Hypertension

REVIEW

Hypertension in Diabetes: An Update of Basic Mechanisms and Clinical Disease

Guanghong Jia, James R. Sowers

ABSTRACT: Epidemiological studies have documented that insulin resistance and diabetes not only constitute metabolic abnormalities but also predispose to hypertension, vascular stiffness, and associated cardiovascular disease. Meanwhile, excessive arterial stiffness and impaired vasorelaxation, in turn, contribute to worsening insulin resistance and the development of diabetes. Molecular mechanisms promoting hypertension in diabetes include inappropriate activation of the renin-angiotensin-aldosterone system and sympathetic nervous system, mitochondria dysfunction, excessive oxidative stress, and systemic inflammation. This review highlights recent studies which have uncovered new underlying mechanisms for the increased propensity for the development of hypertension in association with diabetes. These include enhanced activation of epithelial sodium channels, alterations in extracellular vesicles and their microRNAs, abnormal gut microbiota, and increased renal sodium-glucose cotransporter activity, which collectively predispose to hypertension in association with diabetes. This review also covers socioeconomic factors and currently recommended blood pressure targets and related treatment strategies in diabetic patients with hypertension.

Key Words: blood pressure ■ cardiovascular diseases ■ insulin resistance ■ obesity ■ vascular stiffness

Individuals with metabolic disorders, including insulin resistance, diabetes, and cardiometabolic syndrome, have a high prevalence of hypertension, a powerful risk factor for cardiovascular disease (CVD), kidney disease, stroke, and microvascular complications.[1] Not only is hypertension more common in patients with diabetes but also diabetes is also more common in hypertensives than in the general population. Therefore, there is a chicken-egg relationship between hypertension and diabetes (Figure 1).[2] To this point, hypertension occurs in 50% to 80% of patients with type 2 diabetes, who make up over 90% of the diabetic population versus ≈30% of patients with type 1 diabetes who develop hypertension.[3,4] That hypertension is especially common in type 2 diabetes suggests that insulin resistance may play an important role in the pathogenesis of this hypertension. Additionally, a prospective cohort study of 12 550 adults 45 to 64 years old found that type 2 diabetes was almost 2.5 times as likely to develop in patients with hypertension as in those with normal blood pressure.[3–5] Data from the ARIC study (Atherosclerosis Risk in Communities), the CARDIA study (Coronary Artery Risk Development in Young Adults), and the Framingham Heart Study offspring cohort in 10 893 participants showed that hypertension is a risk factor for diabetes and often precedes the development of diabetes.[4] Our understanding of mechanisms by which insulin resistance contributes to the development of hypertension in type 2 diabetes is evolving. This review focuses on basic mechanisms and environmental factors involved in promoting hypertension in diabetes, especially type 2 diabetes. It also discusses approaches for the prevention and contemporary strategies to lessen CVD and renal disease in patients with diabetes with hypertension.

EPIDEMIOLOGY OF INSULIN RESISTANCE AND DIABETES-RELATED HYPERTENSION

There are fundamental differences in type 1 and type 2 diabetes-related hypertension. Although type 1 diabetes with insulin deficiency tends to appear in childhood or

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Nonstandard Abbreviations and Acronyms

Akt	protein kinase B
ARIC	Atherosclerosis Risk in Communities
AT-1R	angiotensin type 1 receptor
CARDIA	Coronary Artery Risk Development in Young Adults
COVID-19	coronavirus disease 2019
CREDENCE	Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation
CVD	cardiovascular disease
DECLARE-TIMI 58	Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58
EMPA-REG OUTCOME	Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients
eNOS	endothelial nitric oxide synthase
ET-1	endothelin-1
EVs	extracellular vesicles
EXSCEL	Exenatide Study of Cardiovascular Event Lowering
GLP-1	glucagon-like peptide 1
miRs	microRNAs
MR	mineralocorticoid receptor
PI3K	phosphatidylinositide 3-kinase
RAAS	renin-angiotensin-aldosterone system
ROS	reactive oxygen species
SGK-1	serum and glucocorticoid regulated kinase 1
SGLT2	sodium-glucose cotransporter 2
SNS	sympathetic nervous system
SUSTAIN-6	Trial to Evaluate Cardiovascular and Other Long-Term Outcomes With Semaglutide in Subjects With Type 2 Diabetes
TLR	Toll-like receptor

adolescence, type 2 diabetes is characterized by insulin resistance and usually takes years to develop. About 80% of type 1 diabetic individuals present with microalbuminuria and have diabetic nephropathy that typically plays a major role in the development of their hypertension.[5] Resistant hypertension is more common in these patients than nondiabetic hypertensive individuals,[6,7] and this resistance is associated with a higher risk of diabetic nephropathy progression.[5]

