

Cardiovascular disease-related mortality risk in end stage renal disease and type 2 diabetes: A systematic review

Arwa A. Al-Hajji, Hibah A. Alsubaie, Hanan T. Albaqshi, Hayat I. Al-Hajji, Fatemah M. A. AlEssa, Batool M. Abu Ali

Medical Resident in King Fahad Hospital-Al-Hofuf, Hofuf City, Eastern Province, Saudi Arabia

ABSTRACT

Background: Patients with uncontrolled type 2 diabetes can have microvascular and macrovascular complications, including renal impairment and cardiovascular diseases. However, it is unknown how diabetes and renal disease could influence cardiovascular mortality. **Objective:** This study aims at examining the medical literature to evaluate the risk of cardiovascular death in concomitant end stage renal disease with type 2 diabetes. **Method:** Medical literature was reviewed through Medline, PubMed, Embase, and Ovid database in the duration between 2009 and 2019. Searching terms included were a combination of “type 2 diabetes mellitus” AND “end-stage renal disease” AND “cardiovascular mortality”. Following this, results were filtered to include only original research articles investigating cardiovascular mortality in concomitant diabetes and end-stage renal disease. Selected trials mentioned diabetes control as well as the follow-up duration of the included patients. **Result:** A total of 1508 articles were retrieved. Following the exclusion of articles on animals and including only trials on humans, 32 articles appeared. A total of eight articles were identified as eligible, covering a total of 2,06,492 diabetic patients with end-stage renal disease. All the studies were prospective studies, except for three studies that were retrospective. **Conclusion:** There is an elevated cardiovascular mortality risk in concomitant type 2 diabetes mellitus and end-stage renal disease, especially with uncontrolled blood glucose levels.

Keywords: Cardiovascular disease, diabetes mellitus, end-stage renal disease, mortality

Introduction

Diabetic nephropathy is considered a primary causative agent for end-stage renal disease all over the world.^[1] The incidence of cardiovascular mortality is increased in those with end-stage renal disease (ESRD) concomitantly with diabetes mellitus.^[2]

Despite the higher expectation of increased cardiovascular mortality mainly due to atherosclerosis in diabetic and (ESRD), there are no confirming reports on this assumption.^[3] Atherosclerosis has two major presentations; these are classified into thickening,

in addition to the stiffening of the walls of arteries.^[4] Previous data showed that the thickness of carotid artery intima-media is increased in patients with diabetes or ESRD.^[5]

Moreover, high urinary albumin-to-creatinine ratio (UACR) as well as low estimated glomerular filtration rate (eGFR), showed to be predictors for the increased incidence of diabetic ESRD and mortality.^[6] Kidney Disease Improving Global Outcomes (KDIGO) described a different categorization for chronic kidney disease through the addition of stages that classified urinary albumin excretion in addition to estimated glomerular filtration rate and their impact on clinical diagnosis.^[7]

This novel categorization, mainly depending upon the integrated meta-analysis of general populations, has shown the progress of

Address for correspondence: Dr. Arwa A. Al-Hajji, King Fahad Hospital-Al-Hofuf, Prince Fawaz St., Al-Ruqaiqah Neighborhood, Hofuf City - 31982, Eastern Province, Saudi Arabia. E-mail: Alhajjiarwa@hotmail.com

Received: 10-02-2020

Revised: 10-03-2020

Accepted: 13-03-2020

Published: 30-07-2020

Access this article online

Quick Response Code:



Website:
www.jfmpc.com

DOI:
10.4103/jfmpc.jfmpc_244_20

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Al-Hajji AA, Alsubaie HA, Albaqshi HT, Al-Hajji HI, AlEssa FM, Abu Ali BM. Cardiovascular disease-related mortality risk in end stage renal disease and type 2 diabetes: A systematic review. J Family Med Prim Care 2020;9:3195-9.

the disease based on clinical diagnosis, stage, and other critical factors related to cardiovascular and renal consequences.^[8]

Though, the clinical outcome of urinary albumin-to-creatinine ratio levels in addition to the estimated glomerular filtration rate on outcomes in diabetic nephropathy needs to be identified.^[9]

Hence, in-depth clinical description of ESRD are needed to offer a clue for the pathogenesis and consequences of progressive renal complications, and its correlation to cardiovascular events and mortality in type 2 diabetic patients.^[10]

Therefore, this systematic review aims to examine the literature for the association of cardiovascular mortality in concomitant diabetes and ESRD.

