Review Article

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

Ali Ahmed Mohammed Hezam[1], Hanan Basheer Mohammed Shaghdar[2], Liying Chen[2]

[1]Department of General Practice, School of Medicine, Sir Run Run Shaw Hospital, Zhejiang University, Hangzhou, China, [2]School of Medicine, Zhejiang University School of Medicine, Hangzhou, Zhejiang Province, China

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

How to cite this article: Hezam AAM, Shaghdar HBM, Chen L. The connection between hypertension and diabetes and their role in heart and kidney disease development. J Res Med Sci 2024;29:22.

INTRODUCTION

The risk of type 2 diabetes (T2D), heart disease, and stroke is elevated by a spectrum of illnesses known as metabolic syndrome (METS).[1] 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.[2] METS increases the risk of developing diabetes and hypertension by promoting insulin resistance, abdominal obesity, dyslipidemia, inflammation, and endothelial dysfunction.[3] They are often hereditary.[4] 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.[5] Age, ethnicity, obesity, and diabetes were found to be the most important causes of METS in previous studies.[6] 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).[7,8]

Access this article online

Quick Response Code:

Website: https://journals.lww.com/jrms

DOI: 10.4103/jrms.jrms_470_23

Address for correspondence: Prof. Liying Chen, Department of General Practice, School of Medicine, Sir Run Run Shaw Hospital, Zhejiang University, 3 Qingchun East Rd., Hangzhou 310016, China.
E-mail: 3197020@zju.edu.cn

Submitted: 19-Jul-2023; **Revised:** 24-Nov-2023; **Accepted:** 25-Jan-2024; **Published:** 29-Apr-2024

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%.[9] 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.[10]

Depending on the type of diabetes, patients' clinical condition, and the presence of renal disease, patients with diabetes often experience hypertension.[11-13] 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.[14] 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.[15,16] 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.[11,17,18] Since 1990, ASCVD morbidity and death have decreased, largely as a result of advancements in BP management.[11] T2D affects 171 million people worldwide and is estimated to affect 366 million people worldwide by 2030[19,20] and 642 million by 2040.[21] Similar to diabetes, it is anticipated that by 2025 there will be 1.56 billion adults worldwide with hypertension,[14] with a recent estimate of 1.39 billion cases.[22] 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.[23,24] Furthermore, developing diabetes early can speed up atherosclerosis as people grow older.[25] Hence, to reduce the risk of related morbidity and death, both hypertension and diabetes should be detected early and actively treated.[26-29] 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.[30] 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.[31] This fat tissue produces and releases several pro-inflammatory cytokines that contribute to low-grade inflammation and insulin resistance.[32,33] Insulin resistance further results in the increased production of endothelin-1 a vasoconstrictor[34] and also effects the elevated level of triglycerides thereby promoting hypertension.[35] 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.[29,36,37] 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.[38] 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.[39] Systolic and diastolic BP decreases of 20 mmHg and 10 mmHg during standing position, respectively, are used to characterize orthostatic hypotension (OH).[40] OH is common in people with T2D.[41] Individuals with OH conditions may benefit from choosing the best antihypertensive medications.[42] 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%.[43] 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.[43-46] 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.[46] 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[47] 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.[48-51] 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.[52-54] 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.[55] 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.[56] Diabetes and hypertension patients frequently have metabolic abnormalities, which harm the vascular system and exacerbate atherosclerosis.[57] Previous research confirms the structural and functional abnormalities of the vascular endothelium and their association with diabetic hypertensive conditions.[58] 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.[59] 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.[60]

Adults with diabetes have a 55% increased likelihood of developing coronary artery disease (CAD).[61] Patients with diabetes had a roughly 2-fold greater restenosis risk following coronary balloon angioplasty and myocardial infarction (MI).[62,63] Similar to diabetic patients, hypertension patients are also have an increased risk of silent MI, especially those with left ventricular hypertrophy.[64] In children with chronic kidney disease, arterial hypertension is particularly prevalent.[65] Compared to patients who only have hypertension or diabetes, CAD is substantially more prevalent among diabetic hypertensive patients.[57] Before the emergence of systolic dysfunction, diastolic dysfunction, an early anomaly in diabetic cardiomyopathy, can be identified in young insulin-dependent diabetic patients.[66] 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.[67,68] 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.[69] Additional findings include higher septal and posterior wall size and the prevalence of the left ventricular hypertrophy.[64]