Patients with the much more common type 2 diabetes often present with coexisting hypertension and diabetes in the absence of clinical renal disease. Epidemiological studies indicate that there is a very high incidence of hypertension, including increases in resistant hypertension and associated CVD in patients with type 2 diabetes.[1] In the Framingham Heart Study, type 2 diabetes was associated with a 2- to 4-fold increased risk of hypertension, peripheral arterial disease, and myocardial infarction.[8] A recent analysis of the Framingham data further showed that the population with hypertension at the time of diabetes diagnosis had higher rates of mortality for all causes and CVD events compared with normotensive persons with diabetes.[9] These data support a strong relationship between coexistent type 2 diabetes and hypertension and associated increases in CVD.

Our understanding of the role of insulin resistance in the development of elevated blood pressures is evolving. A clinic observation in 1966 from 19 patients without diabetes with essential hypertension found that these patients had significantly higher plasma insulin concentrations than a normotensive control group.[10] Approximately 50% of patients with hypertension are insulin resistant, and this defect in insulin metabolic actions increasingly appears to contribute to development of hypertension and associated CVD.[11] The Framingham Offspring Study investigated the relationship between insulin sensitivity and the 4-year incidence of hypertension and blood pressure progression in 1933 nonhypertensive participants. This analysis showed that the association between insulin sensitivity/resistance and hypertension was attenuated but remained statistically significant after adjustment for increases in body mass index.[12] These findings suggest that obesity and insulin resistance are inextricably linked in promotion of hypertension including that in type 2 diabetes.

GENDER, RACE, ENVIRONMENTAL, AND SOCIOECONOMIC FACTORS IMPACTING PERSONS WITH DIABETES AND HYPERTENSION

Gender and race impact the relationship between insulin resistance and diabetes-related hypertension.[13] In nondiabetic individuals the prevalence of hypertension is higher in men as compared to women until the age of 64 years when the gap closes and prevalence in females reaches that of males.[9] Interestingly, women with impaired glucose tolerance and diabetes have a higher incidence of hypertension than men with equivalent impairment in glucose homeostasis.[14] Additionally,

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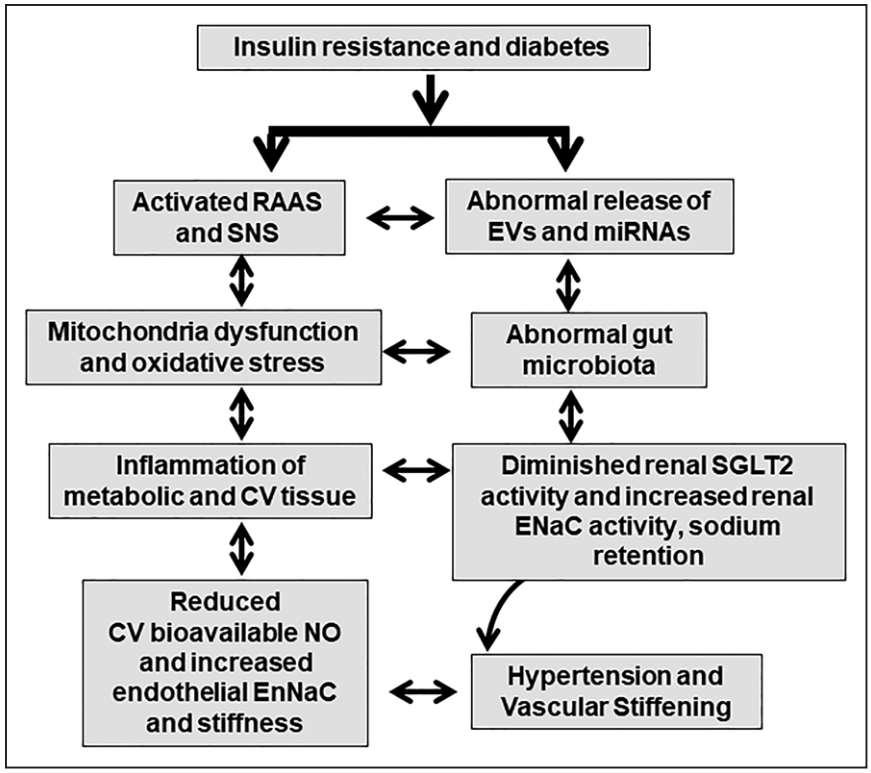