Review

Methodology

This systematic review of the literature was carried out to be compliant with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist recommendations for systematic review and meta-analysis.^[11] This systematic review was carried out through searching electronic databases to include eligible trials till October 2019 in four databases, including Medline, Pubmed, Ovid, and Embase.

Search strategy

Searching terms included “type 2 diabetes mellitus” AND “end-stage renal disease” AND “cardiovascular mortality”. All the titles, as well as abstracts that appeared from this search, were reviewed thoroughly to prevent missing any eligible articles. The results were then refined to include only original research articles investigating the correlation between cardiovascular mortality in concomitant type 2 diabetes in addition to end-stage renal disease.

Moreover, the selected trials mentioned the control of blood glucose of included patients as well as the duration of follow-up for patients. Additionally, all study designs from different countries were included. Only trials that are published in the English language were classified as related articles, which can be further evaluated in the second step.

Eligibility criteria

After this stage, the inclusion criteria to select the studies that will be considered in the systematic review were determined. Abstracts were examined manually to choose the appropriate abstracts to be considered. The inclusion criteria were mentioning enough data on the patient population and data on cardiovascular mortality and other comorbidities. Moreover, only trials recruiting adult participants were included. Furthermore, references of selected trials were evaluated to identify any related articles. Finally, the required data sets were gathered from the final record of eligible articles and summarized. Articles were excluded in case of *in vitro* or animal involvement, overlapped or incomplete

data, and unavailability of full-text articles or inappropriate study design. Full details on the search strategy are shown in Figure 1.

Data review and analysis

The first step included a preliminary review, a specially designed excel sheet was used for data extraction. Selected data from eligible studies were then revised through the excel sheet. Any articles that were published by one research group that investigate similar variables were reviewed for any possible duplication. Cochrane, a quality assessment tool, was also used to evaluate the quality of the included clinical studies.^[12] Data was then statistically estimated as frequencies and valid percentages for categorical variables. Mean, standard deviations, medians, and interquartile ratios were utilized to identify the numerical variable. All statistical assessment was performed by IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release 21 for Microsoft Windows.

Before conducting any study-related procedures, institutional approval was obtained. There was no need to get consent form as the study is not involving any interventions on patients.

Results

After searching the abstracts and checking for the eligibility criteria in identified potential abstracts, a total of eight articles were considered as eligible to be included in the present systematic review that were published between 2009 and 2019, covering a total of 2,06,492 patients with concomitant diabetes combined with end-stage renal disease.

Among the eight included studies,^[3,12-18] three studies had a retrospective design,^[12,14,16] for other five studies, two studies^[13,17] had a prospective observational design while three studies^[3,15,18] had a randomized prospective design.

Turning to diabetes control, all the studies^[3,12-18] included patients who had controlled blood glucose levels on either oral antidiabetic agents or insulin. However, it was not clear the percent of patients on each treatment.

Concerning the follow-up period, the average follow-up duration for all studies was 3.325 years, having a minimum follow up duration of two years and a maximum follow up of seven years.

According to extracted results, all the trials considered the glycemic control of patients as well as mentioning the follow-up duration under investigation. The included trials are discussed in detail in Table 1.

Discussion

Diabetes is a common chronic condition all over the world. Diabetes complications are the major causative factor for death globally. Renal impairment as well as cardiovascular diseases are the most frequent complications correlated to diabetes;

