20] In the DAIS study, fenofibrate reduced progression of urinary albumin excretion (8% vs. 18% on placebo, $p<0.05$); delayed progression from normoalbuminuria to microalbuminuria: 3/101 patients vs. 20/113 patients on placebo ($p <0.001$).[21] The results from FIELD study by Davis and colleagues reported that Fenofibrate: reduced progression of albuminuria in T2DM by 24% vs. 11% with placebo ($p<0.001$) with a mean difference of 14% ($p<0.001$); 14% less progression and 18% more regression of albuminuria ($p<0.001$); improved preservation of estimated GFR ($p<0.001$).[8] The ACCORD group results indicated that fenofibrate increased mean serum creatinine from 0.93 to 1.10 mg/dL at 12 months ($p<0.05$); reduced development of microalbuminuria (38.2% vs. 41.6% with placebo, $p= 0.01$); reduced development of macroalbuminuria (10.5% vs. 12.3% with placebo, $p= 0.04$); no difference in end-stage renal disease (fenofibrate: 75 patients, placebo: 77 patients).[22]

The meta-analysis of the DAIS (2005), Davis (2011), ACCORD (2010) is summarized in Figure 2. The pooled RR of the studies suggest that an overall result

favours fibrate in delaying the albuminuria when compared to either placebo arms or statin without fibrates. The overall RR 0.89 (0.85, 0.94) suggests a decrease in albuminuria risk in the fibrates group by an average of 11%. This reduction ranges from 6% - 15 % as indicated by the 95% confidence interval of the RR. The heterogeneity measured by Cochran's Q-test (p-value = 0.07) and I2 (53%). The heterogeneity result is statistically significant which indicates inconsistency in the results of the studies. Random effects model was employed to reduce the effect of heterogeneity over the total results; however, we will not extend the analysis to stratified because of the small number of studies. The quality assessment showed a high quality studies included in the quantitative analysis. The assessment of publication bias was not produced due to the small number of included studies.

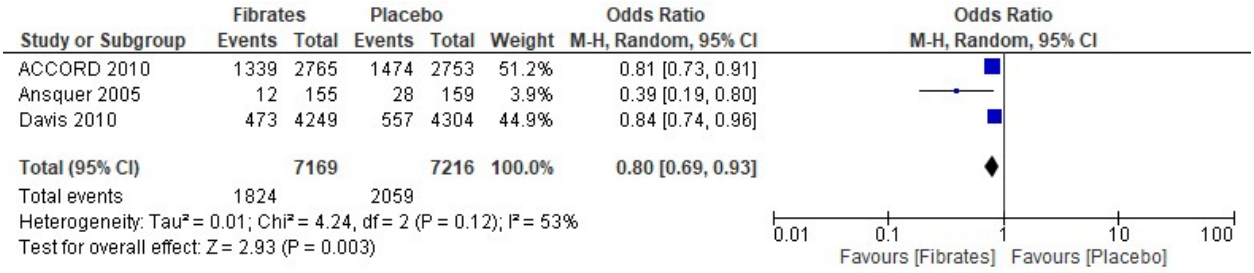

Fig 2: Forest plot showing the effect of fibrates on albuminuria (n=3 studies).