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

Evidence from epidemiology links diabetes to a 2- to 4-fold higher frequency of peripheral artery disease (PAD).[76] 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).[77] PAD is significantly linked to cardiovascular mortality and exhibits the initial clinical features of atherosclerosis.[78] Short-term risks of heart attack and stroke are significantly raised in patients with PAD.[79] Cilostazol and exercise have both shown promise in extending the walking distance of people with PAD.[80] The majority of diabetic patients with PAD require revascularization.[81] 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.[82] 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.[83,84] 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.[85] 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.[85,86] BP has been demonstrated to decrease with moderately intense exercise.[87] 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.[88,89] 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.[90] 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[91] 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,[92] angiotensin receptor blockers (ARBs),[93] thiazide-like diuretics,[94] and dihydropyridine calcium channel blockers (CCBs)[95] 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 $P = 0.002$.[96] 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.[97]

To reach BP objectives, especially when there is diabetic renal impairment, multiple medication treatments are highly imperative.[98] 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.[99] 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.[100,101] 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.[11] Only down to an eGFR of 30 mL/min/1.73 m^2 can thiazide-like diuretics work to maintain volume and reduce the risk of hyperkalemia.[102,103] Torsemide, should be administered instead if the eGFR is <30 mL/min/1.73 m^2. There may be a little advantage to taking antihypertensive drugs in the evening as opposed to the morning, according to the available research.[104] 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.[105] Moreover, MRAs lower albuminuria and provide additional cardiovascular advantages.[106] 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.[107]

Low-dose aspirin is advised for pregnant women with a high risk of preeclampsia.[108] 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.[109]

Older adults may experience an increase in systolic and a decrease in diastolic BP as a result of arterial stiffness that develops with aging.[110,111] Thereby, older diabetic hypertensive patients typically present with a high risk for cardiovascular events and other age-related diseases.[112] When developing treatment plans and BP goals, a thorough functional status of comorbid conditions are crucial factor to take into account.[113] 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.[114]

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.[115]

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.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Blaton V. How is the metabolic syndrome related to the dyslipidemia? EJIFCC 2007;18:15-22.
2. Cornier MA, Dabelea D, Hernandez TL, Lindstrom RC, Steig AJ, Stob NR, *et al.* The metabolic syndrome. Endocr Rev 2008;29:777-822.
3. Liu S, Manson JE. Dietary carbohydrates, physical inactivity, obesity, and the 'metabolic syndrome' as predictors of coronary heart disease. Curr Opin Lipidol 2001;12:395-404.
4. Reiner Ž, Guardamagna O, Nair D, Soran H, Hovingh K, Bertolini S, *et al.* Lysosomal acid lipase deficiency – An under-recognized cause of dyslipidaemia and liver dysfunction. Atherosclerosis 2014;235:21-30.
5. Horvath S, Gurven M, Levine ME, Trumble BC, Kaplan H, Allayee H, *et al.* An epigenetic clock analysis of race/ethnicity, sex, and coronary heart disease. Genome Biol 2016;17:171.
6. Prasad DS, Kabir Z, Dash AK, Das BC. Prevalence and risk factors for metabolic syndrome in Asian Indians: A community study from urban Eastern India. J Cardiovasc Dis Res 2012;3:204-11.
7. Nithin R. A Study on the Role of Constitutional Medicine in the Management of Metabolic Syndrome Based on ATP III Criteria in School going Children. Kulasekharam: Sarada Krishna Homoeopathic Medical College; 2019.
8. Roddy GW. Metabolic syndrome is associated with ocular hypertension and glaucoma. J Glaucoma 2020;29:726-31.

