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Treating hypertension while protecting the vulnerable islet in the cardiometabolic syndrome

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Abstract

Hypertension, a multifactorial-polygenic disease, interacts with multiple environmental stressors and results in functional and structural changes in numerous end organs, including the cardiovascular system. This can result in coronary heart disease, stroke, peripheral vascular disease, congestive heart failure, end-stage renal disease, insulin resistance, and damage to the pancreatic islet. Hypertension is the most important modifiable risk factor for major health problems encountered in clinical practice. Whereas hypertension was once thought to be a medical condition based on discrete blood pressure readings, a new concept has emerged defining hypertension as part of a complex and progressive metabolic and cardiovascular disease, an important part of a cardiometabolic syndrome. The central role of insulin resistance, oxidative stress, endothelial dysfunction, metabolic signaling defects within tissues, and the role of enhanced tissue renin-angiotensin-aldosterone system activity as it relates to hypertension and type 2 diabetes mellitus is emphasized. Additionally, this review focuses on the effect of hypertension on functional and structural changes associated with the vulnerable pancreatic islet. Various classes of antihypertensive drugs are reviewed, especially their roles in delaying or preventing damage to the vulnerable pancreatic islet, and thus delaying the development of type 2 diabetes mellitus.

Keywords

antihypertensive treatment; islet amyloid; insulin resistance; renin inhibitor; reactive oxygen species; oxidative stress

INTRODUCTION

Primary hypertension has complex causes and is considered a multifactorial-polygenic disease that interacts with multiple environmental conditions and stressors, with numerous diverse harmful effects (Table 1 and Figure 1) [1]. It accounts for approximately 80% to 90% of all

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patients with hypertension and has no single identifiable cause, whereas specific causes of secondary hypertension include various renal (including chronic kidney disease) and endocrine disorders. Another emerging cause of secondary hypertension is obstructive sleep apnea, which may be the most frequent of this latter subset of conditions, partially due to the obesity epidemic (Table 1). Obesity and aging are powerful factors contributing to an increased prevalence of hypertension; however, excessive activity of the renin-angiotensin aldosterone system (RAAS), the sympathetic nervous system (SNS), endothelial dysfunction, oxidative-redox stress, and inflammation act synergistically with obesity, insulin resistance (IR), and aging.

Hypertension and type 2 diabetes mellitus (T2DM) are common comorbidities that are associated with substantially increased cardiovascular disease (CVD) morbidity and mortality and chronic kidney disease (CKD) [2,3]. Of patients with newly diagnosed T2DM, more than half have coexisting hypertension, and approximately 50% of patients with hypertension develop T2DM over a 10- to 15-year period [4]. Hypertension is linked to other CVD risk factors, including IR and compensatory hyperinsulinemia-hyperamylinemia, which is associated with multiple metabolic toxicities [5]. A common pathologic abnormality associated with these comorbidities is enhanced oxidative stress and resultant increased reactive oxygen species (ROS), which results in detrimental cellular and extracellular matrix (ECM) remodeling in end organs, including the endocrine pancreas [6].

An important consideration for the clinician is mounting evidence that the various classes of antihypertensive drugs have different metabolic and structural effects, which may ultimately encourage, delay, or prevent the onset of the development of T2DM [7,8]. Additionally, nonpharmacologic interventions represent an important complementary and essential approach to T2DM prevention [1].

This review discusses the pathophysiologic characteristics of hypertension from metabolic and structural perspectives in the islet, summarizes the effects of major classes of antihypertensive agents on the development of T2DM, and describes pharmacologic and nonpharmacologic approaches to reduce the risk for new-onset T2DM in individuals with hypertension.

HYPERTENSION: CLUSTERING OF CARDIOMETABOLIC-CARDIOVASCULAR RISK FACTORS

Numerous metabolic abnormalities contribute to and result from hypertension. A characteristic feature of the cardiometabolic syndrome (CMS), T2DM, and hypertension is diminished sensitivity of tissues to insulin, including hepatocytes, adipocytes, endothelium, vascular smooth muscle cells (Figure 2) [4,5,9] and, specifically, skeletal muscle (Figure 3) [5]. A brief overview of these abnormalities, summarized in Figure 3 [5], has been the focus of recent reviews [4,5,7,9]. An activated tissue RAAS and associated overproduction of ROS contribute to IR. Skeletal muscle resistance to the metabolic actions of insulin is associated with **signaling defects**: glucose transporter-4 translocation, phosphatidylinositol 3 (PI3) and its downstream protein kinase B (Akt)-mitogen-activated protein (MAP) kinase signaling pathway, and diminished production of endothelial-derived nitric oxide (NO); **skeletal muscle changes**: increase in type II muscle fibers, increased lipid deposition, decreased sarcolemma mitochondrial numbers, and decreased lipoprotein lipase activity; **ROS generation**: endothelial dysfunction (endothelial NO synthase [eNOS] uncoupling), tissue remodeling, endothelial-tissue uncoupling, and decreased insulin stimulation of PI3 kinase (PI3K) as well as development of hepatic steatosis and pancreatic islet β -cell loss; **hyperinsulinemia-hyperamylinemia**: resorption, excretion, and transport defects, SNS activation, RAAS activation-angiotensin II (Ang II) excess, and oxidative stress; **Ang II/aldosterone actions**: interference with insulin signaling, decreased insulin secretion, and triglyceride accumulation in skeletal muscle, liver, and pancreas; and **pancreatic functional and structural**

abnormalities: altered islet perfusion by increased RAAS activation, formation and deposition of pancreatic islet amyloid, and islet fibrosis.

