

Role of Diabetes Mellitus and Hypertension in the Progression of Chronic Kidney Disease A Systematic Review

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Abstract

Chronic kidney disease (CKD) is defined as an EGFR (Estimated glomerular filtration rate) < 60 ml/min/1.73 m² or an EGFR ≥ 60 ml/min/1.73 m² together with albuminuria (≥ 30 mg/g). It causes significant mortality and morbidity. It is a silent killer. The prevalence of CKD has been increasing worldwide. There are many established risk factors for chronic kidney disease, the two most important ones being hypertension and diabetes mellitus (DM). In this systematic review, we aim to know the roles of hypertension (HTN) and diabetes in the progression of chronic kidney disease. We did a detailed search on PubMed and found 1216 articles screened, and finally, 20 articles were chosen for study. As we analyzed, we observed that most studies showed that diabetes and hypertension have a positive association with the progression of CKD, even though the exact mechanism or link has not been explained in the studies we reviewed.

Keywords

Chronic kidney disease, diabetes, hypertension, glomerular filtration rate, blood pressure, mortality.

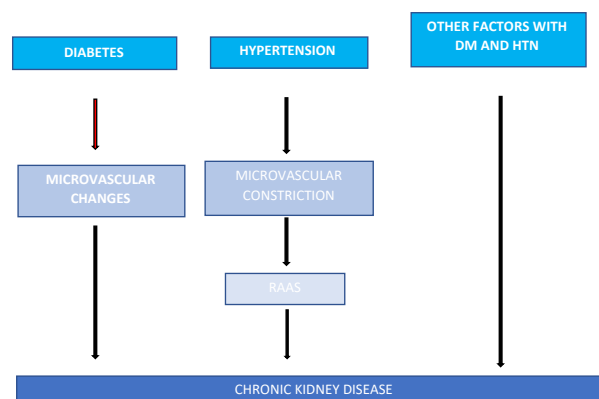
Introduction

Chronic kidney disease (CKD), defined as an estimated Glomerular Filtration Rate (eGFR) < 60 mL/min/1.73 m² or an eGFR ≥ 60 mL/min/1.73 m² together with albuminuria (≥ 30 mg/g). Chronic kidney disease is the most severe form of kidney illness, characterized by inadequate filtration.

Discussion

The present systematic review sought to describe what is known about the relation between hypertension and diabetes in chronic kidney disease. Most studies concluded that diabetes and hypertension are positively associated with CKD; however, many limitations were there. Figure 2 contains the flow diagram of risk factors.

The figure 2.



Factors Causing Complications in Diabetes and Chronic Kidney Disease

The risk of developing chronic kidney disease has increased as a result of hypercholesterolemia and cardiovascular disease [1]. We discovered that the female gender is highly associated with rapid linear advancement. In studies that looked at how gender increases CKD risk, researchers found conflicting results [2].

In recent years, the prevalence of chronic kidney disease has risen, owing to the rapid rise in non-communicable chronic diseases, particularly diabetes mellitus. Around 13.3 million individuals worldwide are affected with CKD yearly, with 85 percent of cases occurring in developing nations. Kidney illness is responsible for around 1.7 million fatalities yearly [1].

Given that decreasing estimated glomerular filtration rate (eGFR) and rising albuminuria are frequent and independent risk factors for developing the end-stage renal disease (ESRD), experiencing cardiovascular events, and dying from any cause, chronic kidney disease (CKD) is a significant public health concern [2]. The presence of hypertension also adds risk to a decline in renal function [3,4]. Findings are supporting the evaluation of systolic blood pressure (SBP) lowering strategies to reduce the development of CKD [5]. The burden of both communicable and non-communicable diseases plays a part in the complex etiology of CKD in people with type 2 diabetes mellitus (T2DM). Isolated systolic hypertension (ISH) was linked to cardiac damage regardless of age, and ISH was associated with an increased risk of impaired renal function, correlated with higher blood creatinine in older participants. On the other hand, isolated diastolic hypertension (IDH) was only found to be linked to a higher risk of renal impairment, such as albuminuria, in younger participants [6,7].