Figure 1. Interaction of insulin resistance, diabetes, and hypertension in metabolic syndrome. Inappropriate activation of the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS), mitochondria dysfunction, oxidative stress, inflammation, abnormal release of extracellular vesicles (EVs) and related microRNAs (miRNAs), as well as dysregulation of gut microbiota, GLP-1 (glucagon-like peptide) and SGLT2 (sodium-glucose cotransporter 2), are involved in insulin resistance and type 2 diabetes-induced vascular stiffness and hypertension. CV indicates cardiovascular; EnNaC, endothelial epithelial sodium channel; and NO, nitric oxide.

the prevalence of hypertension is different within various ethnic groups.[15,16] In Black populations, the incidence of hypertension is higher when compared with White people between the age of 45 and 75 years.[15] Recent data from the Jackson Heart Study further support that greater insulin resistance is associated with a greater risk of incident hypertension and progression of blood pressure elevation among Black participants. These findings suggest that increased insulin resistance may play an important role in the high prevalence of hypertension as well diabetes in Black populations.

Socioeconomic and environmental factors likely have a substantial impact on the development of hypertension in persons with obesity, insulin resistance, and diabetes.[16–18] For example, foods that are traditionally considered healthy and promoted as components of the dietary approach to stop hypertension diet[18] are often unavailable to people living in disadvantaged communities of color due to either lack of access or reasons of affordability.[19] Instead, they become consumers of cheap high salt and high caloric foods, leading to obesity, diabetes, and hypertension.[18,19] Furthermore, lack of safe outdoor spaces discourages exercise, and exposure to environmental air and water pollution also predispose to insulin resistance, diabetes, and hypertension.[19] These social and environmental disparities likely help explain the poorer outcomes with coronavirus disease 2019 (COVID-19) infections that are seen in minorities as well as those with both diabetes and hypertension.[19]

OBESITY CONTRIBUTES TO INSULIN RESISTANCE AND DIABETES-RELATED HYPERTENSION

Studies in primary care settings found that 60% to 76% of overweight or obese patients have hypertension,[20] suggesting that there is a positive relationship between high blood pressure and indices of obesity. The high incidence of overweight/obesity is closely related to overconsumption of inexpensive and palatable high fat and high refined carbohydrate diets.[21] Indeed, a positive association even exists between a progressive increase in body mass index within the normal and overweight range and the risk of hypertension and CVD.[22] Related to this, data from the Framingham Heart Study showed that excess body weight accounted for appropriate 26% of cases of hypertension in men and 28% in women.[23] In addition, obese children were at ≈3-fold higher risk for hypertension than nonobese children.[24] Increased visceral adipose tissue and abdominal subcutaneous adipose tissue are especially associated with obesity-related metabolic and vascular complications.[25] For instance, in a study of 382 diabetic individuals, higher visceral adipose tissue, independent of body mass index, was associated with a higher prevalence of dyslipidemia and increased the risk for hypertension, atherosclerosis, and CVD.[26] Mechanistically, proinflammatory adipokines, including leptin and aldosterone, released from visceral fat may promote systemic and vascular insulin resistance and inflammation, impaired relaxation and vascular stiffness and development of hypertension.[27]

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EXCESSIVE ARTERIAL STIFFNESS IS RELATED TO INSULIN RESISTANCE AND DIABETES-INDUCED HYPERTENSION