THE CMS and HYPERTENSION

Hypertension is a major component of the CMS, a condition known by several names, including the metabolic syndrome and syndrome X [6]. Important contributors to the CMS, a constellation of risk factors affecting approximately 50 million people in the United States [10], are obesity, genetics, and a sedentary lifestyle [4]. In addition to hypertension, other components include IR (with compensatory hyperinsulinemia-hyperamylinemia), abdominal obesity, atherogenic dyslipidemia (increased triglyceride levels, small low-density lipoprotein [LDL] particles, low levels of high-density lipoprotein [HDL] cholesterol), microalbuminuria/reduced renal function, fibrinolytic and inflammatory abnormalities, endothelial dysfunction, oxidative-redox stress, hepatic steatosis, and hypercoagulability [10,11]. According to the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, when 3 or more readily measured risk determinants are present, a diagnosis of the CMS should be made (Table 2) [10]. This constellation of risk factors is associated with an increased risk for CVD, including stroke, T2DM, CKD, polycystic ovary syndrome, and nonalcoholic fatty liver disease. These conditions are associated with end-organ structural remodeling of the arterial vasculature, heart, islet, kidney, ovary, and liver.

INSULIN RESISTANCE

IR occurs when the ability of insulin to stimulate glucose uptake and disposal by skeletal muscle is impaired [12]. A strong relationship between IR and hypertension has been identified [5, 13]. Defective insulin signaling occurs in patients with hypertension, and drug-naïve patients with hypertension have greater fasting and postprandial insulin levels than age- and sex-matched normotensive individuals regardless of weight (Figure 3) [5,12–15]. However, there is no link between increased plasma insulin levels and secondary hypertension [12,13]. IR and hypertension coexist in rats with genetic IR [13,16,17], suggesting that genetic predisposition contributes to both IR and hypertension [13]. The presence of altered glucose metabolism in normotensive children of parents with hypertension supports this hypothesis [12,13,15]. In addition, some persons with coexisting IR and hypertension have specific metabolic genetic defects [18,19]. There is an increasing body of evidence that increased tissue activation of the RAAS and associated oxidative stress impairs insulin signaling in skeletal muscle and other tissues (Figure 3) [5].

Compensatory Hyperinsulinemia

Normally insulin exerts vasodilatory effects, in part, through activation of endothelial-derived vascular relaxation. IR results in decreased endothelial and vascular smooth muscle metabolic responses to insulin: this results in diminished vasorelaxation responses to insulin and insulin-like growth factor [4,5,20].

Hyperinsulinemia is intimately linked to IR and hypertension; however, an intact β cell–insulin compensatory secretory axis to IR plays a key role in vasodilation, as well as in glucose transport and homeostasis, because insulin normally has vasodilatory properties [4,5,20]. Although the compensatory hyperinsulinemia that results from IR temporarily delays the development of diabetes, as demonstrated in rat studies, it has other effects that may ultimately increase blood pressure (BP) [4]. Hyperinsulinemia promotes reabsorption of sodium and water in proximal renal tubules, leading to volume expansion and BP increase [4], which may amplify SNS activity [12] and may activate the RAAS [21,22]. However, there is no direct experimental evidence suggesting that corrections in these defects of insulin action will decrease BP; this

remains a challenge for the clinician/researcher to prove “cause and effect”. Hyperinsulinemia may also increase the number of angiotensin type 1 (AT₁) receptors [4,23], stimulate vascular smooth muscle cell proliferation and migration, contribute to oxidative stress and increased inflammation [5,7], and promote vascular ECM remodeling [4]. Overwhelming experimental data suggest that the primary pathologic contributors to hypertension are related to decreased vascular sensitivity to the metabolic signaling mediated vasodilatory responses to insulin [5].

Changes in Skeletal Muscle Tissue

In persons with hypertension, IR contributes to altered insulin action in skeletal muscle tissue, which comprises 40% of body mass and is the main site of insulin-stimulated glucose utilization [7,24]. Skeletal muscle mass and insulin sensitivity decrease in older persons and those with sedentary lifestyles, and consequently, aging and inactivity also increase the risk for IR and hypertension [7,25]. Aging and sedentary lifestyle lead to a reduction in oxidative slow twitch, insulin-sensitive muscle fibers. Further, with hypertension there is vasoconstriction and rarefaction of the microcirculatory vasculature supplying the skeletal muscle tissue and these changes lead to the reduced delivery of insulin and glucose to the skeletal muscle tissue. Finally, in hypertension there is often decreased insulin metabolic signaling leading to diminished insulin sensitivity.[5]

IR in skeletal muscle is associated with increased intracellular lipid and fat between muscle fibers [25]. An accumulation of triglycerides in muscle also occurs as a result of the ability of Ang II to increase the lipid storage capacity of adipose and skeletal tissue [26]. Increased RAAS activity decreases the differentiation of adipocytes, which are insulin sensitive and take up lipids, while increasing central, less differentiated, adipose tissue [27–29]. This decrease in mature peripheral adipocytes results in more ectopic lipid accumulation in skeletal muscle, liver, and myocardial tissue. There is also increasing evidence that deficiencies in sarcolemmal mitochondrial function and decreased numbers of mitochondria contribute to insulin resistance in the CMS and T2DM [30].

Lipoprotein lipase, a secretory enzyme highly expressed by skeletal muscle, may play an important role in the link between hypertension and skeletal muscle IR [7]. Mutations of the lipoprotein lipase gene account for 52% to 73% of the total interindividual variation in systolic BP [31]. Increased lipoprotein lipase activity improves insulin sensitivity in transgenic rabbits [32]. Microvascular lipoprotein lipase enzyme activity in rat skeletal muscle decreases by about 50% during aging [33], by 80% in type II fibers compared with type I fibers [34], and by about 90% during sustained inactivity [35]. Thus, genetic or acquired deficiencies in lipoprotein lipase activity appear to contribute to the development of both IR and hypertension.

The link between impaired glucose tolerance, hypertension, and CVD may be stronger than the link found between fasting hyperinsulinemia, hypertension, and CVD [36]. These adverse effects of postprandial elevations in glucose are likely mediated, in part, by hyperglycemia-induced endothelial dysfunction resulting from eNOS uncoupling. In concert with this notion, the Diabetes Prevention Program study found a significant (but only modest) relation between fasting insulin and the prevalence of hypertension, systolic BP, and diastolic BP in 3,819 patients that had impaired glucose tolerance [37].

