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METFORMIN IS LINKED TO REDUCED MORTALITY IN TYPE 2 DIABETES WITH COMORBID CKD AND CHF: A SYSTEMATIC REVIEW

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Abstract

Introduction: *Due to DM diagnosis criteria, determining its incidence is difficult. Diabetes affects 10.2 million Americans. Due to conflicting data on mortality and antihyperglycemic therapy benefits, managing hyperglycemia in type 2 diabetes mellitus (T2DM) patients at risk of cardiovascular problems is difficult.*

The aim: *This article showed about metformin is Linked to reduced mortality in type 2 diabetes with comorbid chronic kidney disease (CKD) and congestive heart failure (CHF).*

Methods: *By comparing itself to the standards set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. So, the experts were able to make sure that the study was as up-to-date as it was possible to be. For this search approach, publications that came out between 2013 and 2023 were taken into account. Several different online reference sources, like Pubmed and SagePub, were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.*

Result: *In the PubMed database, the results of our search brought up 85 articles, whereas the results of our search on SagePub brought up 57 articles. The results of the search conducted for the last year of 2013 yielded a total 34 articles for PubMed and 21 articles for SagePub. In the end, we compiled a total of 19 papers, 13 of which came from PubMed and seven of which came from SagePub. We included five research that met the criteria.*

Conclusion: *Metformin use was found to be related with a reduced risk of death from any cause as well as progression toward ESRD in patients with CKD and CHF in the current investigation.*

Keyword: *Chronic kidney disease; Congestive heart failure; Metformin; Mortality; Type 2 diabetes*

INTRODUCTION

Diabetes Mellitus (DM) is a group of metabolic diseases marked by high blood sugar. This high blood sugar is caused by problems with insulin production, insulin action, or both. Long-term damage, malfunctioning, and failure of glands, especially the eyes, kidneys, nerves, heart, and blood vessels, are linked to diabetic chronic hyperglycemia.[1] Determining the incidence of DM poses challenges due to variations in the criteria employed for diagnosing the condition. Approximately 10.2 million individuals inside the United States are affected by diabetes mellitus. In Indonesia, the prevalence of diabetes mellitus (DM) among those aged over 15 years is estimated to be between 1.5% and 2.3%. Notably, in the Manado area, the incidence of DM is reported to be 6.1%. The prevalence of Type 2 diabetes mellitus is greater in females compared to males.[2–4]

The numerous dysfunctions that comprise diabetes mellitus type 2 are defined by hyperglycemia and result from a combination of insulin resistance, inadequate insulin secretion, and excessive or incorrect glucagon secretion. Type 2 diabetes mellitus can also be referred to as adult-onset diabetes. Uncontrolled type 2 diabetes is connected to a range of complications that can impair the microcirculation, the macrocirculation, and the nerves. These complications can be fatal. When diabetes is not under control, having consistently high blood sugar can cause a variety of complications, some of which are immediate and others of which are chronic.[5]

Due to an increase in type 2 diabetes mellitus (T2DM) diagnoses, chronic kidney disease (CKD) is a global public health issue. CKD affects 43% of type 2 diabetics and 61% of US diabetics over 65. Metformin, a biguanide diabetic medication, reduces intestinal glucose absorption and liver glucose production and increases insulin sensitivity, however its full benefits are unknown.[6] Because of its low cost, efficacy, weight independence, and cardiovascular advantages, type 2 diabetics often start with metformin. Due to the risk of lactic acidosis, kidney dysfunctional people cannot take metformin. Pharmacologically, when 3b and G4 CKD patients took 1,000 mg/d and 500 mg/d for 4 months, serial blood metformin levels were always below the upper limit of normal, and lactate levels were preserved below 5.0 mmol/L.[7]

Two recent comprehensive evaluations found no indication that metformin causes more lactic acidosis than other antidiabetic medications. In another comprehensive review, metformin intake reduced all-cause mortality in moderate CKD patients, but it lacked subgroup analysis, heterogeneity, and publication bias. Metformin should be used cautiously in mild CKD. Metformin's safety for advanced CKD patients is uncertain, and new guidelines advise caution until more is known. Recent studies also contradict metformin use in type 2 diabetes and advanced CKD. Metformin administration may not reduce all-cause mortality in advanced CKD patients. However, metformin use may significantly alter death rates.[6,8–11]

According to the findings of this study, the use of metformin is associated with a lower risk of mortality in patients with type 2 diabetes who also have concomitant chronic renal disease and congestive heart failure.

