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TYPE 2 DIABETES MELLITUS AND CHRONIC KIDNEY DISEASE : A SYSTEMATIC REVIEW

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Abstract
Hyperglycemia is the primary symptom of diabetes mellitus, which is a set of metabolic illnesses that can be caused by abnormalities in insulin secretion, insulin action, or both. Diabetes Mellitus (DM) is the most common form of diabetes. Chronic hyperglycemia brought on by diabetes is linked to long-term damage, dysfunction, and even failure of a number of glands, most notably the eyes, kidneys, nerves, heart, and blood arteries. 1 Because there are a variety of criteria that must be satisfied before a diagnosis of diabetes can be made, it is challenging to estimate the disease's prevalence. Diabetes-related nephropathy, also known as diabetic nephropathy or diabetic kidney disease, can affect approximately forty percent of patients who have been diagnosed with type 2 diabetes mellitus (DKD). Patients who are diagnosed with type 2 diabetes are often of an older age at the time of their diagnosis, and it is possible that these patients will develop kidney damage due to factors other than diabetes. Patients diagnosed with type 2 diabetes are at an increased risk of developing chronic kidney disease (CKD) due to a number of variables, including hypertension, a history of kidney disease, neuropathy, dyslipidemia, and substance abuse.

Keyword: *Chronic Kidney Disease; Diabetes Mellitus; Obese; Risk Factor*

INTRODUCTION

Diabetes Mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both. Diabetic chronic hyperglycemia is associated with long-term damage, dysfunction, and failure of various glands, especially the eyes, kidneys, nerves, heart, and blood vessels.[1] The prevalence of DM is difficult to determine because the standard for establishing a diagnosis is different. About 10.2 million people in the United States have DM. Meanwhile, in Indonesia the prevalence of DM is 1.5-2.3% of the population aged >15 years, even in the Manado area the prevalence of DM is 6.1%. The incidence of Type 2 DM in women is higher than men.[2–4]

Type 2 diabetes mellitus consists of multiple dysfunctions characterized by hyperglycemia and resulting from a combination of resistance to insulin action, inadequate insulin secretion, and excessive or inappropriate glucagon secretion. Uncontrolled type 2 diabetes is associated with various microvascular, macrovascular and neuropathic complications.[5] Persistent hyperglycemia in uncontrolled DM can cause several complications, both acute and chronic.[6]

Diabetes is not only a prominent cause of chronic renal disease but also a substantial contributor to the development of cardiovascular disease (CVD).[7] Approximately forty percent of people diagnosed with type 2 diabetes mellitus may develop diabetes-related nephropathy, commonly known as diabetic nephropathy or diabetic kidney disease (DKD). In addition to this, the number of deaths that can be ascribed to DKD has increased by 94% between the years 1990 and 2012. According to projections made by the World Health Organization, the number of deaths caused by diabetes would more than double by the year 2030. Notably, the majority of the extra risk is connected to mortality from cardiovascular disease.[8–10]

As with other diabetes-related problems, the conventional strategy for slowing the progression of DKD involves appropriate control of hyperglycemia, blood pressure, lipids, and lifestyle. While evidence supports a role for renin-angiotensin-aldosterone system (RAS) blockade in limiting the progression of diabetic kidney disease (DKD),[11] recent data from cardiovascular outcome trials and renal specific trials has shed new light on the additional benefits of sodium-glucose cotransporter-2 inhibitors (SGLT2i) in reducing the progression of DKD and cardiovascular risk. This study evaluates the current evidence-based approach to optimizing renal protection in diabetic individuals.[12–14]

This article investigate the connection between type 2 diabetes mellitus and chronic kidney disease (CKD).

METHODS

Protocol

The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 checklist served as the foundation for the development of the rules governing the conduct of this systematic review.

Eligibility Criteria

This systematic review was developed to analyze papers on "Type 2 Diabetes Mellitus" and "Chronic Kidney Injury." These are the subjects that were mentioned in the evaluated studies. The following requirements must be met in order for your work to be considered: 1) Articles must be available in their full online; 2) Articles must be written in English; and 3) Articles must have been published between 2012 and the time this systematic review is prepared. The following kind of textual submissions will under no circumstances be accepted: 1) Editorial letters, 2) contributions without a Digital Object Identifier (DOI), and 3) article reviews and similar submissions.