REACTIVE OXYGEN SPECIES

Patients with CMS and hypertension experience numerous metabolic abnormalities, which can be summarized with the acronym A-FLIGHT-U (Table 3) [4]. These abnormalities are marked by increased tissue levels of ROS, leading to endothelial dysfunction and harmful tissue ECM remodeling [4,6]. Increased ambient levels of ROS are known as oxidative stress and can result from increased generation or reduced removal of these charged particles. In the CMS, both

abnormalities appear to contribute to excess oxidative stress. In addition to providing an important source of ROS, a free-fatty acid increase specifically promotes IR in skeletal muscle and cardiovascular, renal, and hepatic tissue [4,6].

The increase in vascular ROS may be associated with uncoupling of the eNOS enzyme and allows the endothelium to become a net producer of even more ROS, rather than to be a net producer of the protective (local antioxidant and anti-inflammatory) gaseous NO molecule. In addition to eNOS enzyme uncoupling, there is concomitant remodeling at the endothelial tissue site, resulting in structural endothelial tissue uncoupling and dysfunction because of pericapillary ECM fibrosis in many of the end organs affected by the CMS and T2DM [38, 39].

Excess glucose (glucotoxicity) is strongly associated with the impaired glucose tolerance and T2DM of the CMS and is a major contributor to islet redox stress (Figure 4) [6]. Glucose auto-oxidation, glycooxidation, A-FLIGHT-U metabolic abnormalities, the polyol-sorbitol pathway, and a decreased/depleted antioxidant network enzyme system within the β cell and pancreatic islet contribute to islet redox stress with resultant β -cell dysfunction and apoptosis [6]. Additionally, glucose is capable of scavenging endothelial NO, which contributes to the uncoupling of the eNOS enzyme. Over time, both glucotoxicity and lipotoxicity-FFA contribute to the progressive deterioration in glucose homeostasis and β -cell dysfunction. Seldom does either of the toxicities exist alone in the postprandial clinical setting of IR and the CMS and T2DM. Both contribute to the excess islet redox stress associated with the other A-FLIGHT-U abnormalities, having multiplicative adverse effects within the islet on β -cell function [40].

Hypertension is also associated with the production of ROS. Recently, we demonstrated that enhanced vascular membranous nicotinamide adenine dinucleotide phosphate (NAD[P]H) oxidase enzyme and its various subunits (including RAC-1, RhoA, and GP^{phox} 91-67-47-22) are intricately involved with the development of hypertension in conditions of activated vascular RAAS [6]. This results in the excess production of ROS and oxidative stress in a transgenic hypertensive rodent model that also demonstrates IR in the kidney, heart, and islets [6]. Thus, there is considerable evidence that RAAS-induced generation of ROS contributes to both the development of hypertension, impaired insulin secretion and IR. In summary, ROS begets ROS via a vicious positive feedback cycle and this plays a key role in the pathogenesis of CMS and T2DM (Figure 3) [5].

SIGNALING DEFECTS

Persons with hypertension may be at greater risk for the development of T2DM than normotensive individuals because of an impaired ability for insulin to promote relaxation in vascular tissue and glucose transport in skeletal muscle tissue [4]. Excess Ang II and aldosterone may inhibit insulin action in these tissues, partly by interfering with insulin signaling through the PI3K/Akt signaling pathway [5]. The effects of Ang II and aldosterone are partially mediated through increased generation of ROS and activation of low-molecular-weight G proteins, such as RhoA and Rac [5]. Enhanced ROS generation and RhoA activation inhibit actions mediated by PI3K/Akt signaling, resulting in decreased endothelial cell production of NO, increased myosin light chain activation (calcium sensitization) with resulting vasoconstriction, and decreased skeletal muscle glucose transport [4,5]. This mechanism promotes vascular and ECM remodeling due to impairment of the metabolic PI3K/Akt signaling pathway and promotion of MAP/Jak kinase growth and remodeling pathway [4], a process termed the PI3/Akt–MAP/Jak kinase shunt (Figure 3)[4].

RAAS EFFECTS ON THE PANCREAS

In persons with IR, development of diabetes depends on the progressive loss of β cells and the insulin-secreting capacity of the pancreatic islets [7]. The pancreas, like many organs and tissues, has a local RAAS [41–43] that appears to affect pancreatic function primarily by altering islet perfusion [44]. Ang II causes vasoconstriction in the endocrine pancreas of animals [41], contributes to the delay in first-phase insulin release in response to glucose in perfused preparations in rats [45], and blunts insulin secretion in healthy persons [46]. Additionally, activation of a local RAAS results in ECM fibrosis and further islet cell destruction related to excess ROS [41–43].

STRUCTURAL REMODELING OF THE ENDOCRINE PANCREAS

The human islet pancreas in T2DM is characterized by the histologic findings of islet amyloid, intra- and peri-islet fibrosis, islet adipogenesis, arteriosclerosis, and atherosclerosis [47]. Furthermore, a recent human case report demonstrated a previously unreported finding that the insulo-acinar-portal islet efferent vessels, which carry pancreatic islet contents (including insulin) to the liver, were involved with both peri-islet fibrosis and peri-islet amyloid deposition. This peri-islet vasculopathy due to fibrosis and amyloid deposition could contribute to the impaired first-phase insulin secretion and impaired glucose intolerance seen early in the development of T2DM in humans [48].

Intra- and peri-islet fibrosis is also a prevalent finding in the obese IR T2DM Zucker rat model, and treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) each may attenuate the development of islet fibrosis and associated impaired glucose tolerance [49]. In the transgenic Ren2 model of IR and hypertension, we recently identified with transmission electron microscopy very early peri-islet fibrosis with banded collagen deposition and pericyte-pancreatic stellate cell proliferation, migration, hypertrophy, and activation [50]. Additionally, in the novel human islet-amyloid polypeptide transgenic rat model of T2DM, we were able to identify the concurrent finding of not only intra-islet amyloid, but also very early banded collagen representing intra- and peri-islet fibrosis [51]. These animal models may help us better understand the role of activated islet RAAS and oxidative stress and how these are related to structural remodeling within the islet and the peri-islet or islet exocrine interface of the pancreas in models as well as humans that we now term “isletopathy” [52,53].

