

# The connection between hypertension and diabetes and their role in heart and kidney disease development

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Hypertension and diabetes are two common metabolic disorders that often coexist in the same individual. Their concurrence increases the risk of cardiovascular disease, renal dysfunction, and other complications. Cardiovascular disease is the primary cause of morbidity and mortality in individuals with diabetes, and hypertension further aggravates this condition. Interestingly, hypertension and diabetes share several common pathophysiological mechanisms including insulin resistance, vascular inflammation, endothelial dysfunction, obesity, and oxidative stress suggesting a cross-talk between these two conditions that could potentially contribute to the development of other human diseases. Effective management of diabetes should include a multifaceted approach that addresses not only glycemic control but also blood pressure (BP) and lipid control. Treatment plans should be individualized to each patient's needs and should involve a combination of lifestyle modifications and medications to achieve optimal control. With the availability of newer antidiabetic medications such as SGLT inhibitors and GLP1 receptor agonists, it is crucial to consider their potential to reduce BP, enhance kidney function, and lower the risk of cardiovascular diseases when initiating treatment for glycemic control. A more profound comprehension of the shared underlying mechanisms between these conditions could pave the way for the development of innovative therapeutic approaches to tackle them. Our review offers an in-depth analysis of the literature, providing a holistic view of the mechanisms underlying diabetes-hypertension comorbidity and its implications on heart and kidney diseases. The present article concludes by discussing current approaches for managing hypertensive diabetic patients to create a set of comprehensive individualized recommendations.

**Key words:** Blood pressure, cardiovascular disease, coronary heart disease, diabetes, guidelines, hypertension, interaction, stroke

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## INTRODUCTION

The risk of type 2 diabetes (T2D), heart disease, and stroke is elevated by a spectrum of illnesses known as metabolic syndrome (METS).<sup>[1]</sup> METS is a cluster of conditions that include abdominal obesity, high blood pressure (BP), high blood sugar levels, and abnormal cholesterol levels. With these conditions, persons are predisposed toward developing T2D and hypertension.<sup>[2]</sup> METS increases the risk of developing diabetes and hypertension by promoting insulin resistance, abdominal obesity, dyslipidemia,

inflammation, and endothelial dysfunction.<sup>[3]</sup> They are often hereditary.<sup>[4]</sup> Typically, symptoms appear when the body's metabolism is under stress, such as following a protracted fast or a feverish illness. Families with a prior history of metabolic illnesses or those belonging to a specific ethnic group are usually offered prenatal diagnostic screening.<sup>[5]</sup> Age, ethnicity, obesity, and diabetes were found to be the most important causes of METS in previous studies.<sup>[6]</sup> Up to one-third of adults in the United States are estimated to have METS, which is becoming more and more prevalent and has few overt symptoms (apart from a big waist circumference).<sup>[7,8]</sup>

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The problem is becoming increasingly common in India as well due to changes in lifestyle, diet as well as genetic factors. According to a systematic review and meta-analysis published in 2020, the overall prevalence of METS in India was estimated to be around 24.9%.<sup>[19]</sup> Another study published in 2020 found that METS was more common in women than men (39.1% vs. 28.6%). The worldwide occurrence is on the increase, with the global incidence expected to be 20%–25% of the adult population.<sup>[10]</sup>

Depending on the type of diabetes, patients' clinical condition, and the presence of renal disease, patients with diabetes often experience hypertension.<sup>[11–13]</sup> About 70% of diabetic patients suffer from hypertension, which is roughly twice as frequent in people with diabetes as it is in people without it.<sup>[14]</sup> Minorities and other underprivileged populations are particularly impacted by environmental concerns including access to healthy food and environmental pollution. As low energy expenditure and high-calorie intake, lifestyles become more prevalent, especially in low-income and emerging nations, the incidence of these two major medical disorders continues to climb globally.<sup>[15,16]</sup> Furthermore, heart disease, microvascular complications, and atherosclerotic cardiovascular disease (ASCVD) are all strongly correlated with hypertension. Antihypertensive treatment for patients with diabetes minimizes the aforementioned consequences, according to various researchers.<sup>[11,17,18]</sup> Since 1990, ASCVD morbidity and death have decreased, largely as a result of advancements in BP management.<sup>[11]</sup> T2D affects 171 million people worldwide and is estimated to affect 366 million people worldwide by 2030<sup>[19,20]</sup> and 642 million by 2040.<sup>[21]</sup> Similar to diabetes, it is anticipated that by 2025 there will be 1.56 billion adults worldwide with hypertension,<sup>[14]</sup> with a recent estimate of 1.39 billion cases.<sup>[22]</sup> Chronic renal disease, retinopathy, and sexual dysfunction are all significantly more likely to develop when hypertension and diabetes coexist. Pre-eclampsia and end-organ disease are risks for pregnant women and minors with diabetes and hypertension, respectively.<sup>[23,24]</sup> Furthermore, developing diabetes early can speed up atherosclerosis as people grow older.<sup>[25]</sup> Hence, to reduce the risk of related morbidity and death, both hypertension and diabetes should be detected early and actively treated.<sup>[26–29]</sup> T2D and hypertension share elements of the pathophysiology related to obesity and insulin resistance, it is possible to identify the coexistence of these two disorders at the patient's bedside.<sup>[30]</sup> Obesity is a major risk factor for the development of both T2D and hypertension. It leads to accumulation of fat tissue particularly in the abdominal region.<sup>[31]</sup> This fat tissue produces and releases several pro-inflammatory cytokines that contribute to low-grade inflammation and insulin resistance.<sup>[32,33]</sup> Insulin resistance further results in the increased production of endothelin-1 a vasoconstrictor<sup>[34]</sup>