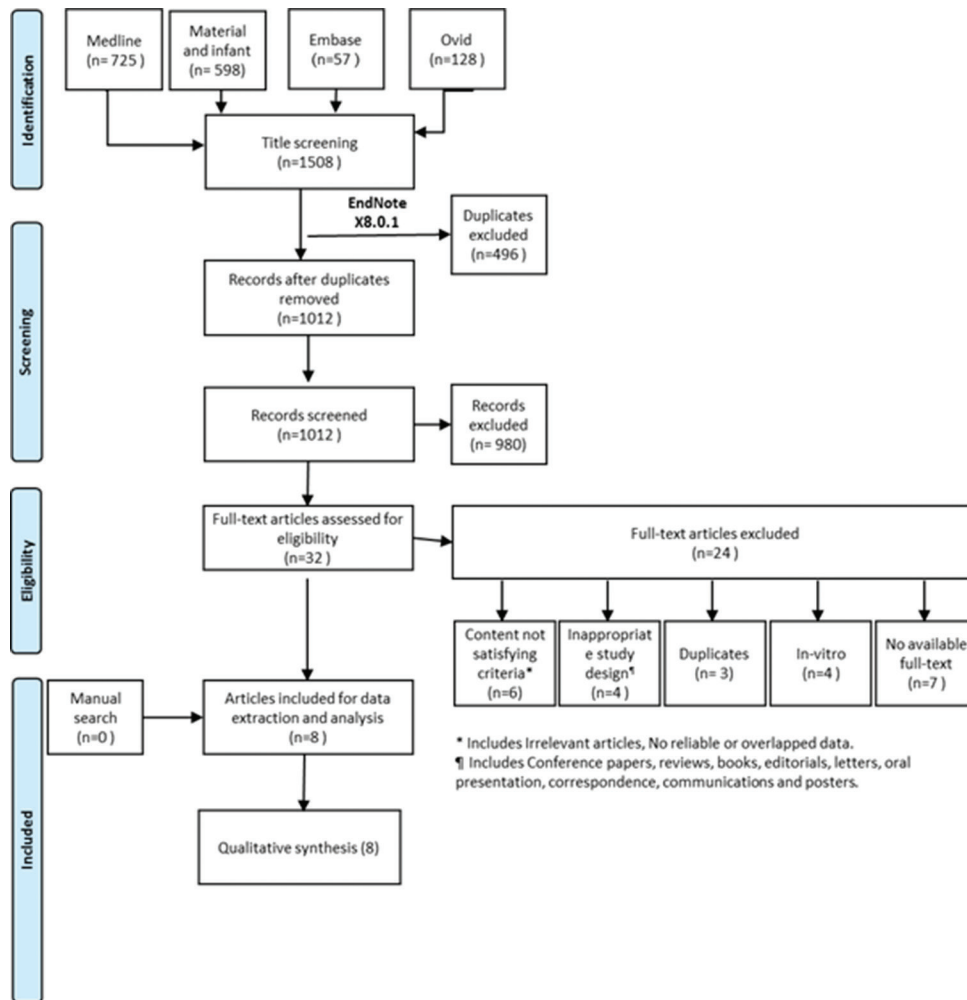


Figure 1: Flow chart of the included articles

however, there is a scarcity of data concerning mortality in patients with diabetes, with concomitant advanced renal disease and cardiovascular disease.

The present review investigated the correlation between cardiovascular mortality on the one hand and the co-occurrence of diabetes in addition to ESRD on the other hand. The current investigation revealed that concomitant diabetes with ESRD was at increased hazard of cardiovascular mortality after a mean follow-up of 3.325 years.

All the included studies recruited patients who had controlled diabetes in different settings. Lim *et al.*^[13] revealed that mortality due to cardiovascular disease was increased in case of diabetes and ESRD, especially in the case of hemodialysis and older age.

The findings of Lim *et al.*^[13] were also confirmed by Chin *et al.*^[15] who showed that diabetic patients with concomitant ESRD were at increased hazard of heart failure as well as cardiovascular mortality. It should be noted that Lim *et al.* included 56,552 patients in a prospective study, which strengthens the design, yet the study was prospective observational.

Additionally, Packham *et al.*^[12] investigated the cardiovascular mortality as well as all-cause mortality for concomitant diabetes and ESRD.

After a follow up period of 2.8 years, Packham *et al.*^[12] showed that in case of concomitant diabetes and ESRD, patients are at an elevated risk of cardiovascular complications compared to their peers. However, their should be cautiously interpreted because of the retrospective nature of the study.

Another retrospective study that followed up patients for the most extended duration in all the included studies was Wada *et al.*^[16]. This study examined the risk of cardiovascular mortality in case of concomitant diabetes and ESRD identified through albumin to creatinine ratio over seven years.

Wada *et al.*^[16] demonstrated that cases with concomitant diabetes and ESRD were at an increased hazard of cardiovascular and all-cause mortality. It should be taken into account that the findings of Wada *et al.*^[16] are derived from the Japanese population, which requires careful consideration before being extrapolated to other populations.

