THE SIDE EFFECTS OF METFORMIN IN KIDNEY DISEASE: A REVIEW

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A Systematic Review

ABSTRACT *Metformin is one of the most commonly used drugs in the treatment of type 2 diabetes mellitus. It is the only biguanide class that is still used as an oral hypoglycemic drug. Metformin works to reduce blood glucose levels by increasing glucose transport into muscle cells. This drug can increase glucose uptake by up to 10-40%. The effect of administering metformin on GFR values and lactic acidosis condition in patients with impaired renal function. This review was conducted by extracting data from PubMed, Google Scholar, ScienceDirect. The articles related to metformin, kidney disease, and lactic acidosis in English-language in 2010 to July 2020. Article that been selected are based on inclusion and exclusion. Although renal metformin was cleared, drug levels generally remained within the therapeutic range, and lactate concentrations did not increase substantially when used in patients with mild to moderate chronic kidney disease (estimated glomerular filtration rate of 30-60 ml/min / 1.73 m2). The Data shows an increased risk of lactic acidosis in patients treated with metformin with severe chronic kidney disease, with a GFR value <30 ml/min / 1.73 m2. Available evidence supports the careful use of metformin for use in patients with mild to moderate chronic kidney disease.*

Keywords: side effects, lactic acidosis, GFR, Kidney disease

INTRODUCTION

The kidney is an important organ in the body that functions to metabolize the results of metabolism, regulate body fluids and electrolytes, maintain acid-base balance, and endocrine function. In its role of eliminating drugs and toxic substances, the kidneys are very susceptible to interference (Injury). Acute kidney injury is a specific clinical condition with manifestations that vary greatly from mild to asymptomatic to severe accompanied by multiple organ failure. AKI is a sudden decline in kidney function, in a few hours to several weeks, followed by kidney failure to excrete the rest of metabolism. Chronic kidney disease is a pathophysiological process with diverse etiologies, resulting in a progressive decline in kidney function, and generally ends in kidney failure. Kidney failure is a clinical condition that is characterized by a decrease in irreversible kidney function, to a degree that requires permanent kidney replacement therapy [1].

Diabetic nephropathy (DN) is a type of disorder that attacks the kidney organs caused by conditions of high sugar levels in the blood. If not treated quickly, this disease will lead to more serious diseases such as kidney failure. DN is characterized by progressive albuminuria followed by a gradual decrease in glomerular filtration rate (GFR) leading to kidney failure accompanied by loss of podocytes, progressive glomerulosclerosis, and finally progressive tubulointerstitial fibrosis [2].

Therefore, DN can be categorized into three different stages. In stage I of DN, there will be no signs of microalbuminuria and blood pressure will be normal in the patient. Plasma flow and GFR increase, which leads to a reduction in serum creatinine levels. Stage II of DN is characterized by stable serum creatinine levels, i.e. absence of proteinuria, and normal GFR except for some morphological changes including increased basement membrane thickness and mesangial expansion. DN is most evident in stage III where the patient is diagnosed with microalbuminuria, hypertension and GFR decreases with the appearance of glomerulosclerosis [3].

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Table 1. The 5 stage of CKD are based on eGFR [4].

Stage	Estimate GFR (ml/min/1.73 m^2)	Comment
1	≥90	Normal GFR with proteinuria
2	60-89	Age-related decline in GFR with proteinuria
3A	30-59	Low risk of progression to kidney failure
3B		
4	15-29	High risk of progression to kidney failure
5	<15	Kidney failure
5D		
5T		

Metformin has been prescribed in the United States for the management of type 2 diabetes mellitus for 20 years. Metformin is widely approved as initial therapy by professional organizations because of its low cost, the good safety profile [5]. Other biguanides, such as phenformin, were withdrawn in 1977 because of the risk of lactic acidosis. Because metformin is cleansed by the kidneys, it can accumulate when kidney function decreases, with the

potential to depend on exposure to toxicity that can trigger lactate accumulation[6].

Metformin administration in patients with renal failure must be considered especially in patients with creatinine clearance below 45mL/min, whereas for patients with creatinine clearance below 30ml/ min the use of metformin is avoided to avoid the effects of lactic acidosis. Lactic acidosis is a clinical condition where there is an increase in H + ions characterized by blood lactate levels >5 mmol and arterial fluid pH <7.25. In the study data, patients using metformin had a creatinine clearance of 17.97 mL/min. Such patients should no longer be given metformin because of its contraindications to kidney function [7].