and also effects the elevated level of triglycerides thereby promoting hypertension.<sup>[35]</sup> These interrelated mechanisms highlight the importance of addressing obesity and insulin resistance through lifestyle modifications and pharmacological treatments to manage T2D and hypertension. According to previously published results based on the UK prospective diabetes study (UKPDS) and the Heart Outcomes Prevention Assessment study, people with T2D can avoid cardiovascular issues by controlling their BP, changing their lifestyles, and managing their weight.<sup>[29,36,37]</sup> Despite significant improvements in health-care delivery, diabetes mellitus remains the main contributor to both microvascular and macrovascular problems. While hypertension is crucial in the onset and development of macrovascular illness, adequate glycemic management is associated with microvascular problems.<sup>[38]</sup> Hence, a multidimensional strategy incorporating the results of several risk variables is necessary for the effective care of individuals with diabetes and hypertension.

Hypertension and diabetes, prevalent metabolic disorders, often coexist, compounding the risk of cardiovascular disease, renal dysfunction, and related complications. Despite the well-established connection between these conditions, our study seeks to address a critical gap in understanding by delving into the intricate molecular mechanisms underlying the co-occurrence of hypertension and diabetes. This review aims to provide a comprehensive analysis of the shared pathophysiological pathways, including insulin signaling, inflammation, renin–angiotensin–aldosterone system (RAAS), endothelial function, and lipid metabolism, with a focus on elucidating the complexities of their interplay. Through this exploration, we aim to contribute to the development of more effective therapeutic strategies for managing these coexisting conditions.

For individuals with diabetes and hypertension, BP should be checked at regular intervals.<sup>[39]</sup> Systolic and diastolic BP decreases of 20 mmHg and 10 mmHg during standing position, respectively, are used to characterize orthostatic hypotension (OH).<sup>[40]</sup> OH is common in people with T2D.<sup>[41]</sup> Individuals with OH conditions may benefit from choosing the best antihypertensive medications.<sup>[42]</sup> Current studies and trials offer the strongest evidence addressing BP and offer significant guidance for treatment targets, especially for individuals with T2D. BP is a main indicator of both hypertension and T2D. By lowering BP, the UKPDS found that the combined risk of microvascular and macrovascular complications from T2D was lowered by 24%.<sup>[43]</sup> Moreover, meta-analyses of clinical trials show that treating populations with antihypertensives lowers the chances of heart failure, retinopathy, and albuminuria in people with diabetes whose baseline BP is <140/90 mmHg.<sup>[43–46]</sup> Hence, maintaining BP goals of 140/90 mmHg is essential for managing people with

hypertension and diabetes. Diastolic BP can be addressed in younger adults and is a major predictor of cardiovascular outcomes in people under 50 without diabetes.<sup>[46]</sup> Younger adults with T1D may be able to keep strict BP limits more readily and may see significant long-term benefits. The photoplethysmogram (PPG) signal captures variations in blood volume within the microvascular tissue bed. The study conducted by Karavaev *et al.* in 2020<sup>[47]</sup> demonstrated that the low-frequency component of PPG is not solely influenced by local myogenic activity but also reflects the processes associated with the autonomic control of BP. This finding implies that the LF component of the PPG signal has the potential to offer valuable insights into the autonomic regulation of BP, going beyond local factors. Consequently, it underscores the significance of the LF component of the PPG signal as a valuable tool in assessing cardiovascular health and providing information on autonomic function. The results of this study contribute to a growing body of evidence highlighting the utility of PPG analysis for understanding the intricate interplay between autonomic control and cardiovascular dynamics.