Search Strategy

The search for studies to be included in the systematic review was carried out from November 12-17th, 2022 using the PubMed and SagePub databases by inputting the words: "Type 2 Diabetes Mellitus" and "Chronic Kidney Disease". Where *(("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[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 ((clinicaltrial[Filter] OR randomizedcontrolledtrial[Filter]) AND (2012:2022[pdat]))* is used as search keywords.

Data retrieval

Following the completion of a literature search, in which the titles and abstracts of previously published studies were read, the author revised the criteria for what should be included and what should be excluded from the study. Only the studies that were able to meet all of the requirements were taken into consideration for inclusion in the systematic review. It is possible to collect information in the form of a title, author, publication date, origin of study location, research study design, and research variables in each individual study. This information is laid out in a particular format for your perusal.

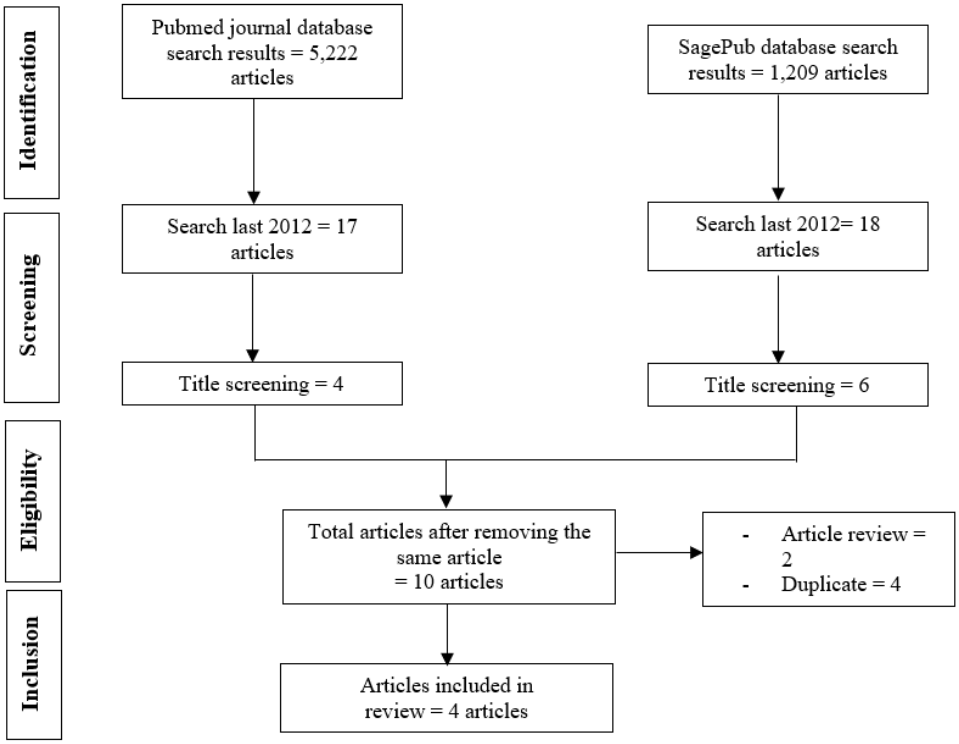

Figure 1. Article search flowchart

Quality Assessment and Data Synthesis

To determine which studies might be eligible for consideration, the authors conducted their own independent reviews of a selection of the studies found in the articles' titles and abstracts. Following this, the full texts of the studies that qualify for inclusion in the systematic review will be read in order to determine which studies can be used as final inclusions for the purpose of the review.

RESULT

Debele, 2021 conducted a study when 15.56% of patients ended up developing CKD, with an incidence rate of 2.29 per 1,000 person-month (PM) and a 95% confidence interval ranging from 1.79 to 2.93. Positive proteinuria (AHR=2.85, 95% CI=1.48– 5.55), having hypertension (HTN) (AHR=2.31, 95% CI=1.03–5.56), and high-density lipoprotein cholesterol (HDL-C) 40 mg/dL (AHR=3.19, 95% CI=1.73–5.98) were significant predictors of chronic kidney disease (CKD). Female sex was found to be a protective factor of chronic. In Ethiopia's healthcare facilities, CKD among diabetic individuals continues to be a significant public health problem.[15]