An increased likelihood of albuminuria is also associated with an increase in systolic blood pressure [8]. In hypertensive patients, a composite kidney outcome of a 50% decrease in eGFR from baseline or incidental renal replacement therapy was reported [9]. Prediabetes and a healthy lifestyle are also crucial in CKD [10,11]. Antihypertensive medications, such as angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEI), are currently recommended by National Institute for Health and Care Excellence (NICE) guidelines as first-line management for proteinuric and nonproteinuric CKD in patients with hypertension [12]. Arterial stiffness rises as people get older and renal function degrades [13]. Hypertension (HTN) is common in patients with CKD and is a significant risk factor for morbidity and mortality. The link between masked uncontrolled hypertension and kidney disease progression has been inconsistent [14].

According to a study on the worsening of renal function in type 2 diabetes mellitus, glycemic control was the most indisputable risk factor for the development of diabetes-related complications and the risk of CKD in Type 2 diabetes mellitus (T2DM). Albuminuria, diabetic retinopathy, and poor glycemic control (hemoglobin A1c 7%) are all independent risk factors for the development of CKD in type 2 diabetes patients [3]. The majority of studies support the positive relationship between diabetes and CKD. The majority of studies support a link between diabetes and chronic renal disease. Diabetes Mellitus is a well-known risk factor for chronic renal disease. According to the findings, the prevalence of chronic kidney disease (CKD) is over fifty percent in a community of T2DM patients and has a high incidence rate of approximately 7% within a year [3]. It was also recognized that, despite the increased risk associated with T2DM, the patterns of evolution and mortality for individuals with and without T2DM were similar. Other risk factors related to the incidence and progression of CKD, in addition to T2DM, have been identified, including age, gender, glycemic control, blood pressure, non-white race, obesity, smoking, HDL cholesterol, cardiovascular disease, and depression. These risk factors were intrinsically more predominant among T2DM patients [12]. None of the studies reviewed shows the mechanism of progression. Some studies also show that serum plasma uric acid levels are higher in patients with diabetes [16].

We observed that other factors like age, sex, race, obesity, hyperlipidemia, and depression which have higher chances to co-exist with type 2 diabetes, also increased the rate of complications and progression of chronic kidney diseases.

Diabetes and Glomerular Filtration Rate

According to research on T2DM patients, renal function declines with time, eventually leading to end-stage renal disease and dialysis in a subset of patients. GFR decline in diabetes patients is twice that of nondiabetic people [3]. Patients with T2DM had a higher likelihood of progressing to the next higher eGFR group than non-T2DM patients with normal eGFR. T2DM and non-T2DM patients progressed similarly from advanced CKD to ESKD [12]. T2DM appeared to be a risk factor for kidney function decline and all-cause death.

The global prevalence of CKD has increased independently of diabetes due to increased lifespan, changes in food and lifestyle, and an increased incidence of bouts of acute kidney injury (AKI) [15]. Obesity, hyperglycemia, hypertension, and dyslipidemia are only a few renal risk factors that can be successfully treated [16]. The high frequency of chronic kidney disease (CKD), microalbuminuria, and macroangiopathy, including coronary heart disease (CHD), and rapid deterioration in renal function have been described in senior diabetic individuals [17]. Pulse pressure (PP) is an essential component of blood pressure (BP) determined by arterial and cardiac function. It is frequently used as a surrogate measure of arterial stiffness. However, previous research on the predictive relationship between PP and incident CKD has yielded mixed results [18].

To effectively manage patients with CKD, accurate hypertension diagnosis and treatment are critical. Clinical blood pressure (CBP) measurement was used to diagnose and treat hypertension. However, the Ambulatory blood pressure (ABP) monitoring approach, which can measure blood pressure in nonmedical situations throughout the twenty-four-hour cycle, is linked to a better long-term prognosis. Normal blood pressure, white coat hypertension (WCH), masked hypertension (MH), and sustained hypertension (SH) are the four different blood pressure patterns identified by a combination of arbitrary CBP and ABP cut-off values [19].