METHODS

In accordance with the requirements outlined in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study took measures to guarantee strict adherence to these standards. This measure is implemented in order to guarantee the precision of the investigation's outcomes. The objective of this literature review was to demonstrate the association between metformin usage and decreased mortality rates in individuals with type 2 diabetes who also had concomitant chronic kidney disease (CKD) and congestive heart failure (CHF). The main aim of this composition is to showcase the significance of the stated difficulties throughout the text.

In order to be eligible for participation in the study, researchers were obligated to meet the following criteria: The paper should be composed in the English language and should discuss the association between metformin and decreased mortality in individuals with type 2 diabetes who also have concomitant CKD and CHF. In order to be eligible for publication, the manuscript must satisfy both of these criteria. Several of the scrutinized articles were published between 2013 and the predetermined time frame considered relevant for this systematic review. Prohibited include editorials, submissions lacking a DOI (Digital Object Identifier), review articles that have been previously published, and entries that are effectively duplicates of previously published journal papers.

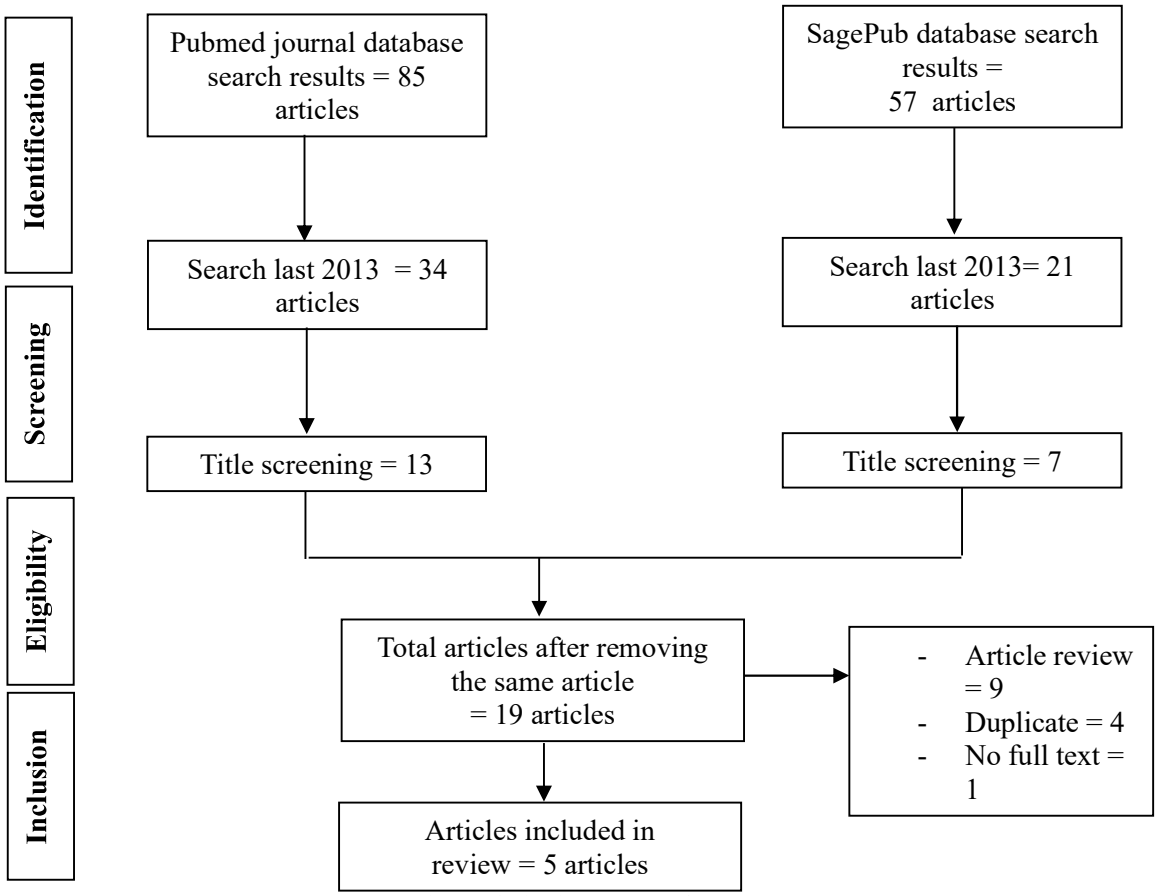

Figure 1. Article search flowchart

We used "metformin"; "mortality"; "type 2 diabetes"; "comorbid"; "chronic kidney disease" and "congestive heart failure" as keywords.The search for studies to be included in the systematic review was carried out from August, 7th 2023 using the PubMed and SagePub databases by inputting the words: *(("metformin"[Supplementary Concept] OR "metformin"[All Fields] OR "metformin"[MeSH Terms] OR "metformine"[All Fields] OR "metformin s"[All Fields] OR "metformins"[All Fields]) AND ("mortality"[MeSH Terms] OR "mortality"[All Fields] OR "mortalities"[All Fields] OR "mortality"[MeSH Subheading]) AND ("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields] OR "type 2 diabetes"[All Fields]) AND ("comorbid"[All Fields] OR "comorbidity"[MeSH Terms] OR "comorbidity"[All Fields] OR "comorbidities"[All Fields] OR "comorbids"[All Fields]) AND ("renal insufficiency, chronic"[MeSH Terms] OR ("renal"[All Fields] AND "insufficiency"[All Fields] AND "chronic"[All Fields]) OR "chronic renal insufficiency"[All Fields] OR ("chronic"[All Fields] AND "kidney"[All Fields] AND "disease"[All Fields]) OR "chronic kidney disease"[All Fields]) AND ("heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields] OR ("congestive"[All Fields] AND "heart"[All Fields] AND "failure"[All Fields]) OR "congestive heart failure"[All Fields])) AND (clinicaltrial[Filter] OR randomizedcontrolledtrial[Filter])* used in searching the literature.