Other study in Ethiopia with a median occurrence time of 5 years showed overall cumulative incidence of chronic renal disease was 10.8% [95%; CI: 7.7–14.0%]. The yearly incidence rate was 193/10,000, with a confidence interval ranging from 144.28 to 258.78. Both hypercholesterolemia [AHR = 3.31; 95%CI: 1.3323–8.2703] and cardiovascular disease/s were predictors of chronic renal disease. The adjusted hazard ratio for cardiovascular disease was 3.82, and the 95% confidence interval for hypercholesterolemia was 1.4470–10.1023. Patients with diabetes had a higher risk of developing chronic renal disease, which affected one patient in ten.[16]

Five years was the average amount of time that passed before the onset of chronic renal disease. The risk of developing chronic kidney disease (CKD) has increased as a result of hypercholesterolemia and cardiovascular illnesses. It is therefore advised that diabetic individuals receive health education and promotion in order to achieve optimal cholesterol levels and prevent cardiovascular disease. This is done with the goal of reducing the incidence of this life-threatening condition.[16]

Table 1. The litelature include in this study

Author	Origin	Method	Period	Sample Size / Characteristic	Result
Debele, 2021[15]	Ethiophia	Retrospecctive study	September 5, 2012 and August 2015	437 newly-diagnosed diabetes patients	15.56% of patients developed CKD at a rate of 2.29 per 1,000 person-month (95% CI=1.79–2.93). Female sex (AHR=0.51, 95% CI=0.27–0.94) was a protective factor of CKD, while proteinuria (AHR=2.85, 95% CI=1.48–5.55), hypertension (AHR=2.31, 95% CI=1.03–5.56), and HDL-C 40 mg/dL (AHR=3.19) were significant predictors of CKD.
Ahmed, 2022[16]	Ethiophia	Retrospecctive study	1st of May 2012 to the 1st of May 2017	415 participants with type-II diabetes mellitus	Chronic renal disease had a cumulative incidence of 10.8% [95%; CI: 7.7–14.0%] over 5 years. 193/10,000 cases per year (95% CI: 144.28–258.78). Cardiovascular illness [AHR = 3.82; 95%CI: 1.4470–10.1023] and hypercholesterolemia predicted chronic kidney disease in T2DM patients.
Tuero, 2012[17]	Spain	Cross-sectional study	During 2007	2,642 T2DM patients	Patients had 34.1% KD, 22.9% RI, 19.5% albuminuria, and 16.4% diabetic nephropathy (DN). Albuminuria without RI (13.5%) was similar to nonalbuminuric RI (14.7%). RI was linked with female gender (OR 2.20; CI 95% 1.86–2.59), microvascular disease (OR 2.14; CI 95% 1.8–2.54), and insulin treatment (OR 1.82; CI 95% 1.39–2.38), and inversely with HbA1c (OR 0.85 for every 1% increase; CI 95% 0.80–0.91). Albuminuria without RI was inversely linked with female gender (OR 0.27; CI 95% 0.21–0.35), diabetes duration (OR 0.94 per year; CI 95% 0.91–0.97), and HbA1c (OR 1.19 per 1% rise; CI 95% 1.09–1.3).
An, 2022[18]	China	Retrospective multicentre cross-sectional study	No data	5123 patients	The prevalence of CKD, impaired eGFR and albuminuria was 29.6%, 5.8% and 27.1% at baseline, with 70.4%, 20.3%, 7.0% and 2.3% of patients distributed in low, moderate, high and very high risk group. There were 3457 (67.5%), 1120 (21.8%) and 546 (10.7%) patients had CKD outcome risk stable, progressed and regressed respectively. The proportion of patients reaching targets of BP ≤ 130/80 mmHg, HbA1c<7.5%, LDL-C<2.60 mmol/L increased from baseline to FU and LV, together with increased usage of insulin, RAS inhibitors and lipid lowering medications. After multivariable adjustment, the HbA1c<7.5% (OR: 0.66, 95%CI 0.56-0.78), TG< 1.7 mmol/L (OR: 0.81, 95%CI 0.68-0.96) at FU and BP ≤ 130/80 mmHg at LV (OR: 0.82, 95%CI 0.70-0.95) was negatively associated with CKD outcome risk progress.