This systematic review aimed to investigate and integrate the pertinent material on this link.

Method

We conducted a systematic literature search following Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The free full-text articles indexed in PubMed was searched from 2020, MAY 17th 2022, using the regular keywords.

"chronic kidney disease" , "diabetes mellitus" and "hypertension "and medical subject headings (MeSH) terms "I" "Hypertension/blood"[Mair] OR "Hypertension/classification"[Mair] OR "Hypertension/complications"[Mair] OR "Hypertension/genetics"[Mair] OR "Hypertension/mortality"[Mair] OR "Hypertension/pathology"[Mair] OR "Hypertension/pharmacology"[Mair] OR "Hypertension/physiology"[Mair] OR "Hypertension/physiopathology"[Mair] , Diabetes Mellitus, Type 2/complications"[Mair] OR "Diabetes Mellitus, Type 2/genetics"[Mair] OR "Diabetes Mellitus, Type 2/mortality"[Mair] OR "Diabetes Mellitus, Type 2/pathology"[Mair] OR "Diabetes Mellitus, Type 2/physiology"[Mair] OR "Diabetes Mellitus, Type 2/physiopathology"[Mair] , "Renal Insufficiency, Chronic/blood"[Mair] OR "Renal Insufficiency, Chronic/etiology"[Mair] OR "Renal Insufficiency, Chronic/pathology"[Mair] OR "Renal Insufficiency, Chronic/physiology"[Mair] OR "Renal Insufficiency, Chronic/physiopathology"[Mair] alone and in combination,

This is consistent with an atherosclerosis risk in communities[ARIC] research that found a nearly twice as rapid drop in eGFR among people with diabetes versus those without [12].

Controlled Diabetes and Chronic Kidney Disease

Diabetes treatment differs between diabetics and non-diabetics because oral hypoglycemic medications are preferred for T2DM without chronic kidney disease, but insulin is preferred for those with chronic kidney disease. Diabetes control in patients has not been achieved, despite improvements in the administration and care of T2DM patients with CKD. According to one study, only 36.1% of patients achieve the glycemic goal of hemoglobin A1c 7%.

We also discovered that T2DM patients with CKD were more likely than those without CKD to suffer diabetes-related comorbidities such as ischemic heart disease, cerebrovascular disease, diabetic retinopathy, and albuminuria [7].

Hypertension and Chronic Kidney Disease

Hypertension is a known risk factor and the use of antihypertensive medication, including the use of ACE inhibitors or ARBs is expected to prevent the decrease in eGFR. This was recently confirmed by an analysis of the atherosclerosis risk in communities(ARIC) study. In our study, the prevalence of hypertension was higher in individuals with rapidly deteriorating renal function [3]. Blood pressure is the major contributor to the development of CKD [4]. Higher SBPs have been linked to an increased risk of CKD G3-G5 [5]. Hypertension is the second most common cause of end-stage renal disease after diabetes.

High systolic blood pressure (SBP) between 120 and 139 mm Hg, often known as high normal prehypertension, is associated with an elevated risk of CKD [8]. Although rigorous blood pressure control reduced cardiovascular events and mortality in one trial, this lower target was associated with more negative kidney outcomes, raising concerns that intense blood pressure control could lead to kidney function loss [8]. SBP had a greater association with adverse kidney outcomes than DBP [9].

The details of the search are given in Table.1 and Table.2

Keyword Database-PubMed

Table.1

KEYWORD	DATABASE	WITHOUT INCLUSION/EXCLUSION CRITERIA	WITH INCLUSION/EXCLUSION CRITERIA
Hypertension	PUBMED	53,727	10,835
Diabetes mellitus	PUBMED	55,729	10,831
Chronic renal failure	PUBMED	15,664	2,416