Amylin and Pancreatic Remodeling

A hallmark of T2DM is remodeling of the endocrine pancreas due to the deposition of amylin-derived islet amyloid within the islet [54]. Islet amyloid is present in up to 96% of autopsied patients with T2DM, and amylin is the monomeric substrate responsible for the polymerization, fibril formation, and amyloid deposition [55]. Amylin levels increase in persons with obesity and IR, those with impaired glucose tolerance, and persons with early T2DM [54].

The Physiologic Role of Amylin

Amylin, or islet amyloid polypeptide, is a 37-amino-acid polypeptide (Figure 5) [54–56]. Like insulin, amylin (the second β -cell-derived hormone) is synthesized and secreted by islet β cells in response to glucose or nutrient stimuli and contributes to the maintenance of glucose homeostasis [4,54]. Amylin is a potent inhibitor of gastric emptying and helps control carbohydrate delivery from the small intestine [57]. It inhibits hepatic production and release of glucose after a meal [54] and inhibits glucagon and somatostatin secretion, slowing the secretion of insulin [4]. Amylin contributes to the perception of satiety and may have a site of action within the central nervous system [58]. It has binding sites within the renal cortex [54,

59], where it promotes renin secretion [59,60]. Amylin is cosynthesized, copackaged, and cosecreted in the insulin secretory granule of the β cell and parallels insulin secretion [4].

Formation and Deposition of Islet Amyloid

Unlike insulin, human amylin is amyloidogenic [4]. Amylin-derived islet amyloid formation and deposition occur in islets in individuals with the CMS, IR, prediabetes, and early T2DM [54]. In addition, islet amyloid and its soluble toxic oligomers (small polymers of islet amyloid polypeptide) contribute to β -cell apoptosis in T2DM (Figure 6) [55]. The oligomers of islet amyloid are responsible for β -cell apoptosis, and not the mature insoluble islet amyloid within the pancreatic islets [61]. Amylin, like other proteins, must fold properly into 3-dimensional structures to carry out its proper functions [55]. In IR, amylin may become unfolded and subsequently misfolded due to endoplasmic reticulum stress and overtax the protective refolding chaperone proteins, giving rise to islet amyloid (Figure 7A–C) [55]. Islet amyloid creates a diffusion barrier, as well as a secretory and absorptive defect, within the islet, and structurally, islet amyloid appears to interfere with trafficking and docking of the insulin secretory granule to the endothelium (Figure 7D) [4,55,61].

Humans normally have approximately 1 million to 1.5 million islets, and under normal conditions, there is a stable combination of replicative, senescent, and apoptotic β cells [54]. In persons with IR, glucose homeostasis continues until about half the β cells are lost or dysfunctional, and additional decrease leads to impaired glucose tolerance and, eventually, overt T2DM [54]. The progressive deposition of amylin-derived islet amyloid may be responsible for the progressive nature of T2DM.

Hyperamylinemia can activate the RAAS independently of and synergistically with hyperinsulinemia and hyperproinsulinemia, further strengthening the links between hypertension, IR, and T2DM [4]. Hyperamylinemia also predicts the future development of hypertension in normotensive children of parents with hypertension and may become a useful marker for hypertension in the future [62]. In summary, hyperamylinemia and amylin-derived islet amyloid seem to play an important role, along with IR and β -cell dysfunction, in the development and progression of T2DM.

T2DM RISK AND SELECTION OF ANTIHYPERTENSIVE THERAPY

Clinical outcome studies have shown differences in the development of T2DM with various classes of antihypertensive agents, including thiazide diuretics, β -blockers, calcium channel blockers (CCBs), α -adrenergic blockers, and RAAS inhibitors. Outcome data related to new-onset T2DM, possible mechanisms by which different classes of agents promote or prevent T2DM, and treatment recommendations are summarized in Table 4, Table 5, and Table 6. Table 4 presents the results of major outcome trials [7,63–76]; Table 5 summarizes actions of the different classes of antihypertensive agents that may contribute to their effects on T2DM; Table 6 lists treatment recommendations supported by individual study results [7,77–85]. A network meta-analysis (which accounts for both direct and indirect comparisons between classes of drugs) of 22 randomized clinical trials, involving 143,153 participants, was conducted to estimate the relative odds of developing T2DM with an initial class of antihypertensive drug [86]. With diuretic therapy as the referent (odds ratio 1.0), the odds ratio of developing T2DM was lowest with ARB or ACE inhibitor therapy (0.57 and 0.67, respectively), followed by CCB (0.75), placebo (0.77) and β -blocker therapy (0.90). This robust meta-analysis provides evidence that ARB and ACE-inhibitor therapy are the optimal classes of antihypertensive therapy to potentially avoid the development of T2DM.

THIAZIDE DIURETICS

Clinical Data

Even though there is an abundance of evidence supporting the beneficial effects of thiazide diuretics on cardiovascular outcomes, these agents may accelerate the onset of T2DM in patients with hypertension (particularly when used in high doses) [77,87–93], although older studies often had method limitations [93]. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attacks Trial (ALLHAT) [70], the odds ratio of developing of developing T2DM at 2 years was significantly lower for lisinopril and amlodipine (0.55, $P < .001$ and 0.73, $P = .006$; respectively) than for chlorthalidone [94]. Although the odds ratios remained lower for lisinopril and amlodipine than for chlorthalidone at 4 and 6 years, these differences were no longer significant. A recent analysis of 3 large cohorts, participants in the Nurses' Health Study (NHS) I, the NHS II, and the Health Professionals Follow-Up Study (HPFS), found that the multivariate relative risks of incident diabetes in participants using a thiazide diuretic compared with participants not using a thiazide diuretic were 1.20 (95% confidence interval [CI], 1.04–1.40) in older women, 1.51 (95% CI, 1.15–1.98) in younger women, and 1.31 (95% CI, 1.07–1.60) in men [78]. A meta-analysis of data from nearly 77,000 participants in major outcome trials found that patients receiving regimens including a thiazide diuretic and a β -blocker were at greater risk for developing diabetes than those receiving other regimens (risk ratio [RR] for alternative therapy, 0.81; 95% CI, 0.77–0.86) [95]. It is important to note that even when low-dose diuretics (hydrochlorothiazide, 12.5 mg) are added to RAAS-blocking agents (losartan) in hypertensive patients with metabolic syndrome, normal renal function, and impaired glucose tolerance, there may be a worsening of glycemic control [96]. Despite these findings, the development of diabetes has not been associated with cardiovascular outcomes [90,94]. The landmark Systolic Hypertension in the Elderly Program (SHEP) trial found that cardiovascular mortality did not increase in patients who developed diabetes or with preexisting diabetes who were treated with low-dose thiazide diuretics compared with placebo [90]. In addition, the ALLHAT trial also concluded that no direct evidence exists between diuretic-induced diabetes and clinical events [94].