9. Krishnamoorthy Y, Rajaa S, Murali S, Rehman T, Sahoo J, Kar SS. Prevalence of metabolic syndrome among adult population in India: A systematic review and meta-analysis. PLoS One 2020;15:e0240971.
10. Bhalwar R. Metabolic syndrome: The Indian public health perspective. Med J Armed Forces India 2020;76:8-16.
11. de Boer IH, Bangalore S, Benetos A, Davis AM, Michos ED, Muntner P, *et al.* Diabetes and hypertension: A position statement by the American diabetes association. Diabetes Care 2017;40:1273-84.
12. Today Study Group. Rapid rise in hypertension and nephropathy in youth with type 2 diabetes: The TODAY clinical trial. Diabetes Care 2013;36:1735-41.
13. Al-Azzam N, Al-Azzam S, Elsalem L, Karasneh R. Hypertension prevalence and associated factors among patients with diabetes: A retrospective cross-sectional study from Jordan. Ann Med Surg (Lond) 2021;61:126-31.
14. Lago RM, Singh PP, Nesto RW. Diabetes and hypertension. Nat Clin Pract Endocrinol Metab 2007;3:667.
15. Pulgaron ER, Delamater AM. Obesity and type 2 diabetes in children: Epidemiology and treatment. Curr Diab Rep 2014;14:508.
16. Deepa M, Anjana RM, Mohan V. Role of lifestyle factors in the epidemic of diabetes: Lessons learnt from India. Eur J Clin Nutr 2017;71:825-31.
17. Hudspeth B. The burden of cardiovascular disease in patients with diabetes. Am J Manag Care 2018;24:S268-72.
18. American Diabetes Association. 9. Cardiovascular disease and risk management. Diabetes Care 2017;40:S75-87.
19. Carstensen B, Rønn PF, Jørgensen ME. Prevalence, incidence and mortality of type 1 and type 2 diabetes in Denmark 1996-2016. BMJ Open Diabetes Res Care 2020;8:e001071.
20. Chatterjee S, Khunti K, Davies MJ. Type 2 diabetes. Lancet 2017;389:2239-51.
21. Ogurtsova K, da Rocha Fernandes JD, Huang Y, Linnenkamp U, Guariguata L, Cho NH, *et al.* IDF diabetes atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. Diabetes Res Clin Pract 2017;128:40-50.
22. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. Nat Rev Nephrol 2020;16:223-37.
23. Hall D. Treatment of hypertension during pregnancy. SA Heart 2014;11:68-74.
24. Hwang JW, Park SJ, Oh SY, Chang SA, Lee SC, Park SW, *et al.* The risk factors that predict chronic hypertension after delivery in women with a history of hypertensive disorders of pregnancy. Medicine (Baltimore) 2015;94:e1747.
25. Alonso A, Mosley TH Jr., Gottesman RF, Catellier D, Sharrett AR, Coresh J. Risk of dementia hospitalisation associated with cardiovascular risk factors in midlife and older age: The Atherosclerosis Risk in Communities (ARIC) study. J Neurol Neurosurg Psychiatry 2009;80:1194-201.
26. Fowler MJ. Microvascular and macrovascular complications of diabetes. Clin Diabetes 2008;26:77-82.
27. Rhodes ET, Prosser LA, Hoerger TJ, Lieu T, Ludwig DS, Laffel LM. Estimated morbidity and mortality in adolescents and young adults diagnosed with Type 2 diabetes mellitus. Diabet Med 2012;29:453-63.
28. Fowler MJ. Microvascular and macrovascular complications of diabetes. Clin Diabetes 2011;29:116-22.
29. Girach A, Manner D, Porta M. Diabetic microvascular complications: Can patients at risk be identified? A review. Int J Clin Pract 2006;60:1471-83.
30. Petrie JR, Guzik TJ, Touyz RM. Diabetes, hypertension, and cardiovascular disease: Clinical insights and vascular mechanisms. Can J Cardiol 2018;34:575-84.
31. Koenen M, Hill MA, Cohen P, Sowers JR. Obesity, adipose tissue and vascular dysfunction. Circ Res 2021;128:951-68.