Mesh Keyword :Database: Pubmed

MESH KEYWORD	WITHOUT INCLUSION/EXCLUSION CRITERIA	WITH INCLUSION/EXCLUSION CRITERIA
"Hypertension/blood"[Majr] OR "Hypertension/classification"[Majr] OR "Hypertension/complications"[Majr] OR "Hypertension/genetics"[Majr] OR "Hypertension/mortality"[Majr] OR "Hypertension/pathology"[Majr] OR "Hypertension/pharmacology"[Majr] OR "Hypertension/physiology"[Majr] OR "Hypertension/physiopathology"[Majr]	87,197	905
"Diabetes Mellitus, Type 2/complications"[Majr] OR "Diabetes Mellitus, Type 2/genetics"[Majr] OR "Diabetes Mellitus, Type 2/mortality"[Majr] OR "Diabetes Mellitus, Type 2/pathology"[Majr] OR "Diabetes Mellitus, Type 2/physiology"[Majr] OR "Diabetes Mellitus, Type 2/physiopathology"[Majr]	64220	2167
"Renal Insufficiency, Chronic/blood"[Majr] OR "Renal Insufficiency, Chronic/etiology"[Majr] OR "Renal Insufficiency, Chronic/pathology"[Majr] OR "Renal Insufficiency, Chronic/physiology"[Majr] OR "Renal Insufficiency, Chronic/physiopathology"[Majr]	46171	1218

Study Selection And Eligibility Criteria

After the completion of the search, we checked for duplicates. The relevant articles were screened through the titles and the abstracts. Articles published in English until 2022, May 17th, were only included. The articles documenting diabetes and hypertension with chronic kidney disease were included. Articles were excluded in cases of unavailability of free full-text articles, overlapped with other articles, studies done on animals, and ones with incomplete data.

Isolated Systolic and Diastolic Hypertension in Chronic Kidney Disease

Regardless of age, isolated systolic hypertension was related to cardiac and renal damage. Isolated diastolic hypertension, on the other hand, was harmful to renal function [6]. The incidence rate of albuminuria increased significantly with rising SBP [8]. The cumulative incidence curves also demonstrated that the CKD event-free survival rate was considerably lower in the increasing SBP trajectory [8]. It was discovered, however, that the risk of CKD began in those with SBP of 120 mm Hg. A declining SBP trajectory was related to a lower risk of CKD in patients with SBP of 120 mm Hg in subgroup analysis. Furthermore, whereas some randomized controlled trials revealed that lowering blood pressure by 120 mm Hg resulted in an increase in CKD occurrences in hypertensive people, lowering blood pressure drastically resulted in a decrease in CKD events. In keeping with these findings, we discovered that a rising SBP trajectory was linked to a higher probability of albuminuria recurrence [8].

We observed that hypertension alone or isolated systolic or diastolic bp is associated with CKD progression and complications.

Pulse Pressure and White Coat Hypertension in Chronic Kidney Disease

Over a median follow-up of 3.8 years, higher arterial stiffness, as defined by pulse pressure, was associated with an increased risk of renal disease progression in older people with hypertension and a high risk of cardiovascular events. This link was substantial in people who did not have CKD at the start but not in those who did [13]. The likelihood of eGFR reduction was substantially linked to high pulse pressure, low SBP, and high SBP. Low SBP was linked to a sixty-five percent increased risk of eGFR decline in participants under fifty-five. In the general population, the combination of high SBP and high pulse pressure and low SBP and high pulse was linked to an increased risk of eGFR decline [18]. Whitecoat hypertension is characterized by increased clinical blood pressure but not out-of-office blood pressure. Whitecoat hypertension was linked to an increased incidence of renal events in Chinese patients with CKD. They were not on dialysis [19].

Results

Using the advanced search method and a combination of common keywords and MeSH phrases, 1218 relevant articles were identified in PubMed. Only 40 of the examined publications were significant to this study topic. All of the studies in this section are from 2020 to 2022, involve a population of middleaged and older people, and were published in English. Finally, 40 articles were chosen for examination. Only 20 of these were included in our analysis. We used the NewcastleOttawa Checklist to conduct a complete quality evaluation on the 13 confirmed articles, and all articles were qualified after the quality assessment. Figure 1 depicts the details of the search techniques and their results summarised in the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA)flowchart [21].