After reviewing the abstract and title of each study, the authors determined whether or not it met the inclusion criteria. The authors then determined which prior studies would serve as the article's sources and selected those studies. Examining a variety of studies that all appeared to indicate the same trend led to this conclusion. All submissions must be written in English and have never been published before. Only publications that satisfied all inclusion criteria were considered for the systematic review. This restricts the search results to those which are germane to your query. We do not consider the results of any study that does not meet our criteria. The research findings will then be thoroughly analyzed. The following information was uncovered as a result of the research conducted for this study: names, authors, publication dates, location, study activities, and parameters.

Before deciding which publications to investigate further, each author conducted independent research on the research included in the publication's title and abstract. The subsequent step is to evaluate all of the articles that satisfy the inclusion criteria for the review. Then, we will choose which articles to include in the review based on the findings. This criterion is employed to select documents for additional evaluation. To facilitate as much as possible the selection of papers for evaluation. This section discusses which prior studies were conducted and what aspects of those studies made their inclusion in the review appropriate.

RESULT

In the PubMed database, the results of our search brought up 85 articles, whereas the results of our search on SagePub brought up 57 articles. The results of the search conducted for the last year of 2013 yielded a total 34 articles for PubMed

and 21 articles for SagePub. In the end, we compiled a total of 19 papers, 13 of which came from PubMed and seven of which came from SagePub. We included five research that met the criteria.

Kwon, et al (2020)[8]According showed mortality from all causes and incident ESRD were reduced in the metformin group. PSM was conducted because the two groups had significantly different baseline characteristics. Metformin use remained associated with lower all-cause mortality (adjusted hazard ratio [aHR] = 0.65; 95% confidence interval [CI] = 0.57-0.73; P <0.001) and ESRD progression (aHR = 0.67; 95% CI = 0.58-0.77; P <0.001). One case of lactic acidosis associated with metformin was documented. In both the original and PSM groups, the use of metformin did not increase the risk of lactic acidosis events due to any cause (aHR = 0.92; 95% CI = 0.668-1.276; P = 0.629).

