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 Faisal 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. The incidence of cardiovascular mortality is increased in those with end-stage renal disease (ESRD) concomitantly with diabetes mellitus.

Despite the higher expectation of increased cardiovascular mortality mainly due to atherosclerosis in diabetic and (ESRD), there are no confirming reports on this assumption. Atherosclerosis has two major presentations; these are classified into thickening, in addition to the stiffening of the walls of arteries. Previous data showed that the thickness of carotid artery intima-media is increased in patients with diabetes or ESRD.

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. 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.

This novel categorization, mainly depending upon the integrated meta-analysis of general populations, has shown the progress of...
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the disease based on clinical diagnosis, stage, and other critical factors related to cardiovascular and renal consequences.\[^9\]

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.\[^14\] 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.

**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,\[^12,16\] 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;
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.
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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.

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**Conflicts of interest**

There are no conflicts of interest.

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