On April 2016, the FDA revised its statement relating to the use of metformin in patients with impaired kidney function, defining kidney disorders according to the estimated glomerular filtration rate (eGFR). The revision states that the use of metformin is only absolutely contraindicated in patients with severe chronic kidney disease (eGFR <30 ml/min/1.73m^2). Therefore, patients with moderate CKD (eGFR 30-56 ml/min/1.73m^2) are eligible to receive metformin. An earlier study reported that the use of metformin in patients with type 2 DM and CKD was associated with a significant increase in the risk of all causes of death compared to open metformin users [8].

Usually, the initial dose of metformin hydrochloride is 500-850 mg for patients with normal kidney function (glomerular filtration rate (GFR)> 90 ml/min). Depending on kidney function, the maximum daily dose should be 1,000 mg (for patients with GFR 30-44 ml / min) to 3,000 mg (for patients with GFR> 60 ml/min). After 10-15 days of therapy, the dose must be adjusted to the concentration of blood glucose. For patients with GFR<30ml/min, metformin therapy is contraindicated [9]. The reason for this is the potential accumulation of metformin in patients with renal insufficiency and associated risk of lactic acidosis. Therefore metformin therapy is considered to be contraindicated in many chronic hypoxemic conditions that may be associated with lactic acidoses, such as cardiovascular, kidney, liver, lung, and old age diseases [10].

Recent reports support the use of metformin even in patients with kidney disease based on estimated glomerular filtration rate (GFR), which is a better measure of kidney function than serum creatinine levels. EGFR 30 to 45 mL/min is equivalent to a serum creatinine level of around 2 mg / dL and this can be considered a cut-off to evaluate the use of metformin in patients with established kidney disease [11].

METHODS.

Literature Search Strategy

A systematic review is a comprehensive summary of several research studies that are determined based on a particular theme. Extraction data was conducted in June-July 2020. The data used in this review are secondary data obtained not from direct observation, but obtained from the results of research conducted by previous researchers. Secondary data sources obtained in the form of articles of national and international reputation with a predetermined theme. A literature search in this systematic review uses 3 databases, Pubmed, ScienceDirect, and Google Scholar from January 2010 to July 2020.

Keywords used in article searches are (AND, OR) that are used to expand or specify a search, making it easier to determine the article or journal used. The main search strategy is done in PubMed with the keyword as follows: "((((side effect) AND (metformin)) AND (kidney disease)) OR (diabetic nephropathy)". This keyword is used as a guide to search for articles in other databases. The search is carried out by identifying articles in sequence (title, abstract, and then full text).

Study Selection

Based on literature search results through publication in three databases and using keywords that have been adapted to *Medical Subject Heading* (MeSH) (Table 2). Which includes studies on the side effects of metformin in impaired kidney function. Where the search results are independently assessed eligibility to be included in the review based on inclusion criteria and exclusion criteria. Any dissenting opinions between the two authors are resolved by looking at the author of the third article. Included in the inclusion criteria are studies that report metformin side effects on patients with kidney disorders by looking at the incidence of lactic acidosis and GFR values of patients, patients who have eGFR values of 30-60 ml/min and <30 ml/min, patients who have a diagnosis of type 2 diabetes mellitus, patients who have kidney disorders. While exclusion criteria are the history of metformin intolerance, animal studies, case reports, and comments, articles published under 2010. PRISMA (Item Reporting Options for Systematic Review and Meta-Analysis) flowcharts are used to document the process of selecting literature and the reasons for the exclusion of literature (Figure 1).

Table 2. Keywords systematic review Side Effects Of Metformin In Kidney Disease on MeSH

No	Search Item	Number of hits
1.	"Drug-Related Side Effects and Adverse Reactions"[Mesh]	12 result
2.	"Metformin"[Mesh]	6 result
3.	"Kidney Diseases"[Mesh]	37 result
4.	(("Drug-Related Side Effects and Adverse Reactions"[Mesh]) AND "Metformin"[Mesh]) AND "Kidney Diseases"[Mesh]	8 result
After filter		2 article

Validity Assessment and Data Extraction

The data collected as an extraction from the articles that have been obtained are the name of the author, year of research, research location, research title, research objectives, research methods, duration of treatment with metformin, and table of research results (Table 3).

The quality assessment of articles used was based on the following criteria: Title and abstract, research design, inclusion and exclusion criteria, study duration of treatment using metformin, the effect of kidney disease on lactic acidosis, and data on the results of the article's research. This

study is based on published data, therefore, ethical approval is not a necessity.