32. Zatterale F, Longo M, Naderi J, Raciti GA, Desiderio A, Miele C, *et al.* Chronic adipose tissue inflammation linking obesity to insulin resistance and type 2 diabetes. Front Physiol 2019;10:1607.
33. Ahmed B, Sultana R, Greene MW. Adipose tissue and insulin resistance in obese. Biomed Pharmacother 2021;137:111315.
34. Jenkins HN, Rivera-Gonzalez O, Gibert Y, Speed JS. Endothelin-1 in the pathophysiology of obesity and insulin resistance. Obes Rev 2020;21:e13086.
35. Kosmas CE, Silverio D, Tsomidou C, Salcedo MD, Montan PD, Guzman E. The impact of insulin resistance and chronic kidney disease on inflammation and cardiovascular disease. Clin Med Insights Endocrinol Diabetes 2018;11:1179551418792257.
36. Turner RC, Millns H, Neil HA, Stratton IM, Manley SE, Matthews DR, *et al.* Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United kingdom prospective diabetes study (UKPDS: 23). BMJ 1998;316:823-8.
37. McFarlane SI, Kumar A, Sowers JR. Mechanisms by which angiotensin-converting enzyme inhibitors prevent diabetes and cardiovascular disease. Am J Cardiol 2003;91:30H-37.
38. Naha S, Gardner MJ, Khangura D, Kurukulasuriya LR, Sowers JR. Hypertension in diabetes. Endotext [Internet] 2021.
39. Naschitz JE, Rosner I. Orthostatic hypotension: Framework of the syndrome. Postgrad Med J 2007;83:568-74.
40. Hiitola P, Enlund H, Kettunen R, Sulkava R, Hartikainen S. Postural changes in blood pressure and the prevalence of orthostatic hypotension among home-dwelling elderly aged 75 years or older. J Hum Hypertens 2009;23:33-9.
41. Benvenuto LJ, Krakoff LR. Morbidity and mortality of orthostatic hypotension: Implications for management of cardiovascular disease. Am J Hypertens 2011;24:135-44.
42. Arnold AC, Raj SR. Orthostatic hypotension: A practical approach to investigation and management. Can J Cardiol 2017;33:1725-8.
43. Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood pressure lowering in type 2 diabetes: A systematic review and meta-analysis. JAMA 2015;313:603-15.
44. Ganda OP, Mitri J. Current consensus and controversies in guidelines for lipid and hypertension management in diabetes. Curr Cardiol Rep 2016;18:114.
45. American Diabetes Association. 9. Cardiovascular disease and risk management: Standards of medical care in diabetes-2018. Diabetes Care 2018;41:S86-104.
46. Hong KN, Fuster V, Rosenson RS, Rosendorff C, Bhatt DL. How low to go with glucose, cholesterol, and blood pressure in primary prevention of CVD. J Am Coll Cardiol 2017;70:2171-85.
47. Karavaev AS, Borovik AS, Borovkova EI, Orlova EA, Simonyan MA, Ponomarenko VI, *et al.* Low-frequency component of photoplethysmogram reflects the autonomic control of blood pressure. Biophys J 2021;120:2657-64.
48. Velloso LA, Folli F, Perego L, Saad MJ. The multi-faceted cross-talk between the insulin and angiotensin II signaling systems. Diabetes Metab Res Rev 2006;22:98-107.
49. Bakker W, Eringa EC, Sipkema P, van Hinsbergh VW. Endothelial dysfunction and diabetes: Roles of hyperglycemia, impaired insulin signaling and obesity. Cell Tissue Res 2009;335:165-89.
50. Steckelings UM, Rompe F, Kaschina E, Unger T. The evolving story of the RAAS in hypertension, diabetes and CV disease: Moving from macrovascular to microvascular targets. Fundam Clin Pharmacol 2009;23:693-703.
51. Eid S, Sas KM, Abcouwer SF, Feldman EL, Gardner TW, Pennathur S, *et al.* New insights into the mechanisms of diabetic complications: Role of lipids and lipid metabolism. Diabetologia