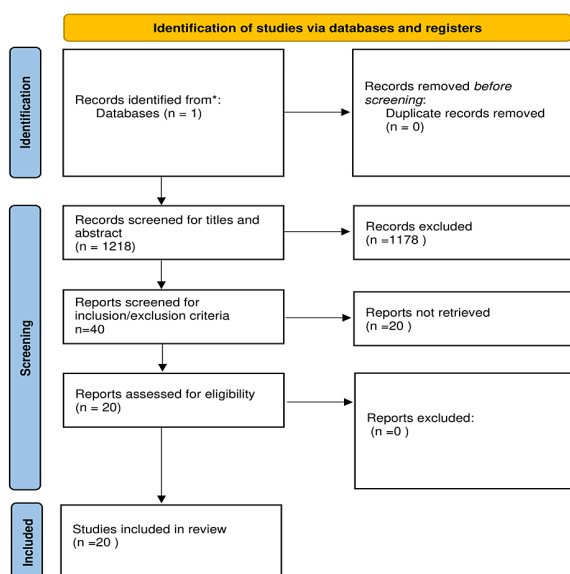


Figure 1- Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA)flowchart

Study Characteristics

Table 3 shows the data extracted from the studies. Out of the 20 articles, ten were cohort, six were cross-sectional, one study analysis, two observational, and one retrospective follow-up study. The quality assessment tool that was used is mentioned as Newcastle-Ottawa Checklist (observational studies).

Prediabetes and Chronic Kidney Disease

Prediabetes was not linked to a higher risk of eGFR decline or end-stage renal disease development in patients with CKD. In the middle-aged and generally healthy population, there was no proof that a healthy lifestyle score during childhood and from childhood to adulthood is related to subclinical kidney damage [10]. However, it was linked to a higher risk of proteinuria progression, an increased risk of unfavorable cardiovascular events, and a tendency toward increased all-cause mortality [11]. Studies are consistent with the positive association of diabetes with the development of complications and progression of chronic kidney diseases. However, adolescents' prediabetes and unhealthy lifestyle did not affect the development or progression of chronic kidney disease.

Masked Hypertension and Chronic Kidney Disease

Masked uncontrolled hypertension is independently related to a greater risk of cardiovascular and kidney outcomes when compared to regulated blood pressure. Independent of clinic BP, greater mean 24-hour systolic BP is linked to a higher risk of cardiovascular, renal, and death outcomes. Diurnal variations in blood pressure were linked to a higher risk of renal disease, stroke, and peripheral artery disease development. The association between masked uncontrolled hypertension and kidney outcome is most prominent in patients with lower levels of GFR [14].

Nocturnal hypertension was linked to a higher risk of renal failure and cardiovascular events. Patients with isolated nocturnal systolic hypertension had a higher risk of cardiovascular events. In comparison, those with nocturnal systolic-diastolic hypertension had a higher risk of kidney and cardiovascular complications [20].

Limitations

To begin with, the research was chosen from a single database, which means the subject was likely overlooked. Because we only included free full-text papers from the last two, much valuable research that occurred during screening may have been overlooked, resulting in the obliteration of our overall review.