Mechanisms

Thiazide diuretics worsen glycemic control in a dose-dependent fashion by decreasing insulin secretion and peripheral insulin sensitivity [77,87–89,97]. Hypokalemia (and perhaps hypomagnesemia) may play an important role in thiazide-induced glucose intolerance [77, 97–99], and deterioration in glucose metabolism occurs even with minimal decreases in serum potassium levels [90]. Patients receiving thiazide diuretics (and β -blockers) have significantly higher plasma fibrinogen levels and lower HDL levels than those receiving CCBs, ACE inhibitors, or ARBs [70,100].

A potentially important benefit of thiazide diuretics is their antioxidant effects. In a study that analyzed the level of antioxidative protection afforded by the ferric-reducing ability of plasma, patients treated with thiazide diuretics had better protection, shown by higher ferric-reducing ability of plasma levels, than those treated with β -blockers or ACE inhibitors ($P < .01$) [101].

Place in Therapy

Thiazide diuretics have consistently shown an ability to prevent major cardiovascular events. However in ALLHAT, there was no significant difference between amlodipine and chlorthalidone (RR, 0.98; 95% CI, 0.90–1.07) or lisinopril and chlorthalidone (RR, 0.99; 95% CI, 0.91–1.08) in the primary end point, combined fatal coronary heart disease or nonfatal myocardial infarction [70]. Chlorthalidone was superior to amlodipine, the α -blocker doxazosin, and lisinopril in preventing various cardiovascular events, especially heart failure (amlodipine vs chlorthalidone, 10.2% vs 7.7%, respectively; and lisinopril vs chlorthalidone,

8.7% vs 7.7%, respectively) [70,102]. Patients with hypertension and other cardiovascular risk factors, who are especially likely to benefit from thiazide diuretic therapy, should be closely monitored for the development of diabetes [78].

Most patients require 2 or more antihypertensive drugs to achieve their BP goals [1]. Because older β -blockers, may lead to the development of diabetes, clinicians should be cautious in prescribing early combination therapy with these agents for patients at increased risk for T2DM [95]. Some researchers advocated early combination therapy with a thiazide diuretic and an ACE inhibitor or ARB because these newer agents may counteract some of the limitations of the thiazide diuretics [79–81]. However, controlled outcome trials have not yet assessed these combinations [7].

β -BLOCKERS

Clinical Data

There is substantial evidence that first- and second-generation β -blockers accelerate the onset of T2DM in individuals with hypertension [88,92,93,103–105]. In the Atherosclerosis Risk in Communities Study [105], patients administered a thiazide diuretic, CCB, or ACE inhibitor were at no greater risk for developing diabetes than their untreated counterparts, but the risk for developing T2DM was 28% greater in patients using a β -blocker than in those using no medication (RR, 1.28; 95% CI, 1.04–1.57). In the NHS I, NHS II, and HPFS cohorts, multivariate RRs of diabetes in participants using a β -blocker compared with those not using a β -blocker were 1.32 (95% CI, 1.20–1.46) in older women and 1.20 (95% CI, 1.05–1.38) in men [78].

Mechanisms

First- and second-generation β -blockers decrease insulin sensitivity, inhibit first-phase pancreatic insulin secretion (via β_2 -receptors), decrease peripheral glucose utilization, and decrease insulin clearance [92,93,97,103,104,106,107]. They induce weight gain, decrease skeletal muscle blood flow, and may exert a detrimental effect on glycemic control by enhancing α_2 -receptor-mediated hepatic glucose output [82,92,93,97,103,104,106,107]. Older β -blockers also worsen lipid levels [106].

In contrast, third-generation agents, such as nebivolol and carvedilol, possess vasodilator actions through such proposed mechanisms as NO release, antioxidant effects, β_2 agonism, and calcium blockade [108,109]. These vasodilating agents have beneficial or neutral effects on insulin sensitivity and glycemic control [82,109–111]. Nebivolol, a highly selective β_1 receptor blocker, has been shown to increase vascular NO production and reduce NADPH oxidase-mediated generation of ROS [112,113].

Carvedilol, which is both a vasodilating β -blocker and an α -blocker, increases peripheral blood flow [82]. Third-generation β -blockers also have neutral or favorable effects on lipid parameters [106,109,111]. Representative older and third-generation β -blockers have demonstrated antioxidant properties, including the ability to scavenge ROS, but third-generation agents have shown these effects more consistently [111,113–116].

Place in Therapy

Although they decrease the incidence of cardiovascular events, first- and second-generation β -blockers increase the risk for new-onset T2DM; subsequently, patients treated with older β -blockers should be monitored for the development of T2DM [78]. Clinical outcome data currently are not available, but the favorable metabolic effects of the third-generation β -

blockers may eventually make them the antiadrenergic treatment of choice in patients with the CMS [7,82].

CALCIUM CHANNEL BLOCKERS

Clinical Data

Most experts assign the CCBs to an intermediate position between the thiazide diuretics and older β -blockers, which increase the incidence of new-onset diabetes, and the ACE inhibitors and ARBs, which decrease it [7]. Analysis of data from the NHS I, NHS II, and HPFS found no relation between the use of CCBs and risk for symptomatic diabetes in men or older women [78]. However, when asymptomatic cases of diabetes were included, CCBs were weakly associated with risk in older women (RR, 1.10; 95% CI, 0.99–1.23) [78]. In the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm, treatment with amlodipine with or without perindopril was associated with a 29% decrease in risk for new-onset T2DM compared with atenolol with or without bendroflumethiazide (Table 4) [63]. It is impossible to determine how much of this difference is attributable to beneficial effects of amlodipine and how much to the detrimental effects of atenolol.