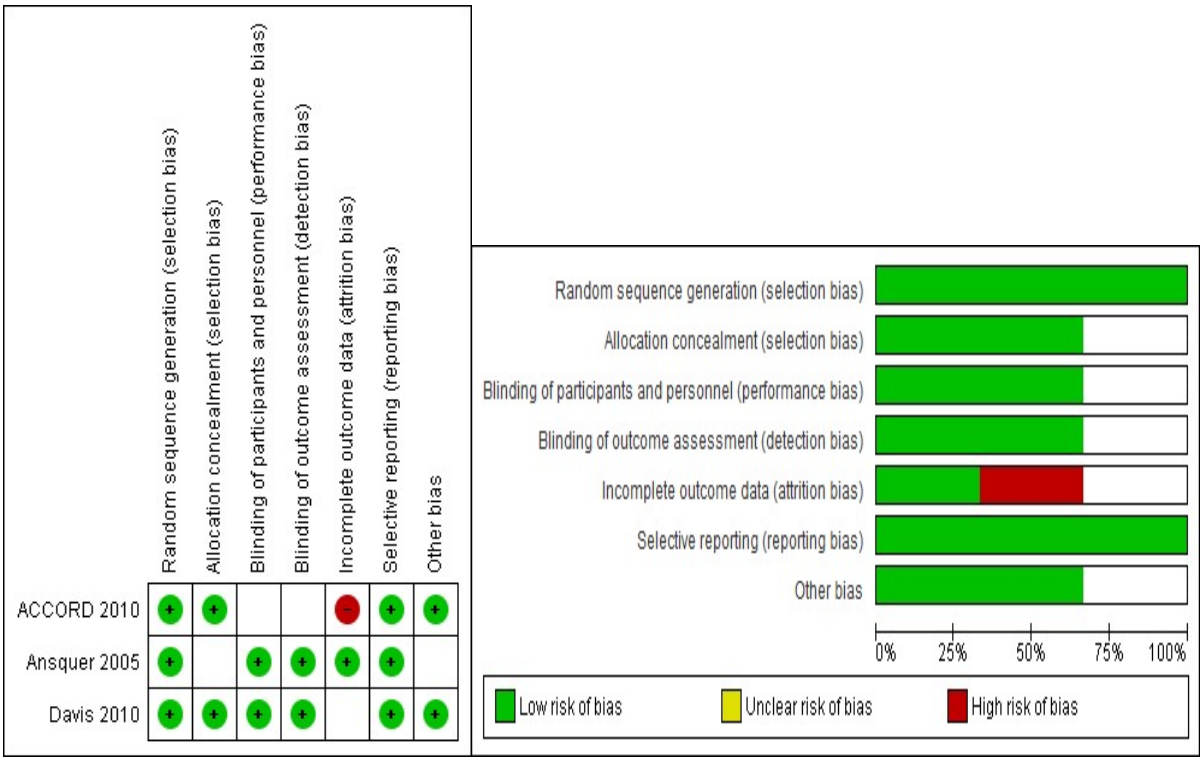

Fig 3: Quality assessment of the included studies in the quantitative analysis.

Discussion

This study proves that fibrates reduces the Albuminuria with sugnificant difference whithin a large number of patients >14000. Those results correspond with the older systematic review conducted by Jun et al. on 2012[ii]. The study proved that the use of fibrates reduce albuminuria within type 2 diabetes patients.

Fibrates have been used in clinical practice for decades in reducing hyperlipidemia.[16] The evidence although scarce in comparison to the statin, it suggests that fibrates may play a role in reducing the risk of cardiovascular disease.[23-26] Patients with T2DM may derive the greatest benefit. In these patients, who typically

present with the combined mixed dyslipidemia, fibrates may be the most appropriate treatment.[10]

Diabetic nephropathy is characterized by thickening of glomerular basement membrane, glomerulosclerosis, glomerular hypertrophy, podocyte loss, expansion of mesangial cells, and tubulointerstitial fibrosis.[3, 27] It is associated with consistently elevated albuminuria, declining GFR, high blood pressure, and fluid retention.[3] The cause of diabetic nephropathy remains not fully understood, but the structural and functional kidney changes may occur due to the chronic hyperglycemia in diabetes and the exposure to hypertension persistently.[28] Additionally, the critical role of the inflammatory process in the development of diabetic nephropathy as suggested by accumulated data indicates that “chronic subclinical inflammation is a common mechanism in the pathogenesis of diabetic vascular complications.”[29, 30] Triglyceride elevation has been suggested as an independent risk factor and a major determinant of the progression of nephropathy in T2DM.[31, 32] Fibrates are effective lipid-lowering agents, especially in obese subjects with T2DM and mixed dyslipidemia.[33] Moreover, fibrates utilize beneficial effects in diabetic nephropathy; a potential explanation is the through fibrates’ pleiotropic, lipid-unrelated actions.[34, 35] PPAR-α activation plays a critical role in the inhibition of several mediators of vascular damage, fibrates act as a PPAR-α activator, and their pleiotropic effects are getting recognition as a potential preventer of diabetic nephropathy with an advantage that fenofibrate apply a uric acid lowering effect.[36]

This review has limitation due to the small number of included studies. Also the difference method of clinical outcome presentation lead to the moderate hetrogeniety that might affect the degree of confidence in the results of the pooled results.

Conclusion

Diabetes has reached very alarming levels globally, and diabetic nephropathy has become a significant health burden. Numerous efforts have been channeled towards further understanding the underlying mechanisms and developing novel therapeutic agents to target diabetic nephropathy. There is some evidence that activation of PPAR-α might play a role in slowing the progression of diabetic nephropathy. The current evidence favors fibrates in slowing the progression of diabetic nephropathy. In spite of the current evidence, data from large clinical trials is still scarce, especially when compared with other therapeutic agents like the statin. Therefore, there is a huge necessity for large randomized trials with the aim to assess the efficacy of fibrates on diabetic nephropathy. There is a need for using diabetic nephropathy as a primary outcome, not just a secondary one.

Conflicts of interest

We declare no conflict of intrest. This review was not funded by any source.

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