While hypertension induces vascular remodeling and can lead to arterial stiffness, insulin resistance and diabetes can also promote arterial stiffening and subsequent hypertension and CVD. An increase in the augmentation index, a measure of arterial stiffness, was independently associated with all-cause mortality and a composite end point of CVD and diabetes-related death in a prospective cohort of patients with type 1 diabetes, suggesting that arterial stiffness predicts both all-cause mortality and the composite end point of CVD and diabetes-related death in patients with type 1 diabetes.[28] Recent data also suggest that the hyperinsulinemia accompanying insulin resistance is an independent risk factor for arterial stiffening.[21] Another study investigated the relationships between arterial stiffness indexes and serum insulin and glucose tolerance measurements in a biracial population of 4701 men and women aged 45 to 64. Patients with borderline abnormal glucose intolerance or type 2 diabetes had stiffer arteries than their counterparts with normal glucose tolerance.[29] It was suggested that interactive effects of elevated glucose and insulin may have a synergistic impact on arterial stiffness and play an important role in the early pathophysiology of hypertension and CVD in patients with type 2 diabetes.[30]

MECHANISMS IN INSULIN RESISTANCE/ DIABETES-INDUCED HYPERTENSION

While diabetic nephropathy is the major driving factor for hypertension in type 1 diabetes, inappropriate activation of the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS), mitochondria dysfunction, oxidative stress, inflammation, abnormal release of extracellular vesicles (EVs), and related microRNAs (miRs), as well as dysregulation of gut microbiota and renal SGLT2 (sodium-glucose cotransporter 2), are emerging as underlying mechanisms in the development of insulin resistance and type 2 diabetes-induced hypertension (Figure 1).

Inappropriate Activation of RAAS and SNS

Activation of the systemic and tissue RAAS in states of insulin resistance, obesity, and associated hyperglycemia plays an important role in the development of hypertension. In vivo and in vitro studies have shown that insulin resistance and hyperglycemia induce systemic RAAS activation in association with increased vascular resistance and arterial pressure.[31] Inhibition of the RAAS with angiotensin-converting enzyme inhibitors, AT-1R (angiotensin type 1 receptor) blockers, and MR (mineralocorticoid receptor) antagonists reduce the incidence of hypertension in patients with diabetes.[32,33] Inappropriate activation of the RAAS observed in insulin resistance and diabetes is likely to impair insulin signaling which contributes to development of hypertension (Figure 2). To this point, angiotensin II and aldosterone increase serine phosphorylation of insulin receptor substrate proteins, leading to decreased activity of insulin downstream signaling pathways in PI3K (phosphatidylinositide 3-kinase) and Akt (protein kinase B), which leads to reduced eNOS (endothelial nitric oxide synthase) activation by insulin and reduced nitric oxide (NO) mediated vasodilation.[1]

The hyperinsulinemia associated with metabolic insulin resistance stimulates production of the vasoconstrictor ET-1 (endothelin-1) via a mitogen-activated protein kinase-dependent signaling pathway (Figure 2). This contributes to vascular insulin resistance, excessive arterial stiffening, and ultimately hypertension.[1] Recently, we found that hyperinsulinemia and aldosterone increase activity of the endothelial epithelial sodium channel which leads to arterial stiffness and hypertension.[21] Related to this, both angiotensin II and aldosterone enhance SGK-1 (serum and glucocorticoid regulated kinase 1) to induce endothelial epithelial sodium channel activation leading to reduction of endothelium eNOS activity, NO production, and the development of arterial stiffening (Figure 2).

Inappropriate activation of the SNS is often a feature of hypertension associated with obesity and insulin resistance. In this regard, overactivity of the SNS induced, in part, by insulin resistance and hyperinsulinemia has been documented in both animal models[34,35] and hypertensive individuals.[36,37] Moreover, the presence of hypertension appears to further elevate the SNS responses to insulin.[37] Increased sympathetic tone induces stimulation of β-adrenergic receptors which promotes insulin resistance through the activation of serine/threonine kinases which blunts insulin metabolic signaling.[38] Elevated blood pressure in response to hyperinsulinemia may also be mediated by changes in baroreflex sensitivity[39] and by central nervous system hypertension promoting effects of hyperinsulinemia.[34]

Role of Mitochondria Dysfunction and Excessive Oxidative Stress

The metabolic actions of insulin are dependent on normal mitochondria function, which plays a key role in energy homeostasis by metabolizing nutrients and producing ATP and cellular energy generation. Insulin resistance and diabetes are associated with mitochondrial dysfunction, characterized by reduced energy production.[40] For instance, defects in mitochondria biogenesis and dynamics in endothelial cells have detrimental consequences on their bioenergetic supply and these abnormalities contribute to endothelial dysfunction and hypertension.[40]