Whitlock, et al (2020)[12] conducted a study with 21,996 individuals (19,990 metformin users and 2006 sulfonylurea users). Metformin use was associated with lower risk for all-cause mortality (hazard ratio [HR] = 0.48; 95% CI = 0.40-0.58; P <0.001), cardiovascular events (HR = 0.67; 95% CI = 0.52-0.86; P = 0.002), and major hypoglycemic episodes (HR = 0.14; 95% CI = 0.09-0.20; P< 0.001) when compared with sulfonylureas. CKD was a significant effect modifier for all-cause mortality (P=.002), but not for cardiovascular events or major hypoglycemic episodes.

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Result
Kwon, 2020[8]	Republic of Korea	Retrospective cohort study	10,426 patients with type 2 DKD	Patients with advanced chronic kidney disease (CKD), particularly those with CKD 3B, who took metformin had a lower risk of death from any cause and of developing incident end-stage renal disease (ESRD). In addition, the risk of developing lactic acidosis was not increased by the use of metformin.
Whitlock, 2020[12]	Canada	Retrospective cohort study	21,996 individuals (19,990 metformin users and 2006 sulfonylurea users)	In comparison to metformin, sulfonylurea monotherapy is associated with a greater risk of death from any cause, significant bouts of hypoglycemia, and cardiovascular events. In patients with CKD, metformin may be a safer alternative to sulfonylureas, despite the fact that the presence of CKD reduced the benefits associated with reduced mortality.
Bergmark, 2019[13]	United State of America	Prospective cohort study	12,156 patients	The use of metformin was linked with decreased rates of mortality from all causes, even after adjusting for clinical factors and biomarkers; however, the use of metformin was not associated with lower rates of the composite end point of cardiovascular death, myocardial infarction, or ischemic stroke. This link was seen to be particularly prominent in patients who did not have a history of heart failure or kidney illness ranging from moderate to severe.
Charytan, 2019[14]	United State of America	Randomized controlled trial	591 individuals who used metformin	Individuals who have reached stage 3 of CKD may have a reduced risk of death and cardiovascular events if they take metformin, which may be safer for usage in CKD than was previously thought.
Hung, 2015[7]	Taiwan	Retrospective cohort study	813 metformin users	Metformin use is connected with a significantly higher risk of death from any cause in patients with type 2 diabetes who have a blood creatinine concentration that is greater than 530 μmol/L. This is in comparison to people who do not use the medication. In this particular patient group, the use of metformin should not be advocated.

Bergmark, et al (2019)[13] conducted a study with 8,971 individuals had been exposed to metformin, 1,611 individuals (13%) had a history of heart failure, and 1,332 individuals (11%) had at least mild chronic renal disease. The utilization of metformin did not demonstrate a significant variation in the risk of the combined outcome (hazard ratio [HR] for inverse probability of treatment weighting = 0.92 (95% confidence interval [CI] = 0.76-1.11). However, it was related with a reduced risk of mortality from any cause (HR for inverse probability of treatment weighting = 0.75 (95% CI = 0.59-0.95).

There was an absence of a statistically significant association observed between the utilization of metformin and the aforementioned outcomes in individuals who had previously experienced heart failure or had moderate to severe chronic renal disease.

Charytan, et al (2019)[14] showed total incidence rate of death, cardiovascular death, cardiovascular events, and the combined endpoint was lower in metformin users than in non-users who had the same risk factors. However, ESRD was slightly higher in metformin users than in non-users (4.0% vs. 3.6%). Metformin use was linked to a lower chance of death from all causes (HR = 0.49; 95% CI = 0.36-0.69), cardiovascular death (HR = 0.49; 95% CI = 0.32-0.74), the cardiovascular composite (HR = 0.67; 95% CI = 0.51-0.88), and kidney disease (HR = 0.77; 95% CI = 0.61-0.98). The associations with ESRD (HR = 1.01; 95% CI = 0.65–1.55) were not significant. In adjusted studies of the whole population, the results were basically the same. Two people were found to have lactic acidosis.