Mechanisms

Twelve-week studies showed that nifedipine controlled-release and cilnidipine improved insulin sensitivity in patients with hypertension [64,117,118]. This improvement may result from vasodilatory action in insulin-sensitive tissues without SNS stimulation [118], prevention of the inhibition of glucose transporters and glycogen synthase by calcium [7], or various antioxidant effects [7,119]. Antioxidant effects include inhibition of Ang II- and aldosterone-induced superoxide formation [120,121], improvement in NO bioavailability [120,121], and reduction of oxidative stress [122,123]. CCBs have minimal effects on lipid levels [117,118,124,125].

Place in Therapy

The CCBs are attractive candidates for use in combination regimens because they improve insulin sensitivity, have a neutral effect on lipid parameters, and have antioxidant effects. They may be especially beneficial when administered with an RAAS inhibitor, which offers more complete and robust metabolic protection.

α -ADRENERGIC BLOCKERS

Clinical Data

Large outcome trials have not determined the effect of α -adrenergic blockers (α -blockers), such as prazosin, doxazosin, and terazosin, on new-onset T2DM. In 2000, the National Heart, Lung, and Blood Institute discontinued the doxazosin arm in the BP component of ALLHAT after a median follow-up of 3.3 years because there was a 25% greater risk for combined CVD outcomes in the doxazosin group compared with the chlorthalidone group [102]. In a randomized, double-blind study of male veterans with hypertension, patients receiving prazosin were more likely to report adverse events and subsequently withdraw from the study than those treated with hydrochlorothiazide, atenolol, diltiazem, or captopril [126]. Commonly reported adverse events with α -blockers include fatigue, sleepiness, nonpostural dizziness, headache, arthralgia, and skin disorders [126,127].

Despite these concerns, selected patients may benefit from combination regimens that include an α -blocker. In a 16-week study, 35% of 264 patients with impaired glucose metabolism and a history of treatment resistance achieved adequate BP control when doxazosin was added to

their regimen [83]. One patient discontinued prematurely due to peripheral edema, but adjunctive doxazosin was generally well tolerated [83].

Mechanisms

α -Blockers increase insulin sensitivity [83,128]. These agents improve glucose utilization by decreasing sympathetic stimulation [129] and blunt hyperinsulinemia after glucose administration [130]. In addition, α -blockers improve lipid parameters, increasing HDL cholesterol and decreasing total cholesterol, LDL cholesterol, triglycerides, and very-LDL levels [83,127–130]. α -Blockers may have a particularly potent effect on hypertriglyceridemia [127,131]. Doxazosin inhibits oxidative stress-related proteins [132].

Place in Therapy

Even in patients with the CMS, α -blockers are rarely used as first-line therapy because of safety concerns [7]. However, because of their favorable effects on glycemic and lipid parameters, α -blockers may be beneficial as adjunctive therapy in carefully selected patients [83].

RAAS BLOCKADE

Introduction

The RAAS cascade has several different points at which ACE inhibitors, ARBs, and renin inhibitors can block the formation of Ang II and its subsequent effects (Figure 8). ACE inhibitors limit the conversion of Ang I to Ang II and increase circulating levels of bradykinin, which contributes to local NO generation [133]. ARBs competitively inhibit the binding of Ang II to the AT₁ receptor [134]. Renin inhibitors, a new class of recently introduced drugs, block the first and rate-limiting step of the RAAS cascade, the conversion of angiotensinogen to Ang I, by binding tightly to the S1/S3 pocket of renin and the hydrophobic subpocket S3^{sp} (Figure 9) [135,136]. Results from several large outcome trials conducted with ACE inhibitors or ARBs (Table 4) suggest that RAAS inhibition may be the most effective strategy for preventing or delaying T2DM in patients with hypertension [7].

ACE INHIBITORS

Clinical Data

Clinical outcome trials showed that ACE-inhibitor-based regimens were more likely to decrease incident T2DM than regimens involving placebo [65,66], thiazide diuretics [67], β -blockers [67,68,70], or CCBs [68,70] (Table 4). For example, in the recently reported African American Study of Kidney Disease and Hypertension [68], the RR for developing diabetes was significantly lower in patients randomly assigned to ramipril compared with metoprolol (RR, 0.53; 95% CI, 0.36–0.78; $P = .001$) or amlodipine (RR, 0.49; 95% CI, 0.31–0.79; $P = .003$).

A meta-analysis of 7 large randomized controlled clinical trials found a 27% overall decrease in risk for new-onset diabetes with ACE-inhibitor-based regimens (RR, 0.73; 95% CI, 0.63–0.84) [137]. Another meta-analysis of 6 trials found a similar risk reduction with ACE-inhibitor-based therapy (RR, 0.79; 95% CI, 0.71–0.89) [138]. The Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial demonstrated that rosiglitazone, a peroxisome proliferator-activated receptor gamma (PPAR- γ) agonist, significantly prevented or delayed the onset of T2DM in patients with impaired glucose tolerance or impaired fasting glucose [139]. The ACE-inhibitor ramipril did not significantly decrease the incidence of T2DM or death, but significantly increased regression to normoglycemia at 3 years [140]. It would be interesting to see whether there are synergistic effects of using ramipril and rosiglitazone in combination.

Mechanisms

ACE inhibitors improve insulin sensitivity and glucose utilization through multiple mechanisms. They reduce adipocyte size, which may increase the number of small insulin-sensitive adipocytes [27]. They may increase the percentage of type I fibers in skeletal muscle [141]. They enhance skeletal muscle blood flow, improving insulin delivery and enhancing glucose uptake and metabolism in insulin-sensitive tissues [25,142,143]. They also improve insulin-mediated glucose uptake by reducing the degradation of bradykinin and increasing the production of NO through their blockade of kininase II and ACE [133,144]. They enhance vascular sensitivity to insulin and improve endothelial function [145,146]. ACE inhibitors may prevent or reduce Ang II-mediated interference with insulin-signaling pathways, evidenced by increased glucose transporter-4 protein content in skeletal muscle [147]. They may improve lipid levels by improving carbohydrate metabolism [125]. Their antioxidant effects include suppression of Ang II-induced superoxide formation [120,121] and reduction in oxidative stress [148,149]. ACE inhibitors have several pancreatic benefits. They preferentially increase islet blood flow in the endocrine pancreas [45,150] and protect β cells from functional damage caused by prolonged exposure to high glucose levels, at least in part by decreasing oxidative stress [151]. Moreover, a study in Zucker diabetic fatty rats showed that perindopril attenuated disordered islet structure, diminished islet fibrogenesis, and improved first-phase insulin secretion [49].