Mitochondrial are also a major source of intracellular reactive oxygen species (ROS), and increased ROS are involved in the pathogenesis of insulin resistance, diabetes, and hypertension.[40] Related to this, almost all vascular

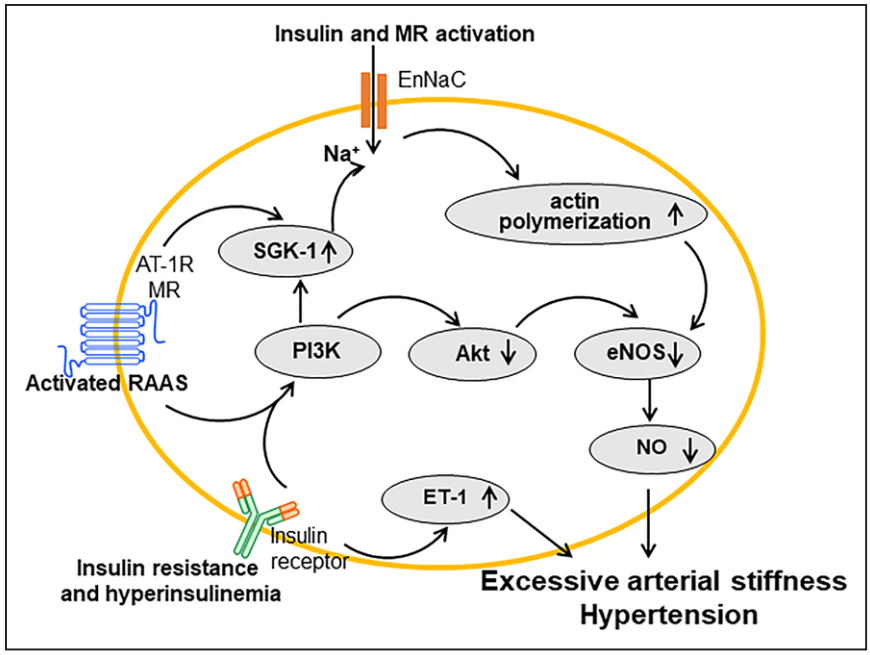

Figure 2. Proposed molecular mechanism in activated renin-angiotensin-aldosterone system (RAAS) and insulin resistance-related hypertension.
Akt indicates protein kinase B; AT-1R, angiotensin type 1 receptor; EnNaC, endothelial epithelial sodium channel; eNOS, endothelial nitric oxide synthase; ET-1, endothelin-1; MR, mineralocorticoid receptor; NO, nitric oxide; PI3K, phosphatidylinositide 3-kinase; and SGK-1, serum and glucocorticoid regulated kinase 1.

cells, including endothelial cells, vascular smooth muscle cells, and adventitial cells, possess the ability to generate ROS. In diabetes excessive ROS production can induce damage to DNA, proteins, and lipids, leading to mitochondrial dysfunction. NADPH oxidases are also an important source of excess ROS production in the vasculature in insulin resistance and hypertension.[41] Insulin resistance and diabetes are associated with increased activation of vascular NADPH oxidases thereby inducing excessive ROS production which causes an imbalance between endothelium-derived relaxing factors and endothelium-derived contractile factors leading to associated increases in vascular tone. Excessive ROS reduce NO production and increase destruction of NO leading to diminished bioavailable NO, which contributes to arterial stiffness and hypertension. Therefore, mitochondrial dysfunction and oxidative stress are likely important instigators of hypertension in states of insulin resistance and diabetes.

Inflammation

Systemic and cardiovascular inflammation are important contributors to the development of insulin resistance, diabetes, and hypertension. For instance, enhanced TLR (Toll-like receptor)-mediated proinflammatory signaling induces activation of nuclear factor kappa B and c-Jun N-terminal kinase that promote release of inflammatory cytokines, including tumor necrosis factor alpha, interleukin-6, vascular cell adhesion molecular 1, and monocyte chemoattractant protein-1.[1] These proinflammatory cytokines can impair insulin metabolic signaling and reduce insulin-mediated NO production, leading to arterial stiffness and hypertension. Furthermore, systemic and tissue inflammation are strongly related to visceral obesity. Typically, adipose tissue is composed of a variety of immune cells, such as macrophages, dendritic cells, B cells, T lymphocytes, mast cells, and neutrophils.[42] To this point, macrophages are an important driver of adipose tissue inflammation and associated metabolic disorders and hypertension.