Study in Spain[17] showed patients had a prevalence of the following levels of kidney disease: 34.1% CKD, 22.9% RI, 19.5% albuminuria, and 16.4% diabetic nephropathy (DN). There was no significant difference in the prevalence of albuminuria with or without RI (13.5%) or nonalbuminuric RI (14.7%). RI was significantly associated with female gender (OR 2.20; CI 95% 1.86–2.59), microvascular disease (OR 2.14; CI 95% 1.8–2.54), and insulin treatment (OR 1.82; CI 95% 1.39–2.38), and inversely associated with HbA1c (OR 0.85 for every 1% increase; CI 95% 0.80–0.91). This was determined after adjusting for age, BMI, cholesterol, blood pressure, and macrovascular disease. Albuminuria without RI was found to have an inverse association with being female (OR 0.27; CI 95% 0.21–0.35), having diabetes for a longer duration (OR 0.94 per year; CI 95% 0.91–0.97), and a direct association with HbA1c (OR 1.19 for every 1% rise; CI 95% 1.09–1.3).

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DISCUSSION

The most severe stage of renal disease, chronic kidney disease (CKD) may be irreversible and ultimately results in death. Patients who suffer from NCD, particularly diabetes, are prone to exhibiting symptoms of this disorder. Therefore, determining the incidence, the median occurrence time, and the factors that predict it would have a significant impact on the ability to respond appropriately and promptly in order to increase the chances of the victims surviving the incident.[19,20] Approximately 700 million people, or 9 percent of the global population, have CKD, and nearly four million patients require KRT. CKD is more prevalent in women, particularly in the earlier stages, while men are more likely to advance to ESKD, which requires KRT. In some countries, access to KRT for the treatment of ESKD is as low as 16%. In 2010, lack of access to KRT was responsible for almost 2,3 million fatalities worldwide. The biggest treatment gaps were observed in low-income nations, particularly in Asia and Africa, where 1,9 and 0.4 million patients needed but did not receive KRT, respectively. The prevalence of KRT is anticipated to more than quadruple to 5,4 million people worldwide by 2030, with the greatest increase in Asia.[21]

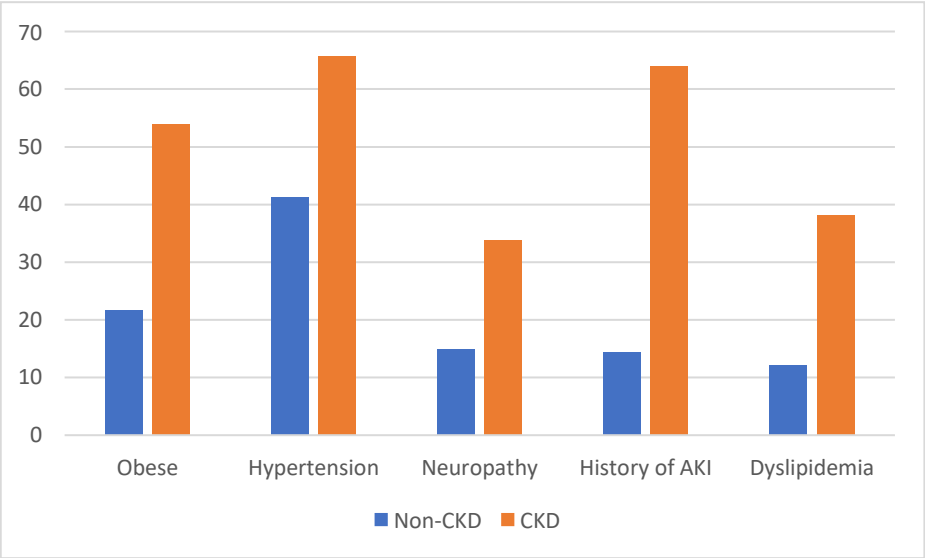

Figure 2. Percentage of comorbid patients with CKD and Non-CKD in type 2 DM patients

Although diabetes microvascular disease is the most common cause of chronic kidney disease in people with type 1 diabetes, there is a wide range of potential causes of chronic kidney disease in people with type 2 diabetes. Patients diagnosed with type 2 diabetes are typically of an older age at the time of their diagnosis, and kidney disease owing to factors other than diabetes is likely to occur. Multiple studies have shown evidence to support the hypothesis that kidney disease brought on by type 2 diabetes may be a more complex condition than that brought on by type 1 diabetes.[22]
Study found that DM patients with HTN have a higher risk of CKD than their counterparts. Controlling blood pressure in DM patients reduces the risk of CKD. This result matches those from Ethiopia, Spain, and China. HTN may impair endothelial cell structure and function, causing aberrant growth and vasoconstriction. This endothelial alteration causes glomerulosclerosis, which causes CKD. Patients with dislipedemia have greater CKD risks. HDL-C transfers artery-wall fats to the liver. This decreases arterial fat and atherosclerosis. It also preserves the inner wall of the arteries, reducing the incidence of vascular problems like CKD. Low HDL-C patients may lack this function and develop CKD.[23–27]