The molecular mechanisms underlying the co-occurrence of diabetes and hypertension are complex and involve dysregulation of multiple pathways, including insulin signaling, inflammation, RAAS, endothelial function, and lipid metabolism.<sup>[48-51]</sup> Understanding these mechanisms is crucial for the development of effective treatments for these conditions, with a focus on targeting multiple pathways to achieve optimal control of blood glucose and BP. By highlighting the shared pathophysiological mechanisms between hypertension and diabetes, such as insulin resistance, vascular inflammation, endothelial dysfunction, obesity, and oxidative stress, the article underscores the need for a comprehensive approach that goes beyond glycemic control. It emphasizes the importance of addressing BP and lipid control as integral components of diabetes management. This multifaceted approach aims to mitigate the detrimental impact of hypertension on cardiovascular health, further reducing the risk of complications and improving overall patient well-being. In addition, in recent years miRNAs and circRNA have emerged as key players in the pathogenesis of type 2 diabetes and hypertension.<sup>[52-54]</sup> These small molecules are known to regulate the aforementioned pathways. Therefore, exploring these pathways may provide new insights into the pathogenesis of these conditions and pave the way for the development of innovative therapeutic interventions.

## ROLE IN HEART AND KIDNEY DISEASE DEVELOPMENT

Diabetes and hypertension are significant risk factors for macro- and microvascular illnesses, their coexistence

in one patient is destructive.<sup>[55]</sup> Together, diabetes and hypertension lead to substantial health issues that are connected with high death rates, morbidity, and health-care expenditures. Patients with diabetes and hypertension are more likely than the general population to experience kidney or cardiovascular issues as a result of a variety of risk factors known to favor these disorders.

Diabetes mellitus, renal disease, and heart failure are often occurring and connected illnesses. The current research demonstrates that more than 40% of patients with heart failure also have diabetes and renal problems. A higher risk of heart failure is linked to both diabetes and renal illness.<sup>[56]</sup> Diabetes and hypertension patients frequently have metabolic abnormalities, which harm the vascular system and exacerbate atherosclerosis.<sup>[57]</sup> Previous research confirms the structural and functional abnormalities of the vascular endothelium and their association with diabetic hypertensive conditions.<sup>[58]</sup> Accelerated atherosclerosis may be caused by increased insulin levels in the blood (as in T2D) and in many people with hypertension, either alone or in combination with insulin-like growth factor. Depending on the severity of the artery abnormalities and the affected arteries, atherosclerosis may result in heart and kidney difficulties.<sup>[59]</sup> Early kidney impairment has been linked to accelerated atherosclerosis. Hematologic disorders that promote thrombosis (involved in complications such as stroke or heart attack) are also linked to diabetic hypertensive conditions.<sup>[60]</sup>

Adults with diabetes have a 55% increased likelihood of developing coronary artery disease (CAD).<sup>[61]</sup> Patients with diabetes had a roughly 2-fold greater restenosis risk following coronary balloon angioplasty and myocardial infarction (MI).<sup>[62,63]</sup> Similar to diabetic patients, hypertension patients are also have an increased risk of silent MI, especially those with left ventricular hypertrophy.<sup>[64]</sup> In children with chronic kidney disease, arterial hypertension is particularly prevalent.<sup>[65]</sup> Compared to patients who only have hypertension or diabetes, CAD is substantially more prevalent among diabetic hypertensive patients.<sup>[57]</sup> Before the emergence of systolic dysfunction, diastolic dysfunction, an early anomaly in diabetic cardiomyopathy, can be identified in young insulin-dependent diabetic patients.<sup>[66]</sup> Compared to nondiabetic individuals, diabetic patients with CAD experience more severe heart failure (by 55% for a 20 mm Hg increase in systolic pressure), more hospitalizations, and a greater chance of death.<sup>[67,68]</sup> The spreading of thick interstitial connective tissue across the myocardium appears to be one of the most remarkable microscopic observations of the hypertensive diabetic heart.<sup>[69]</sup> Additional findings include higher septal and posterior wall size and the prevalence of the left ventricular hypertrophy.<sup>[64]</sup>