Perivascular adipose tissue, a special local deposit of adipose tissue surrounding blood vessels, provides mechanical protection and modulates blood vessel tone.[42] In the setting of obesity, insulin resistance, and type 2 diabetes, increased NADPH oxidase-derived ROS and proinflammatory adipokines from perivascular adipose tissue contribute to vascular insulin resistance and impaired relaxation.[42] Data from the Framingham Offspring and Third Generation cohorts support the notion that altered perivascular adipose tissue volume is linked with higher thoracic and abdominal aortic dimensions and increased stiffness even after adjusting for sex, age, and CVD risk factors, including body mass index and visceral adipose tissue volume.[43]

Abnormal Release of EVs and Their miRs Contribute to Insulin Resistance, Diabetes, and Hypertension

There is emerging evidence that diabetes and hypertension are associated with abnormal release of EVs, which normally mediate cell-to-cell communications.[44] For instance, the patients with hypertension often have increased circulating endothelial and platelet EVs,[45,46] as well as urinary endothelial microparticles.[47] Moreover, the intraperitoneal of plasma exosomes from spontaneously hypertensive rats induced an increases of systolic blood pressure in normotensive Wistar-Kyoto rats,[48] suggesting that abnormal circulating and urinary EVs may be biomarkers associated with the pathogenesis and progression of hypertension. Importantly, EVs contain various molecular constituents, including proteins, mRNA, and

miR, which can be transferred from one cell to another via membrane vesicle trafficking, thereby playing a role in the pathogenesis of hypertension and related CVD.[46] To this point, the 3 subtypes of EVs are exosomes, microvesicles, and apoptotic bodies according to their different cellular origins. Recent data suggest that exosomal miRs are involved in activation of the RAAS, oxidative stress, and inflammation, and these abnormalities may induce vascular dysfunction and hypertension.[49,50] Indeed, increased levels of miR-223, miR-320, miR-501, miR504, and miR1 and decreased levels of miR-16, miR-133, miR-492, and miR-373 have been related to insulin resistance and diabetes-related hypertension.[51] These data suggest that exosomal miRs are important biomarkers in patients with insulin resistance, diabetes, and hypertension.

Gut Microbiota

Emerging evidence indicates that gut microbiota changes contribute to insulin resistance, diabetes, hypertension, and CVD. In this regard, the gut flora has about 100 trillion micro-organism species, and these bacteria modulate normal metabolic activities and physiological functions. For instance, the cecal bacteria from the phylum *Bacteroidetes* that are regarded as good bacteria are reduced in obesity, and this reduction is accompanied by a proportional increase in bad bacteria with the phylum *Firmicutes*.[52] These deleterious changes in gut bacteria have also been observed in insulin resistant *ob/ob*[53] and *db/db*[54] *type 2* diabetic mice. A recent study provides evidence that gut microbiota may have a causal role in insulin resistance and type 2 diabetes.[55] In that study, mice receiving a transplant from an obese twin donor developed increased adiposity compared with those receiving transplants from lean twin donors. Moreover, cohousing mice harboring an obese twin's microbiota with mice containing the lean co-twin's microbiota prevented the development of increased body mass and obesity-associated metabolic phenotypes in obese cage mates.[55] Furthermore, oral administration of good bacteria improves the gut barrier dysfunction and metabolic disorders in obese and type 2 diabetic mice,[56] suggesting that transmissibility of intestinal microbes and the metabolic phenotype are closely linked and that it is possible to impact obesity, insulin resistance, and associated hypertension by modulating the composition of the microbiota. To this point, one study showed that gut microbiota can produce norepinephrine, thereby promoting vascular constriction and hypertension in the insulin resistant state.[57] Moreover, *Enterococcus faecalis* directly contributes to hypertension and renal injury by interfering lipid metabolism.[58] Thus, alterations of gut microbiota provide a new mechanism in exploring insulin resistance and diabetes-induced hypertension.