RESULTS.

From the literature search results through publication in three databases and using keywords that have been adjusted to MeSH, researchers obtained 312 articles that match those keywords. The search results that have been obtained are then checked for duplication, found 93 articles are the same, so that it was issued and the remaining 219 articles. The researcher then screened the title adjusted to the theme or systematic review title, as many as 148 articles was excluded because they were not suitable and there were 71 articles left. Then the selection based on the study abstract has been excluded as many as 36 and the remaining 35 articles. Feasibility assessment of the article based on the overall text and compliance with the eligibility criteria obtained as many as 23 articles and after being re-assessed 9 articles can be used in a systematic review. The results of the study article selection can be described in the Flow Diagram below.

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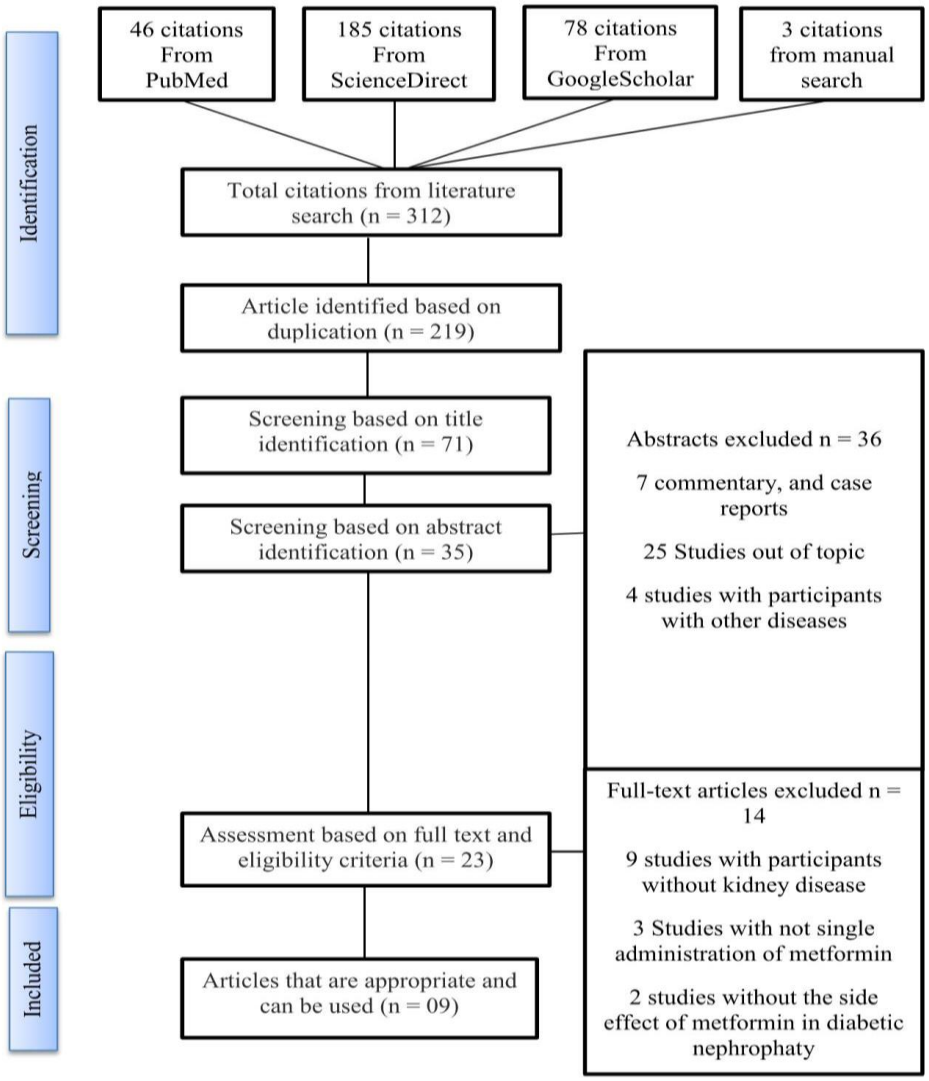

Figure 1. Flow Diagram Flow Diagram of Literature Side Effect of Metformin in Kidney Disease

After an assessment of the quality of studies from 9 articles can be categorized as high then data extraction is carried out. This data extraction is done by analyzing the data based on the author's name, year, title, purpose, research method, metformin treatment duration, and results, namely the grouping of important data in the article. The results of data extraction can be seen in the following table (Table 3).