Diabetes is the main cause of kidney failure since 40% of diabetic patients develop chronic kidney disease.<sup>[70]</sup> The main causes of end-stage renal disease (ESRD) include hypertension and diabetes mellitus.<sup>[71]</sup> Diabetes mellitus and hypertension account for 50% and 27% of all ESRD cases in the US, respectively.<sup>[57,72]</sup> When BP rises, the risk of ESRD increases.<sup>[73]</sup> Chronic hypertension promotes the decline in renal function when it coexists with diabetes mellitus.<sup>[74]</sup> Current studies demonstrate that lowering BP to <130/80 mmHg can halt the course of kidney impairment in diabetic patients.<sup>[75]</sup>

Evidence from epidemiology links diabetes to a 2- to 4-fold higher frequency of peripheral artery disease (PAD).<sup>[76]</sup> Beckman *et al.*, in 2002 showed that the prevalence of aberrant ankle-to-brachial indices is 20.9% in people who require multiple hypoglycemic drugs (7% in normal individuals).<sup>[77]</sup> PAD is significantly linked to cardiovascular mortality and exhibits the initial clinical features of atherosclerosis.<sup>[78]</sup> Short-term risks of heart attack and stroke are significantly raised in patients with PAD.<sup>[79]</sup> Cilostazol and exercise have both shown promise in extending the walking distance of people with PAD.<sup>[80]</sup> The majority of diabetic patients with PAD require revascularization.<sup>[81]</sup> However, further study is required to completely comprehend the processes behind the association between diabetes and hypertension as well as their combined role in heart and renal illnesses. This will allow for the development of more efficient therapies that will improve overall patient outcomes.

## TREATMENT

Treatment for diabetes and hypertension includes lifestyle control, diet, and exercise.<sup>[82]</sup> Lifestyle modification can boost the effectiveness of numerous antihypertensive drugs for people with a systolic BP above 120 mmHg or diastolic BP above 80 mmHg.<sup>[83,84]</sup> There are no controlled trials demonstrating the usefulness of food and exercise in lowering BP in diabetic hypertensive individuals. Nonetheless, a few research confirmed the role of lifestyle intervention.<sup>[85]</sup> Reducing excess body weight by calorie restriction, limiting salt intake, boosting consumption of fruits, low-fat dairy products, and vegetables, avoiding excessive alcohol consumption, quitting smoking, reducing inactive time, and improving physical activity levels are all parts of lifestyle treatment.<sup>[85,86]</sup> BP has been demonstrated to decrease with moderately intense exercise.<sup>[87]</sup> Regular exercise has been associated with a reduction in BP of 1 mmHg for every kilogram of body weight lost. Antihypertension drug dosage adjustments are necessary due to these circumstances.<sup>[88,89]</sup> Some weight-loss drugs must be taken cautiously since they might cause BP to rise. In randomized trials including individuals with diabetes, treatment for obstructive sleep apnea has been proven to

lower BP.<sup>[90]</sup> To prevent hypertension and facilitate timely intervention before significant clinical events occur, it is valuable to assess the likelihood of developing hypertension later in life. A study conducted by Wu *et al.* in 2017<sup>[91]</sup> demonstrated that monitoring beat-to-beat BP levels and variability, particularly frequency domain BP variability holds promise for early-stage prediction of hypertension. By leveraging such insights, healthcare professionals can take proactive measures to mitigate hypertension risks and initiate timely treatment, potentially averting future complications.

Angiotensin-converting enzyme (ACE) inhibitors,<sup>[92]</sup> angiotensin receptor blockers (ARBs),<sup>[93]</sup> thiazide-like diuretics,<sup>[94]</sup> and dihydropyridine calcium channel blockers (CCBs)<sup>[95]</sup> are among the first-line medications for hypertension. In most cases, multiple medication treatment is needed to reach BP goals. In one of the first studies to investigate whether patients with diabetes (with average BPs above 160/100 mmHg) would be more likely to achieve their BP goals when a single medication combination was administered as opposed to monotherapy, patients who received initial treatment with an ACE inhibitor + CCB compared to the ACE inhibitor alone at 3 months showed improved results at  $P = 0.002$ .<sup>[96]</sup> The proportion of patients achieving a BP 140/90 mmHg at 6 months was higher in the combined intervention group with ACE inhibitor plus thiazide-like diuretic than ACE inhibitor alone at  $P = 0.026$  in the simplified treatment intervention to control hypertension trial, which included 2000 patients.<sup>[97]</sup>