Place in Therapy

Because large outcomes trials showed that ACE inhibitors decreased the incidence of T2DM in patients with hypertension, clinicians should consider an ACE inhibitor as the primary treatment for patients with hypertension and other evidence of the CMS, especially when impaired glucose tolerance is present [84]. A limitation of this class is the adverse effect profile, which includes cough, syncope, and, rarely, angioedema [69]. In selecting an antihypertensive agent for a patient, clinicians should weigh the demonstrated effectiveness of ACE inhibitors against the safety and tolerability profile.

ANG II RECEPTOR BLOCKERS

Clinical Data

In major outcome trials, the rate of new-onset T2DM was consistently lower with ARBs than with other treatments, including placebo [70–72], hydrochlorothiazide [73], atenolol [74], and amlodipine [75,76]. Two challenges in interpreting the results of many outcomes trials are that patients often received combination therapy and the comparator may be an agent (eg, β -blocker) that is diabetogenic [84]. Therefore, results of a recent subanalysis of the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial [76] are of particular interest. In the monotherapy subset of the VALUE trial, there was a greater incidence of new-onset T2DM in the amlodipine group (9.9%) than in the valsartan group (7.8%; RR, 0.772; $P = .012$) [76].

A meta-analysis of 3 randomized double-blind trials that included a total of 29,375 patients with hypertension found that ARB treatment decreased the incidence of diabetes (relative risk reduction, 0.80; 95% CI, 0.74–0.86; $P < .0000001$), although there was a slight increase in risk for myocardial infarction (RR, 1.12; 95% CI, 1.01–1.26; $P = .041$) [152]. A meta-analysis of 5 ARB studies that focused on only new-onset T2DM found a similar decrease in risk for T2DM (RR, 0.76; 95% CI, 0.70–0.82) [138]. Thus, currently available data suggest that ARBs and ACE inhibitors have similarly beneficial effects in preventing T2DM [138].

Mechanisms

ARBs improve insulin sensitivity and glucose utilization by means of multiple mechanisms, some of which are common to ACE inhibitors. They increase the number of small insulin-

sensitive adipocytes [27]. They may increase the percentage of type I skeletal muscle fibers [141], enhance skeletal muscle blood flow [153,154], and improve skeletal muscle glucose uptake [21]. Losartan increases serum levels of free insulin-like growth-factor I, which may decrease IR [155].

Telmisartan and irbesartan also improve insulin sensitivity by inducing PPAR- γ activity, an action independent of AT₁ receptor–blocking properties [156–160]. PPAR- γ activation may mediate the induction and prevent the depletion of adiponectin, an adipose-specific protein that enhances insulin sensitivity [161]. Telmisartan and olmesartan decrease triglyceride levels in rats [159,162]. However, a similar effect was not observed in human volunteers with IR [160].

ARBs have shown various antioxidant effects. They suppress superoxide production in skeletal muscle [21,163]. Losartan may decrease oxidative stress and improve endothelial function in rats with salt-induced hypertension [164] and healthy human volunteers with free fatty acid-induced acute endothelial dysfunction [146]. ARBs, like ACE inhibitors, have beneficial effects on the pancreas, preferentially enhancing islet blood flow in rats [150] and improving β -cell function in subjects with IR and abdominal adiposity [160]. In Zucker-diabetic-fatty rats, irbesartan, like perindopril, decreased islet cell ECM fibrosis and oxidative stress and increased β -cell mass, possibly by decreasing oxidative stress and apoptosis and attenuating profibrotic pathways [49]. In addition, in the transgenic Ren2 model of hypertension and IR, an ARB (valsartan) exhibited a significant increase in insulin-mediated glucose uptake compared with untreated animals ($P < .05$), which indicates that oxidative stress plays an important role in Ang II–mediated IR [21].

Place in Therapy

Large outcome trials showed that ARBs, like ACE inhibitors, decreased the incidence of T2DM in patients with hypertension. Therefore, ARB therapy is appropriate first-line therapy for patients with the CMS, especially when impaired glucose tolerance is present [84]. Ongoing outcome trials, including the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research study [7], the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial [165,166], and the Telmisartan Randomised Assessment Study in ACE-inhibitor Intolerant Subjects With Cardiovascular Disease [165,166], will provide additional information on the effects of ARBs on new-onset T2DM and also may identify some differences in efficacy between ARBs and ACE inhibitors. For the present, the better tolerability of the ARBs might influence the choice of initial therapy. Overall, the ARBs offer excellent safety and tolerability, with an adverse-event profile similar to that of placebo [134]. Commonly reported adverse events in outcome trials were headache, edema, angina, and diarrhea [76]. Less frequently reported events were syncope, hyperkalemia (and rarely, hypokalemia), increased serum creatinine levels, and angioedema [71,72,76,167].

Aldosterone Mineralocorticoid Antagonists

Clinical Data

Spirolactone, an aldosterone antagonist that has been available for decades, and eplerenone, a selective aldosterone-receptor antagonist more recently introduced, are available for use in the treatment of congestive heart failure [168,169] and resistant hypertension. Mineralocorticoid blockade has been demonstrated to be effective in reducing total mortality as well as hospitalization for heart failure in patients with systolic left ventricular dysfunction due to chronic heart failure and in patients with congestive heart failure following acute myocardial infarction [170,171]. Sodium retention and volume expansion mediated in part by aldosterone excess are prominent features in low-renin hypertension and the use of these agents

in hypertensive diabetic patients, as well as those with resistant hypertension, are emerging [172]. In a recent study, eplerenone was demonstrated to be more effective than losartan in reducing BP in patients with low-renin hypertension typical of T2DM [173].