2019;62:1539-49.
52. Chang W, Wang J. Exosomes and their noncoding RNA cargo are emerging as new modulators for diabetes mellitus. Cells 2019;8:853.
53. Zaiou M. The emerging role and promise of circular RNAs in obesity and related metabolic disorders. Cells 2020;9:1473.
54. Improta Caria AC, Nonaka CK, Pereira CS, Soares MB, Macambira SG, Souza BS. Exercise training-induced changes in microRNAs: Beneficial regulatory effects in hypertension, type 2 diabetes, and obesity. Int J Mol Sci 2018;19:3608.
55. Messerli FH, Grossman E, Michalewicz L. Combination therapy and target organ protection in hypertension and diabetes mellitus. Am J Hypertens 1997;10:198-201S.
56. Vijay K, Neuen BL, Lerma EV. Heart failure in patients with diabetes and chronic kidney disease: Challenges and opportunities. Cardiorenal Med 2022;12:1-10.
57. Grossman E, Messerli FH. Hypertension and diabetes. Adv Cardiol 2008;45:82-106.
58. Fuster V, Gotto AM, Libby P, Loscalzo J, McGill HC. 27th Bethesda conference: Matching the intensity of risk factor management with the hazard for coronary disease events. Task force 1. Pathogenesis of coronary disease: The biologic role of risk factors. J Am Coll Cardiol 1996;27:964-76.
59. Reiss AB, Miyawaki N, Moon J, Kasselman LJ, Voloshyna I, D'Avino R Jr., *et al.* CKD, arterial calcification, atherosclerosis and bone health: Inter-relationships and controversies. Atherosclerosis 2018;278:49-59.
60. Sardu C, Gambardella J, Morelli MB, Wang X, Marfella R, Santulli G. Hypertension, thrombosis, kidney failure, and diabetes: Is COVID-19 an endothelial disease? A comprehensive evaluation of clinical and basic evidence. J Clin Med 2020;9:1417.
61. Cheung AK, Sarnak MJ, Yan G, Dwyer JT, Heyka RJ, Rocco MV, *et al.* Atherosclerotic cardiovascular disease risks in chronic hemodialysis patients. Kidney Int 2000;58:353-62.
62. Arampatzis CA, Goedhart D, Serruys PW, Saia F, Lemos PA, de Feyter P, *et al.* Fluvastatin reduces the impact of diabetes on long-term outcome after coronary intervention – A lescol intervention prevention study (LIPS) substudy. Am Heart J 2005;149:329-35.
63. Lee CD, Folsom AR, Pankow JS, Brancati FL, Atherosclerosis Risk in Communities (ARIC) Study Investigators. Cardiovascular events in diabetic and nondiabetic adults with or without history of myocardial infarction. Circulation 2004;109:855-60.
64. Grossman E, Messerli FH. Diabetic and hypertensive heart disease. Ann Intern Med 1996;125:304-10.
65. Mitsnefes MM. Cardiovascular disease in children with chronic kidney disease. J Am Soc Nephrol 2012;23:578-85.
66. Aneja A, Tang WH, Bansilal S, Garcia MJ, Farkouh ME. Diabetic cardiomyopathy: Insights into pathogenesis, diagnostic challenges, and therapeutic options. Am J Med 2008;121:748-57.
67. Junttila MJ, Kiviniemi AM, Lepojärvi ES, Tulppo M, Piira OP, Kenttä T, *et al.* Type 2 diabetes and coronary artery disease: Preserved ejection fraction and sudden cardiac death. Heart Rhythm 2018;15:1450-6.
68. Haider AW, Larson MG, Franklin SS, Levy D, Framingham Heart Study. Systolic blood pressure, diastolic blood pressure, and pulse pressure as predictors of risk for congestive heart failure in the Framingham Heart Study. Ann Intern Med 2003;138:10-6.
69. Factor SM, Bhan R, Minase T, Wolinsky H, Sonnenblick EH. Hypertensive-diabetic cardiomyopathy in the rat: An experimental model of human disease. Am J Pathol 1981;102:219-28.