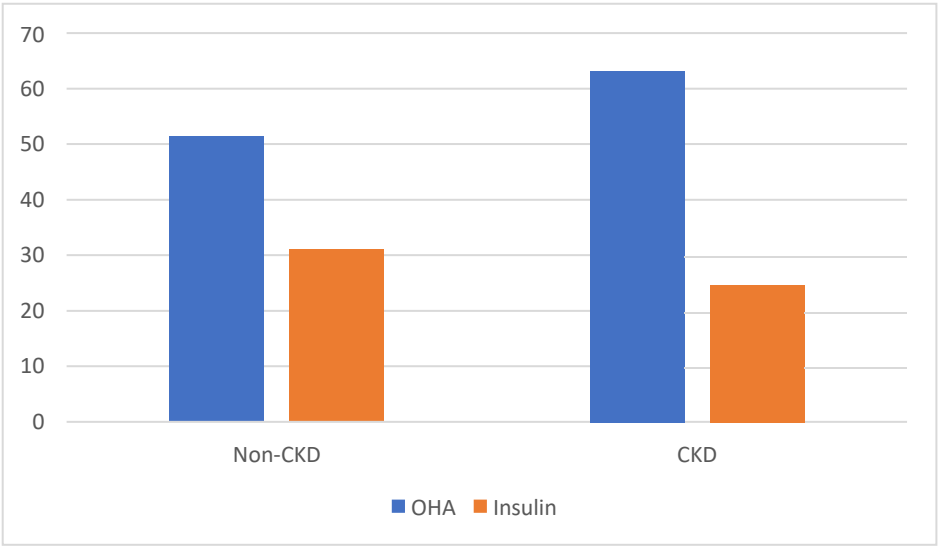

Figure 3. Percentage of types of drugs used by patients with CKD and Non-CKD in type 2 DM patients

One study that was conducted in the United States and looked at kidney biopsies taken from patients with type 2 diabetes and kidney disease found that typical diabetic microvascular disease were present in 37% of the cases, non-diabetic kidney disease in 36% of the cases, such as nephrosclerosis or immunological kidney disease, and mixed forms of diabetic and non-diabetic kidney disease were present in 27% of the cases. It is interesting to note that one study has found that different insulin resistance phenotypes in diabetes are associated with varied risks for chronic kidney disease; nevertheless, this is something that needs to be studied further.[23–27]
Controlling blood glucose levels very closely is the single most essential thing that individuals with type 1 and type 2 diabetes can do to reduce their risk of developing renal disease. This is true regardless of the underlying cause of kidney disease. Normalization of blood glucose may act renoprotectively through a variety of mechanisms, including: reduced hyperfiltration on the nephron level; reduced generation of toxic intermediates, such as reactive oxygen species (ROS); and reduced activity in pathogenetic signalling pathways, such as the polyol, hexasamine, protein kinase C, and advanced glycation end-product pathways.[27,28]

Because of the intricacy of the condition, the pathophysiology of CKD in diabetic patients is not yet completely understood. On the other hand, it is generally believed that diabetes leads to CKD because of increased glucose filtration in the kidneys. This will result in a blockage of the very small blood arteries that make up the nephrons. Therefore, chronic kidney disease is caused by renal injury as a result of blood insufficiency brought on by clotting, as well as gradual damage to nephrons brought on by the deposition of end products of glucose on the basement membrane.[29]

Chronic kidney disease (CKD) is the most significant microvascular complication of diabetes mellitus, and it is distinguished by ongoing albuminuria, an increase in blood pressure, and a gradual loss of kidney function. According to the glomerular filtration rate (GFR), chronic kidney disease (CKD) is divided into five stages, with stage V being the most severe type and requiring renal replacement therapy. This classification was developed by the kidney disease improving global outcome study.[30]

CONCLUSION

There are several risk factors in type 2 DM patients that are associated with the occurrence of CKD, such as hypertension, previous kidney disease, neuropathy, dyslipidemia, and drug use.

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