To reach BP objectives, especially when there is diabetic renal impairment, multiple medication treatments are highly imperative.<sup>[98]</sup> Patients with hypertension and any degree of urine albumin excretion should be given an ACE inhibitor or ARB as part of their BP-lowering medication.<sup>[99]</sup> Although the advantages and dangers of ACE inhibitors and ARBs are thought to be comparable, using alternative medication is frequently an option if one is not tolerated.<sup>[100,101]</sup> Reduced estimated glomerular filtration rate (eGFR) and increased potassium in a patient with diabetic renal disease can increase the chance of developing hyperkalemia eightfold if spironolactone and an ACE inhibitor or ARB are combined.<sup>[111]</sup> Only down to an eGFR of 30 mL/min/1.73 m<sup>2</sup> can thiazide-like diuretics work to maintain volume and reduce the risk of hyperkalemia.<sup>[102,103]</sup> Torsemide, should be administered instead if the eGFR is <30 mL/min/1.73 m<sup>2</sup>. There may be a little advantage to taking antihypertensive drugs in the evening as opposed to the morning, according to the available research.<sup>[104]</sup> When used in conjunction with renin-angiotensin system inhibitor, diuretic, and CCB therapy, mineralocorticoid receptor antagonists (MRAs) are helpful for treating resistant hypertension (BP 140/90 mmHg) in individuals with



T2D.<sup>[105]</sup> Moreover, MRAs lower albuminuria and provide additional cardiovascular advantages.<sup>[106]</sup> Combining MRA with either an ACE inhibitor or an ARB may make hyperkalemic episodes more likely. Restricting daily consumption of potassium, utilizing potassium-wasting diuretics, or employing potassium binders can all aid with treating hyperkalemia.<sup>[107]</sup>

Low-dose aspirin is advised for pregnant women with a high risk of preeclampsia.<sup>[108]</sup> Pregnant women who still need antihypertensive therapy should maintain their BP because it is linked to fetal development. Labetalol, methyldopa, hydralazine, and long-acting nifedipine are examples of antihypertensive medications that are known to be efficient and secure during pregnancy. If necessary for volume control in late pregnancy, diuretics may be used.<sup>[109]</sup>

Older adults may experience an increase in systolic and a decrease in diastolic BP as a result of arterial stiffness that develops with aging.<sup>[110,111]</sup> Thereby, older diabetic hypertensive patients typically present with a high risk for cardiovascular events and other age-related diseases.<sup>[112]</sup> When developing treatment plans and BP goals, a thorough functional status of comorbid conditions are crucial factor to take into account.<sup>[113]</sup> Higher systolic BP targets should be taken into account for older patients with significant functional limitations. In older adults, lowering diastolic pressure below >60 mmHg may lead to an increased risk of death and other harmful cardiovascular outcomes.<sup>[114]</sup>

Simvastatin and other lipid-lowering drugs used as adjunctive therapy have been shown to reduce the incidence of heart disease by about 50%. According to the most recent American College of Physicians guidelines, all patients with T2D and hypertension should get lipid-lowering therapy as the primary method of preventing macrovascular effects. ARBs and calcium antagonists significantly decreased the incidence of new-onset diabetes compared to standard beta blockers. Antihypertensive medication on glucose metabolism in patients with uncomplicated hypertension revealed that during the 4–6 years of the trial, 10% of patients developed newonset diabetes.<sup>[115]</sup>

Those receiving lisinopril-based therapy have a lower risk of developing diabetes than those receiving chlorthalidone-based therapy. The cornerstone of the antihypertensive toolkit for diabetic hypertension patients is a RAAS blocker, either an ACE inhibitor or an ARB. An additional step should involve adding a calcium antagonist or thiazide diuretic. A RAAS blocker, a calcium antagonist, and a low dose of a thiazide diuretic makeup a triple treatment. Combination therapy is not typically practiced as evidence-based medicine, and must therefore continue to be based on scientific research and clinical reasoning.

## CONCLUSION

In summary, the strong connection between diabetes and hypertension is well-established, leading to an increased risk of cardiovascular complications and other health issues such as chronic kidney disease, obesity, and stroke. It is crucial to begin treatment as early as possible, addressing both hypertension and hyperglycemia while also targeting other aspects of METS. The emergence of novel therapeutic agents provides promising opportunities for more effective and comprehensive management of these coexisting conditions. Nonetheless, further research is necessary to fully comprehend their mechanisms of action and potential benefits. Meanwhile, controlling hypertension and promoting vascular health remain pivotal in the management of diabetes, with ample evidence supporting the use of various classes of antihypertensive medications to attain BP targets. Treatment strategies should be tailored to each individual, involving shared decision-making between the clinician and patient, taking into account specific comorbidities and risk profiles. Overall, managing diabetes and hypertension requires a comprehensive, multidisciplinary approach that prioritizes the prevention of complications and the enhancement of patient outcomes.

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