Table 1: Shows included trials

Author(s)	Year	Study design	Sample size	Control of hyperglycemia	Follow up duration	Objective	Result
Lim <i>et al.</i> ^[13]	2018	Prospective cohort	56552	Controlled	2.5 years	To examine the correlation between type 2 diabetes mellitus, with nephropathy, and cardiovascular disease mortality in patients on dialysis or with end stage renal disease.	The mortality risk is elevated in patients with end stage renal disease and dialysis who also have type 2 diabetes than for patients without diabetes, especially in patients who are below 50 years old, and the risk was higher in case of the end-stage renal disease.
Neal <i>et al.</i> ^[3]	2017	Randomized controlled trial	10142	Controlled	3 years	To evaluate the benefit of antidiabetic agents on cardiovascular mortality in diabetic patients with end stage renal disease.	Patients with controlled diabetes using oral ant diabetic agents had a reduced risk of cardiovascular mortality compared to patients on placebo. Patients with estimated glomerular filtration rate were older, females, and had a longer duration of diabetes.
Cornel <i>et al.</i> ^[14]	2016	Retrospective study	14671	Controlled	3 years	To examine the end stage renal disease and cardiovascular mortality in diabetic patients	Cardiovascular event rates were higher in case of decreased baseline estimated glomerular filtration rate rate Impaired kidney function is correlated to worse cardiovascular outcomes.
Chin <i>et al.</i> ^[15]	2014	Randomized controlled trial	2185	Controlled	2 years	To investigate the cardiovascular events in patients with diabetes and end-stage renal disease	End-stage renal disease and diabetes patients were at higher risk of heart failure and cardiovascular death
Wada <i>et al.</i> ^[16]	2014	Retrospective	4328	Controlled	7 years	To evaluate the risk of cardiovascular mortality in patients with diabetes and end-stage renal diseases	Increased urinary albumin to creatinine ratio (UACR) levels were strongly correlated with the elevation in risks for cardiovascular death, and all-cause mortality in Japanese patients with type 2 diabetes and renal impairment.
Packham <i>et al.</i> ^[12]	2011	Retrospective	3228	Controlled	2.8 years	To evaluate the incidence of end stage renal disease, cardiovascular death, and all cause mortality.	Patients with type 2 diabetic nephropathy, characterized by decreased kidney function and significant proteinuria, are more likely to reach end stage renal disease than death during three years follow-up. patients with type 2 diabetes, anemi, and CKD, had elevated cardiac biomarkers. These cardiac-biomarkers enhance the prediction of end stage renal disease beyond established risk factors.
Desai <i>et al.</i> ^[17]	2011	Prospective cohort	1000	Controlled	2 years	To examine the value of cardiac biomarkers in evaluating the risk of cardiac mortality in diabetic patients with chronic kidney disease	Measurement of cardiac biomarkers may improve the identification of patients with chronic kidney disease who are likely to require dialysis. This can support the correlation between diabetes, kidney disease and cardiovascular events.
Galan <i>et al.</i> ^[18]	2009	Prospective study	11140	Controlled	4.3 years	To investigate the impact of controlling cardiovascular disease on renal and mortality outcomes in diabetic patients	Medications controlling cardiac conditions can have an impact on reducing overall mortality and events in patients with diabetes and renal disease.

Also, other studies authored by Neal *et al.*^[3] and Cornel *et al.*^[14] evaluated the impact of antidiabetic agents on controlling

diabetes and, subsequently, the incidence of complications and mortality. Neal *et al.*^[3] and Cornel *et al.*^[14] revealed that patients

who were controlled on oral antidiabetic agents were at a lower risk of developing complications and mortality compared to manage groups.

However, most of the included studies were performed in one center, which may decrease the validity of outcomes. Also, it was not clear if the patients were controlled on oral antidiabetic agents or insulin, and the types of antidiabetics used. These limitations should be considered in future studies.

Finally, till present, this is considered the first systematic review to evaluate the correlation between cardiovascular mortality and diabetes with ESRD.

Conclusion

Cardiovascular mortality is increased with the presence of ESRD. Proper control of diabetes could decrease the risk of diabetes complications. Decision-makers in government should make a priority for increasing the awareness of the public towards the complications of diabetes and ways to prevent or minimize their occurrence.