70. Vijay K, Neuen BL, Lerma EV. When Heart Failure Collides with Diabetes and Chronic Kidney Disease: Challenges and Opportunities. Cardiorenal Medicine 2021.
71. Blythe WB, Maddux FW. Hypertension as a causative diagnosis of patients entering end-stage renal disease programs in the United States from 1980 to 1986. Am J Kidney Dis 1991;18:33-7.
72. Rossing P. Diabetic nephropathy: Worldwide epidemic and effects of current treatment on natural history. Curr Diab Rep 2006;6:479-83.
73. Hsu CY, McCulloch CE, Darbinian J, Go AS, Iribarren C. Elevated blood pressure and risk of end-stage renal disease in subjects without baseline kidney disease. Arch Intern Med 2005;165:923-8.
74. Anders HJ, Huber TB, Isermann B, Schiffer M. CKD in diabetes: Diabetic kidney disease versus nondiabetic kidney disease. Nat Rev Nephrol 2018;14:361-77.
75. Ruggenenti P, Perna A, Loriga G, Ganeva M, Ene-Iordache B, Turturro M, *et al.* Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): Multicentre, randomised controlled trial. Lancet 2005;365:939-46.
76. Criqui MH, Aboyans V. Epidemiology of peripheral artery disease. Circ Res 2015;116:1509-26.
77. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: Epidemiology, pathophysiology, and management. JAMA 2002;287:2570-81.
78. Lau JF, Weinberg MD, Olin JW. Peripheral artery disease. Part 1: Clinical evaluation and noninvasive diagnosis. Nat Rev Cardiol 2011;8:405-18.
79. Garimella PS, Hirsch AT. Peripheral artery disease and chronic kidney disease: Clinical synergy to improve outcomes. Adv Chronic Kidney Dis 2014;21:460-71.
80. Schainfeld RM. Management of peripheral arterial disease and intermittent claudication. J Am Board Fam Pract 2001;14:443-50.
81. Beckman JA, Schneider PA, Conte MS. Advances in revascularization for peripheral artery disease: Revascularization in PAD. Circ Res 2021;128:1885-912.
82. Lackland DT, Voeks JH. Metabolic syndrome and hypertension: Regular exercise as part of lifestyle management. Curr Hypertens Rep 2014;16:492.
83. Orchard TJ, Forrest KY, Kuller LH, Becker DJ, Pittsburgh Epidemiology of Diabetes Complications Study. Lipid and blood pressure treatment goals for type 1 diabetes: 10-year incidence data from the Pittsburgh epidemiology of diabetes complications study. Diabetes Care 2001;24:1053-9.
84. Chobanian AV. Time to reassess blood-pressure goals. N Engl J Med 2015;373:2093-5.
85. Chen L, Pei JH, Kuang J, Chen HM, Chen Z, Li ZW, *et al.* Effect of lifestyle intervention in patients with type 2 diabetes: A meta-analysis. Metabolism 2015;64:338-47.
86. Hallal PC, Andersen LB, Bull FC, Guthold R, Haskell W, Ekelund U, *et al.* Global physical activity levels: Surveillance progress, pitfalls, and prospects. Lancet 2012;380:247-57.
87. Alpsoy Ş. Exercise and hypertension. Adv Exp Med Biol 2020;1228:153-67.
88. Detection JN Co., Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure: National Heart, Lung, and Blood Institute, National High Blood Pressure; 1995.
89. Mertens IL, Van Gaal LF. Overweight, obesity, and blood pressure: The effects of modest weight reduction. Obes Res 2000;8:270-8.
90. Shaw JE, Punjabi NM, Naughton MT, Willes L, Bergenstal RM, Cistulli PA, *et al.* The effect of treatment of obstructive sleep apnea on glycemic control in type 2 diabetes. Am J Respir Crit Care Med 2016;194:486-92.
91. Wu D, Xu L, Abbott D, Hau WK, Ren L, Zhang H, *et al.* Analysis of beat-to-beat blood pressure variability response to the cold pressor test in the offspring of hypertensive and normotensive parents.