Contribution of SGLT2 to Insulin Resistance, Diabetes, and Hypertension

Glucose homeostasis is impaired in individuals with insulin resistant associated diabetes, in part, as a consequence of an increased capacity to absorb renal glucose and via proximal tubule SGLT2, which is responsible for proximal tubule reabsorption of about 90% of filtered glucose.[59] The glucose reabsorption in the kidney normally has a maximal threshold corresponding to glucose plasma levels. However, individuals with insulin resistance and type 2 diabetes have a higher threshold due to the upregulation of SGLT2 that increases proximal tubule glucose and sodium absorption, thereby contributing to hypertension and related CVD.[59] Recent large, randomized, placebo-controlled clinical trials have shown that treatment with SGLT2 inhibitors significantly reduces hypertension and CVD events and prevent the progression of renal dysfunction in individuals with diabetes.[60]

RECENT THERAPY IN PATIENTS WITH DIABETES AND HYPERTENSION

The ADA 2020 Clinical Practice Guidelines suggest that nonpharmacological measures, such as weight loss, regular physical activity, and limitation of fat and total energy intake, should always be part of any blood pressure-lowering treatment as it is the cornerstone of preventive therapy in patients with diabetes with hypertension.[61] RAAS blocker may slow progression to kidney failure and CVD, and thus angiotensin II–converting enzyme inhibitors and angiotensin II receptor blockers are appropriate for initial therapy for managing hypertension in patients with diabetes. Many patients with diabetes with hypertension manifest a resistant form of hypertension requiring the addition of MR antagonists to their combination therapy.[62,63] This includes nonsteroidal MR antagonists (ie, Fineronone) which has recently been shown to reduce CVD events as well as reducing advancement of renal disease in patients with diabetes and kidney disease.[64,65]

In recent years, newer antihyperglycemic medications, such as GLP-1 (glucagon-like peptide 1) agonists and SGLT2 inhibitors, have been found to lower blood pressure as well improving glucose metabolism. For instance, exenatide, an analog of GLP-1, was evaluated in the EXSCEL trial (Exenatide Study of Cardiovascular Event Lowering) clinical trial in patients with diabetes for 5 years, and exenatide reduced systolic blood pressure and low-density lipoprotein cholesterol.[66] Consistent with these data, Semaglutide, injected once-weekly at 2 doses (0.5 or 1.0 mg) for 104 weeks in the SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-Term Outcomes With Semaglutide in Subjects With Type 2 Diabetes), reduced blood pressure, nonfatal myocardial infarction, and stroke in patients with type 2 diabetes at high CVD risk.[67]

SGLT2 inhibition induces glycosuria and promotes natriuresis resulting in reductions in blood pressure. The EMPA-REG OUTCOME study (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) showed that empagliflozin reduced blood pressure and major adverse CVD events, death, and hospitalization for heart failure.[68] In the DECLARE-TIMI 58 trial (Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58) in patients with type 2 diabetes and CVD, dapagliflozin treatment reduced blood pressure but failed to reduce major adverse CVD events.[69] Recent evidence from the CREDENCE trial (Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation) further found that canagliflozin reduced blood pressure and slowed diabetic nephropathy progression.[60] Therefore, both incretin-based and SGLT2 inhibitor therapy are beneficial in patients with diabetes with hypertension.

SUMMARY AND FUTURE PERSPECTIVES

Insulin resistance and diabetes increase the prevalence of hypertension. The underlying molecular and cellular mechanisms include inappropriate activation of the RAAS and SNS, enhanced renal and endothelial sodium channel activation, mitochondria dysfunction, oxidative stress, inflammation, abnormal exosomal miRs, abnormal gut microbiota, as well as increased renal SGLT2 activity. Treatment strategies in patients with hypertension with diabetes include lifestyle interventions and the use of with pharmacological therapy, including RAAS blockade. Meanwhile, these patients may also benefit from treatment with GLP-1 agonists and SGLT2 inhibitors. However, there is a need for randomized and multiple-center clinical trials to better define the role of these medications in patients with diabetes with hypertension. Further research should be directed improving our understanding the pathophysiological role of insulin resistance, diabetes, and related metabolic abnormalities in the pathogenesis of hypertension.

ARTICLE INFORMATION

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Disclosures

None.

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