Table-3-Study characteristics

S.no	AUTHOR	YEAR	STUDY DESIGN	CONCLUSION
1	Ahamed MA et al. [1]	2022	Retrospective follow-up study	The median time for the development of CKD DM was 5 years which was accelerated by hypercholesterolemia
2	Ibrahim et al. [2]	2020	Cohort	There is a heterogeneous interplay of risk factors in rapid linear CKD progression and mortality patients with CKD
3	Bramlage P et al. [3]	2020	Observational	Closer surveillance of patients with diabetes & prescription of RAS blocking agents are mandatory once microalbuminuria or renal function deterioration develops.
4	Carpio EM et al. [4]	2021	Cross-sectional	Poor systolic blood pressure in patients causes an increased risk of mortality for cardiovascular diseases.
5	Chang TI et al. [5]	2020	Cohort	Higher SBP was associated with a higher risk for incident CKD G3-G5.
6	Hao Y et al. [6]	2021	Cross-sectional	ISH was generally related to cardiac and renal damage without age modifications, while ID was only harmful to renal function
7	Jitraknatee Jet al. [7]	2020	Cross-sectional	The relatively high prevalence of CKD among T2DM patients is related to poor glycaemic control.
8	Joo YS et al. [8]	2020	Cohort	Increasing SBP over time without reaching the hypertension threshold is associated with a significantly increased risk of incident CKD healthy adults
9	Lee JY et al. [9]	2020	Cohort	In patients with CKD, higher SBP and DBP levels were associated with a higher risk of composite kidney outcome reflecting CKD progression
10	Liu C et al. [10]	2022	Cohort	A healthy lifestyle score from childhood to adulthood did not predict subclinical kidney damage in a middle-aged population.
11	Neves JS et al. [11]	2020	Study analysis	In individuals with CKD, prediabetes was associated with an increased risk of proteinuria progression and adverse CV outcomes.
12	Nichols GA et al. [12]	2020	Cohort	The presence of albuminuria was associated with accelerated eGFR decline independent of T2D.
13	Nowak KL et al. [13]	2020	Cohort	Among adults at high risk for cardiovascular disease, PP was associated with kidney disease
14	Rahman M et al. [14]	2020	Cohort	Masked uncontrolled HTN and mean 24-hour are associated with a high risk of CVD and progression of kidney disease
15	Sharma M et al. [15]	Cross-sectional	Cross-sectional	The short duration of diabetes, lower glycated hemoglobin, absent DR, and active urinary sediment were independent predictors of non-diabetic renal disease on univariate analysis
16	Suijk DLS et al. [16]	2020	Cross-sectional	Plasma uric acid was negatively associated with GFR, and effective renal plasma flow but positively related to effective renal vascular resistance in T2D patients without overt renal impairment.
17	Takamatsu K et al. [17]	Cross-sectional	Cross-sectional	In elderly patients with type 2 diabetes, renal dysfunction is characterized by low eGFR with normal- and microalbuminuria
18	Wang HY et al. [18]	2021	Observational	Single and combination of high PP and high S could be the risk indicators of eGFR decline among the middle and old aged general population.
19	Wang Q et al. [19]	2020	Cohort	White coat hypertension is associated with a greater risk for renal events in non-dialysis-dependent Chinese patients with CKD.
20	Wang Q et al. [20]	2021	Cohort	Nocturnal systolic hypertension, either alone in combination with diastolic hypertension, is associated with higher risks for adverse outcomes in patients with CKD.

Abbreviations in table.3

- Ckd-chronic kidney disease
- Egfr-estimated glomerular filtration rate
- T2d-type 2 diabetes
- Htn-hypertension
- Pp-pulse pressure
- Sbp-systolic blood pressure
- Ras-renin angiotensin system
- Cvd-cardiovascular diseases.

Furthermore, the majority of the papers we included had a small sample size, which could impact our findings. Rather than focusing on progression, several of the research focused on clinical outcomes. Many trials had unmeasured confounders, and many patients were taking medications such as ace inhibitors, arbs, metformin, and other pharmaceuticals that could have influenced the results. We believe we need more research on progression markers and the relationship between other factors and chronic renal disease.

Conclusion

This systematic review aimed to emphasize the role of diabetes and hypertension in the progression of chronic kidney. Furthermore, the study also aimed at finding other risk factors for chronic kidney disease. Diabetes and hypertension are established risk factors for kidney diseases, but studies purely on the progression are a few. However, most of the studies in our review favor the positive association between diabetes and hypertension in CKD progression. Also, other risk factors like hyperlipidemia, age, smoking, gender, and obesity have led to the progression. Certain factors like pulse pressure and white coat hypertension have also resulted in the progression of CKD. However, more studies are required for a better understanding of pathogenesis and inflammatory markers on progression.

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