Hypertens Res 2017;40:581-9.
92. Arauz-Pacheco C, Parrott MA, Raskin P, American Diabetes Association. Treatment of hypertension in adults with diabetes. Diabetes Care 2003;26 Suppl 1:S80-2.
93. Israili ZH. Clinical pharmacokinetics of angiotensin II (AT1) receptor blockers in hypertension. J Hum Hypertens 2000;14 Suppl 1:S73-86.
94. Duarte JD, Cooper-DeHoff RM. Mechanisms for blood pressure lowering and metabolic effects of thiazide and thiazide-like diuretics. Expert Rev Cardiovasc Ther 2010;8:793-802.
95. Mullins ME, Horowitz BZ, Linden DH, Smith GW, Norton RL, Stump J. Life-threatening interaction of mibefradil and beta-blockers with dihydropyridine calcium channel blockers. JAMA 1998;280:157-8.
96. Dickson M, Plauschinat CA. Racial differences in medication compliance and healthcare utilization among hypertensive Medicaid recipients: Fixed-dose versus free-combination treatment. Ethn Dis 2008;18:204-9.
97. Feldman RD, Zou G, Feagan BG, Wong CJ, Vandervoort MK. The simplified treatment intervention to control hypertension (STITCH) trial: A cluster randomized controlled trial of a step-care algorithm using initial fixed dose combination therapy for the management of hypertension. In: Circulation. Philadelphia, PA, USA: Lippincott Williams and Wilkins; 2007.
98. Jamerson K. Avoiding cardiovascular events through combination therapy in patients living with systolic hypertension: Accomplish trial; 2008.
99. American Diabetes Association. 9. Microvascular complications and foot care. Diabetes Care 2015;38 Suppl: S58-66.
100. Weber MA, Schiffrin EL, White WB, Mann S, Lindholm LH, Kenerson JG, *et al.* Clinical practice guidelines for the management of hypertension in the community: A statement by the American Society of Hypertension and the International Society of Hypertension. J Clin Hypertens (Greenwich) 2014;16:14-26.
101. Messerli FH, Bangalore S, Bavishi C, Rimoldi SF. Angiotensin-converting enzyme inhibitors in hypertension: To use or not to use? J Am Coll Cardiol 2018;71:1474-82.
102. Teles F, Peçanha de Miranda Coelho JA, Albino RM, Verçosa Pacheco FC, Rodrigues de Oliveira E, Silveira MA, *et al.* Effectiveness of thiazide and thiazide-like diuretics in advanced chronic kidney disease: A systematic review and meta-analysis. Ren Fail 2023;45:2163903.
103. Lazich I, Bakris GL. Prediction and management of hyperkalemia across the spectrum of chronic kidney disease. Semin Nephrol 2014;34:333-9.
104. Mackenzie IS, Rogers A, Poulter NR, Williams B, Brown MJ, Webb DJ, *et al.* Cardiovascular outcomes in adults with hypertension with evening versus morning dosing of usual antihypertensives in the UK (TIME study): A prospective, randomised, open-label, blinded-endpoint clinical trial. Lancet 2022;400:1417-25.
105. Alexandrou ME, Papagianni A, Tsapas A, Loutradis C, Boutou A, Piperidou A, *et al.* Effects of mineralocorticoid receptor antagonists in proteinuric kidney disease: A systematic review and meta-analysis of randomized controlled trials. J Hypertens 2019;37:2307-24.
106. Tong L, Adler SG. Diabetic kidney disease. Clin J Am Soc Nephrol 2018;13:335-8.
107. Clase CM, Carrero JJ, Ellison DH, Grams ME, Hemmelgarn BR, Jardine MJ, *et al.* Potassium homeostasis and management of dyskalemia in kidney diseases: Conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) controversies conference. Kidney Int 2020;97:42-61.
108. Zhu J, Huang R, Zhang J, Ye W, Zhang J. A prophylactic low-dose aspirin earlier than 12 weeks until delivery should be considered to prevent preeclampsia. Med Hypotheses 2018;121:127-30.
109. Al Khaja KA, Sequeira RP, Alkhaja AK, Damanhori AH. Drug treatment of hypertension in pregnancy: a critical review of adult guideline recommendations. Journal of hypertension 2014;32:454-63.
110. Franklin SS. Hypertension in older people: Part 1. J Clin Hypertens (Greenwich) 2006;8:444-9.
111. Franklin SS. Systolic blood pressure: It's time to take control. Am J Hypertens 2004;17:49S-54S.
112. Manolio TA, Kronmal RA, Burke GL, Poirier V, O'Leary DH, Gardin JM, *et al.* Magnetic resonance abnormalities and cardiovascular disease in older adults. The Cardiovascular Health Study. Stroke 1994;25:318-27.
113. Suhl E, Bonsignore P. Diabetes self-management education for older adults: General principles and practical application. Diabetes Spectr 2006;19:234-40.
114. Cooper-DeHoff RM, Gong Y, Handberg EM, Bavry AA, Denardo SJ, Bakris GL, *et al.* Tight blood pressure control and cardiovascular outcomes among hypertensive patients with diabetes and coronary artery disease. JAMA 2010;304:61-8.
115. Beevers DG, Lee KW, Lip GY. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT): ALL predictable, and no big surprise out of a HAT? J Hum Hypertens 2003;17:367-72.