Table 3. Objective, Method, and result of the studies

No	Bibliography	Objective	Method	Result
1	(14)	To measure the relationship between metformin use and hospital care with acidosis throughout the estimated range of glomerular filtration rate (eGFR), take into account changes in the eGFR stage over time	Community-based cohort	The use of metformin is safe at eGFR 30 to 60 ml / minute / 1.73 m2. Whereas in eGFR less than 30 ml / min / 1.73 m2 there is an increased risk of lactic acidosis. Be careful using metformin at eGFR 30 ml / min / 1.73 m2.
2	(17)	To investigate the relationship between kidney function, lactic acid levels, and acid-base balance in patients with type 2 diabetes with chronic kidney disease with metformin treatment and after cessation of metformin in real-life settings	Retrospective study	There was no increase in lactic acid in patients with mild to moderate kidney disease. Trials were tested on patients using metformin and looked after cessation of metformin. The patient's lactic acid levels decrease after cessation of metformin.
3	(15)	See the effect of giving metformin in patients with type 2 diabetes mellitus on moderate kidney disease	Retrospective cohort study	The use of metformin in kidney dm patients has been proven to worsen kidney function by decreasing the patient's eGFR value, this will cause an increase in lactic acid in the blood
4	(16)	To study the incidence of lactic acidosis due to metformin in patients with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) stages 3-5.	Cohort Study	Metformin can be used safely in stage 3 CKD and with regular plasma lactate measurements at a later stage
5	(19)	To see the effect of using metformin in patients who have impaired kidney function seen based on the value of eGFR and lactic acidosis	Cohort Study	The use of metformin must be careful in patients with kidney disorders in stages 3-4
6	(18)	To determine whether treatment with metformin in patients with impaired renal function is associated with a higher risk of lactic acidosis or an increase in lactate concentration compared with the use of non-insulin antidiabetic drugs (NIAID) who have never used metformin	Retrospective cohort study	The results of a study with a sample of 223,968 who used metformin and 34,571 diabetic patients who did not use metformin showed an increased incidence of lactic acidosis or lactate concentrations in metformin users at 7.4 / 100,000 people / year while those not using metformin 2.2 / 100,000 people / year. 68 lactic acidosis events (74%) or high plasma lactate concentrations
7	(20)	To see the effect of various doses of metformin given to patients with impaired kidney function, by looking at the lactate levels of each patient	All patients with diabetic kidney disease with eGFR <60 ml / min who used metformin compared to those who used other types of OAD by direct monitoring of the lactic acidosis value of patients at the hospital	Based on research on 57 patients who used metformin and 54 people who did not use metformin, where the two groups were comparable in age, duration of diabetes mellitus, body mass index, and kidney failure rate. Where patients who used metformin were divided into 3 groups of metformin doses of 500 mg / day, 2 g / day, 3 g / day, showed a level of lactate levels increased if using metformin with a dose> 1 g seen with a lactate level of 1.5 mmol / L seen with a dose of 3 g / day
8	(21)	To see the effect of administering metformin dose of 500 mg / day in patients with GFR values> 60 ml / min / 1.73 m2	Testing is done by conducting randomized clinical trials on patients who continue to use metformin	stated that there was no incidence of lactic acidosis in patients using metformin at a dose of 500 mg / day with a patient's eGFR> 60 ml / min / 1.73 m2
9	(22)	To see the effects associated with the dose of metformin	Retrospective	The results related to the effect of metformin dose on kidney function in patients with diabetes that

		given in the development of acute kidney failure		progressed to acute kidney failure showed a decrease in pH and a higher increase in lactate where the effect of metformin on pH and lactate increased significantly with higher drug doses (p = 0.259 and p = 0.092 for 1 g / day, p = 0.289 and p = 0.001 for 1-2 g / day, p = 0.009 and p = 0.001 for 2-3 g / day, for pH and lactate respectively)

DISCUSSION

Metformin, Kidney Disease, Lactic acidosis, GFR

Biguanides such as metformin inhibit the mitochondrial respiratory chain, by interfering with the site of its main generation through aerobic metabolism. This results in anaerobic metabolism, where lactate is a by-product and less energy for gluconeogenesis. Reducing liver glucose production is a mechanism of metformin antihyperglycemic effects, although it was recently proposed that some decreased glucose can be mediated through enteroendocrine [12[. Metformin is fully excreted in the urine and does not change in the urine, so the drug can accumulate in patients with kidney failure [13]. Although mild to moderate CKD reduces metformin clearance, drug levels usually remain within a safe distance.