Future studies should focus on studying the correlation between different antidiabetic agents and the risk of cardiovascular mortality.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

- Ghaderian SB, Hayati F, Shayanpour S, Mousavi SS. Diabetes and end-stage renal disease; a review article on new concepts. *J Renal Inj Prev* 2015;4:28-33.
- van Haalen H, Jackson J, Spinowitz B, Milligan G, Moon R. Impact of chronic kidney disease and anemia on health-related quality of life and work productivity: Analysis of multinational real-world data. *BMC Nephrol* 2020;21:1-5.
- Neal B, Perkovic V, Mahaffey KW, De Zeeuw D, Fulcher G, Erond N, *et al.* Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;377:644-57.
- American Diabetes Association. 15. Diabetes Care in the Hospital: Standards of Medical Care in Diabetes—2020. *Diabetes Care* 2020;43(Suppl 1):S193-202.
- Mann JF, Ørsted DD, Brown-Frandsen K, Marso SP, Poulter NR, *et al.* Liraglutide and renal outcomes in type 2 diabetes. *N Engl J Med* 2017;377:839-48.
- De Zeeuw D, Akizawa T, Audhya P, Bakris GL, Chin M, Christ-Schmidt H, *et al.* Bardoxolone methyl in type 2 diabetes and stage 4 chronic kidney disease. *N Engl J Med* 2013;369:2492-503.
- Provenzano M, Chiodini P, Minutolo R, Zoccali C, Bellizzi V, Conte G, *et al.* Reclassification of chronic kidney disease patients for end-stage renal disease risk by proteinuria indexed to estimated glomerular filtration rate: Multicentre prospective study in nephrology clinics. *Nephrol Dial Transplant* 2020;35:138-47.
- Ma RC, Tam CH, Wang Y, Luk AO, Hu C, Yang X, *et al.* Genetic variants of the protein kinase C- β 1 gene and development of end-stage renal disease in patients with Type 2 diabetes. *JAMA* 2010;304:881-9.
- Parving HH, Brenner BM, McMurray JJ, De Zeeuw D, Haffner SM, Solomon SD, *et al.* Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med* 2012;367:2204-13.
- Zoppini G, Targher G, Chonchol M, Ortalda V, Abaterusso C, Pichiri I, *et al.* Serum uric acid levels and incident chronic kidney disease in patients with type 2 diabetes and preserved kidney function. *Diabetes Care* 2012;35:99-104.
- Hsu CY, Iribarren C, McCulloch CE, Darbinian J, Go AS. Risk factors for end-stage renal disease: 25-year follow-up. *Arch Intern Med* 2009;169:342-50.
- Packham DK, Alves TP, Dwyer JP, Atkins R, De Zeeuw D, Cooper M, *et al.* Relative incidence of ESRD versus cardiovascular mortality in proteinuric type 2 diabetes and nephropathy: Results from the DIAMETRIC (Diabetes Mellitus Treatment for Renal Insufficiency Consortium) database. *Am J Kidney Dis* 2012;59:75-83.
- Lim WH, Johnson DW, Hawley C, Lok C, Polkinghorne KR, Roberts MA, *et al.* Type 2 diabetes in patients with end-stage kidney disease: Influence on cardiovascular disease-related mortality risk. *Med J Aust* 2018;209:440-6.
- Cornel JH, Bakris GL, Stevens SR, Alvarsson M, Bax WA, Chuang LM, *et al.* Effect of sitagliptin on kidney function and respective cardiovascular outcomes in type 2 diabetes: Outcomes from TECOS. *Diabetes Care* 2016;39:2304-10.
- Chin MP, Wrolstad D, Bakris GL, Chertow GM, de Zeeuw D, Goldsberry A, *et al.* Risk factors for heart failure in patients with type 2 diabetes mellitus and stage 4 chronic kidney disease treated with bardoxolone methyl. *J Card Fail* 2014;20:953-8.
- Wada T, Haneda M, Furuichi K, Babazono T, Yokoyama H, Iseki K, *et al.* Clinical impact of albuminuria and glomerular filtration rate on renal and cardiovascular events, and all-cause mortality in Japanese patients with type 2 diabetes. *Clin Exp Nephrol* 2014;18:613-20.
- Desai AS, Toto R, Jarolim P, Uno H, Eckardt KU, Kewalramani R, *et al.* Association between cardiac biomarkers and the development of ESRD in patients with type 2 diabetes mellitus, anemia, and CKD. *Am J Kidney Dis* 2011;58:717-28.
- De Galan BE, Perkovic V, Ninomiya T, Pillai A, Patel A, Cass A, *et al.* Lowering blood pressure reduces renal events in type 2 diabetes. *J Am Soc Nephrol* 2009;20:883-92.