Hung, et al (2015)[7] conducted a study with 813 people who took metformin were matched with 2439 people who didn't take it. Thirty clinical and socioeconomic factors at the start did not make a big difference between the two groups of patients. The matching group was followed up on for a mean of 2.1 years (range = 0.3–9.8). 434 (53%) of the 813 people who took metformin died, while 1,012 (41%) of 2,439 people who didn't take it died. Metformin use was a risk factor for death even after taking other factors into account (adjusted hazard ratio [aHR] = 1.35, 95% confidence interval [CI] = 1.20-1.51; p <0.001). The increased risk of death depended on the dose and was the same in all subgroup studies. However, people who took metformin were more likely to get metabolic acidosis than those who didn't (1.6 vs. 1.3 events per 100 patient-years; aHR = 1.30, 95% CI = 0.88-1.93; p = 0.19).

DISCUSSION

Diabetes mellitus (DM) is a set of metabolic illnesses defined by hyperglycemia caused by abnormalities in insulin secretion, insulin action, or both. Diabetes is linked to long-term damage, dysfunction, and failure of several glands, including the eyes, kidneys, nerves, heart, and blood vessels.[15] The etiology of type 2 DM is a reduced response to insulin or known as insulin resistance. During this state, insulin is ineffective for glucose uptake and lowers blood glucose levels. Initially, this is offset by increased insulin production to maintain glucose homeostasis, but over time, insulin production declines, resulting in type 2 DM.[16]

Metformin enhances insulin sensitivity within the body, hence necessitating the presence of insulin for its pharmacological effects to manifest. The primary mechanism of action involves the inhibition of liver gluconeogenesis, primarily through the suppression of mitochondrial oxidative phosphorylation and mitochondrial glycerophosphate dehydrogenase.[17] It also has some effect on the body's ability to get rid of glucose. Metformin, unlike phenformin, is not broken down in the body. Instead, the kidneys get rid of it all. It is removed from the blood by glomerular filtration and, to a greater extent, by tubular release through a number of transporters. Even though it is spread around a lot, its half-time of elimination is only about 2.7 hours.[18]

The management of hyperglycemia in patients diagnosed with type 2 diabetes mellitus (T2DM) and who have a higher risk of cardiovascular complications has become challenging due to inconsistent findings about mortality and the benefits of various antihyperglycemic treatments.[19,20] Additionally, there have been instances where certain medicines have raised concerns about potential cardiovascular risks. Despite the lack of conclusive cardiovascular outcomes studies, metformin continues to be the preferred initial oral antihyperglycemic medication for T2DM. The approval of medicines from two novel classes by the US Food and Drug Administration for the purpose of reducing cardiovascular events in patients with T2DM has heightened the significance of comprehending the cardiovascular effectiveness and safety of metformin.

The relevance of metformin in patients with a history of heart failure (HF) is significant due to the growing prevalence of HF in individuals with type 2 diabetes mellitus (T2DM), the historical concerns regarding the safety of metformin in HF patients, the widespread use of metformin in this patient population, and the notable effectiveness of novel antihyperglycemic agents in preventing both primary and secondary HF.[21,22] An analysis of the REACH registry demonstrated a lower incidence of cardiovascular death and overall mortality in HF patients treated with metformin, which aligns with the observed association in the entire cohort.[23]

A systematic review of observational studies investigated the use of metformin in patients with heart failure (HF). The review included a total of 9 studies and analyzed data from 6,624 individuals who were prescribed metformin. The findings of this review indicated a reduced occurrence of cardiovascular death and all-cause mortality among patients treated with metformin. However, it is important to note that these studies were observational in nature and did not account for biomarkers, such as natriuretic peptides, which are known to be highly indicative of risk in this particular patient population.[22,23]

CONCLUSION

Metformin use was found to be related with a reduced risk of death from any cause as well as progression toward ESRD in patients with CKD and CHF in the current investigation.

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