The result of analysis show that the side effects of metformin on kidney function disorders due to diabetes are as follows: conducting a study using a cohort method stated there was a higher risk associated with metformin at lower GFR. However, the risks associated with our measurements were not statistically significant at eGFR greater than 90 ml / min / 1.73 m^2, eGFR 60 to 89 ml/min/1.73 m2, eGFR 45 to 59 ml / min/1,73m^2, and eGFR 30 to 44 ml/minute/1.73 m^2. An increased risk of acidosis is associated with the use of metformin in eGFR less than 30 ml/min/1.73 m^2 [14].

According to a study by Hsu *et al*., 2018 stated patients with type 2 DM who received metformin therapy for at least 6 months experienced a greater eGFR reduction if they continued metformin therapy compared to those whose metformin treatment was stopped for at least 100 days. Continuation of metformin therapy is significantly associated with decreased kidney function in patients with moderate DM and CKD. Other risk factors for kidney function decline include high serum LDL-C, high HbA1c, low EGFR baseline, high uric acid levels, high UACR, and use of ACEI and/or ARB [15]. Other studies have shown that the use of metformin can be used safely in stage 3 CKD and with gradual strict monitoring of plasma lactate in stages 4 and 5 [16].

Research Sipahi *et al*., 2016 , Performing comparative measurements before and after stopping metformin revealed a significant decrease in median levels of lactate (from 2.20 to 1.85 mmol/l, p = 0.002) and lactate changes were also evident when adjusted for eGFR and/or blood creatinine. However, there was no significant difference in blood pH at 2-3 weeks of discontinuation of metformin compared with the initial evaluation. Blood bicarbonate and excess bases also did not show significant changes from the beginning after discontinuation of metformin [17].

Research Eppenga *et al*., 2014 who conducted a cohort study with a sample of 223,968 who used metformin and 34,571 diabetic patients who did not use metformin showed an increased incidence of lactic acidosis or lactate concentrations in metformin users of 7.4/100,000 people/year while those not using metformin 2.2 / 100,000 person/year. 68 lactic acidosis events (74%) or high plasma lactate concentrations (26%) [18].

Patients who use metformin show a more cautious approach in using metformin specifically in stage 3-4 CKD. Where the deteriorating kidney function is identified through eGFR and other hemodynamics or switching to insulin or other anti-diabetic drugs whenever an unstable clinical condition is detected [19].

Another study of 57 patients who used metformin and 54 people who did not use metformin, where the two groups were comparable in age, duration of diabetes mellitus, body mass index, and kidney failure rates. Where patients who used metformin were divided into 3 groups of metformin doses of 500 mg/day, 2g/day, 3g/day, showed a level of lactate levels increased if using metformin with a dose>1g seen with a lactate level of 1.5 mmol/l seen with a dose of 3 g / day [19].

A study by Namazi *et al*., 2018 stated that there was no incidence of lactic acidosis in patients using metformin at a dose of 500 mg/day with a patient's eGFR> 60 ml / min / 1.73 m^2 [21]. The results related to the effect of metformin dose on kidney function in patients with diabetes that progressed to acute kidney failure showed a decrease in pH and a higher increase in lactate where the effect of metformin on pH and lactate increased significantly with higher drug doses (p = 0.259 and p = 0.092 for 1 g / day, p = 0.289 and p = 0.001 for 1-2 g/day, p = 0.009 and p = 0.001 for 2-3 g/day, for pH and lactate respectively) [22].

Recommendation

This review of the article supports the consideration of changes to the metformin prescribing guidelines, with permissible use in patients with mild to moderate CKD. Any new extension of the use of metformin in patients with mild to moderate CKD needs to be accompanied by an appropriate dose reduction and careful follow-up assessment of kidney function. Whereas in patients with moderate/severe CKD should be given anti-diabetic drugs other than metformin to avoid the risk of lactic acidosis.

CONCLUSION

It can be concluded that the use of metformin is safe in patients with eGFR >30ml/min or in patients with mild to moderate kidney function, by monitoring the patient's lactic acid levels regularly and monitoring the patient's eGFR values, while in patients with eGFR values <30 ml/min or with severe impairment of kidney function the use of metformin should be avoided.

Abbreviations: eGFR (estimated Glomerular Filtration Rate), DN (Diabetic Nephropathy), DM (Diabetes Mellitus), AKI (Acute Kidney Injury), CKD (Chronic Kidney Disease).

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