Mechanisms

The mechanism of action of aldosterone antagonists have been well defined over the years in regards to the myocardium, congestive heart failure and hypertension [168–172], and recently there has been increased interest regarding its effect in the CMS [174,175]. Our laboratory has recently found evidence to support a positive role for the attenuation of NAD(P)H oxidase production of oxidative stress in the myocardium and cardiac remodeling utilizing mineralocorticoid receptor blockade with low-dose spironolactone in the Ren2 model of hypertension, oxidative stress, and IR [176]. Further, our current studies demonstrate abrogation of many islet and pancreatic structural and functional changes in the Ren2 model [50].

Place in Therapy

Aldosterone antagonists should be considered in combination therapeutic management as a second- or third-line choice for RAAS blockade in the treatment of hypertension in patients with T2DM, especially if the current control of BP guidelines is not being attained with therapeutic regimens discussed previously.

DIRECT RENIN INHIBITORS

Introduction

The therapeutic potential of renin inhibition has been investigated for many years, but a new class of orally active, nonpeptide, low-molecular-weight renin inhibitors has been developed [135,177]. Direct renin inhibitors block the RAAS at its initial point of activation. Aliskiren, first in this new class of antihypertensive drugs, was recently approved in the United States for the treatment of patients with hypertension as monotherapy or in combination with other antihypertensives.

Clinical Data

Safety and efficacy of aliskiren has been demonstrated in phases II and III clinical trials. Once-daily treatment with aliskiren for 4 or 8 weeks has been shown to effectively decrease BP in patients with hypertension [178–182]. Additionally, dose-dependent decreases in BP were demonstrated during an 8-week treatment period of aliskiren monotherapy at 150, 300, and 600 mg, compared with placebo, in patients with mild to moderate hypertension [179]. Furthermore, studies of combination treatment with aliskiren and amlodipine, hydrochlorothiazide, or valsartan were recently published and demonstrated additional lowering of both systolic and diastolic BP with placebo-like adverse effect profiles in patients with hypertension [183–185]. Reductions in BP have also been demonstrated with aliskiren monotherapy or aliskiren and ramipril in patients with hypertension and type 1 diabetes or T2DM [186]. Aliskiren showed a safety and tolerability profile similar to that of placebo [179,182], irbesartan [182], and losartan [181]. The most frequently reported adverse events were headache, dizziness, fatigue or weakness, and gastrointestinal disorders [179,181,182].

Mechanisms

In vitro studies showed that aliskiren is a potent, tight-binding, specific inhibitor of human renin [187]. Oral administration to sodium-depleted marmosets caused complete inhibition of plasma renin activity and sustained decreases in arterial BP [136,187,188]. Oral administration to healthy volunteers induced a dose-dependent decrease in plasma renin activity, blocked the

formation of Ang I and II, and decreased plasma and urinary aldosterone levels at doses of 80 mg or greater [85].

The mechanism of action of renin inhibitors differs from those of other RAAS inhibitors in several important ways. Renin inhibitors prevent the formation of both Ang I and II, whereas ACE inhibitors increase Ang I [85] and ARBs increase Ang II [177]. In addition, direct renin inhibitors prevent the reactive increase in plasma renin activity seen with other RAAS blockers [178,186]. Because renin inhibitors do not increase Ang II levels, they are likely to have more beneficial effects on prothrombotic plasminogen activator inhibitor 1 levels than ARBs [85, 189]. Unlike ACE inhibitors, renin inhibitors do not affect bradykinin metabolism and thus would not be expected to cause the cough or angioedema seen with those agents [134,136, 190]. Despite similar decreases in BP, renin inhibition caused a 50% greater increase in renal perfusion than ACE inhibition, suggesting that renin inhibitors may produce a more effective blockade of tissue Ang II formation than ACE inhibitors [191]. Additionally, renin inhibitors could be useful in clinical situations, such as congestive heart failure, for which ACE escape may be a problem.

Place in Therapy

The therapeutic potential of renin inhibitors in preventing or delaying the onset of T2DM is currently unknown. However, given the success of ACE inhibitors and ARBs in reducing new-onset T2DM, it is possible that renin inhibitors will also provide such benefits [182]. Today, many researchers advocate the coadministration of ACE inhibitors and ARBs to intensify RAAS control, but eventually the combination of an ARB and a renin inhibitor may be shown to have similar effectiveness with better tolerability [85]. In fact, 1 study has shown that aliskiren in combination with the ACE-inhibitor ramipril reduced BP in patients with diabetes and hypertension [186]. Additionally, the Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) trial was designed to determine the effects of combination therapy with aliskiren and the ARB, losartan, on proteinuria in patients with diabetes and results are anticipated in the near future. Also forthcoming is the Aspire Higher clinical development program, which will include a number trials that will evaluate surrogate markers and clinical outcomes in patients with disorders including hypertension, diabetes, left ventricular hypertrophy, and heart failure, and who are treated with aliskiren as monotherapy or combination therapy.

OPTIMIZING OUTCOMES IN PATIENTS WITH HYPERTENSION

Clinicians can optimize outcomes in their patients by helping them make necessary lifestyle modifications, adopting a treatment plan focused on achieving current BP goals, and practicing appropriate BP monitoring. They can also implement a global risk-reduction strategy and adopt approaches that encourage patient adherence to the treatment plan. According to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), BP goals are less than 140/90 mm Hg for the overall population and less than 130/80 mm Hg for persons with hypertension accompanied by diabetes or renal disease [1].

NONPHARMACOLOGIC RECOMMENDATIONS

The JNC 7 emphasizes the need to adopt a healthy lifestyle to help treat hypertension (Table 7) [1]. A recent follow-up to the Finnish Diabetes Prevention Study reported that after a median of 3 years, T2DM incidence per 100 person-years was 4.6 in patients who had received active lifestyle counseling and 7.2 in controls ($P = .04$) [192]. Thus, counseling was associated with a 36% RR reduction [192]. Whether the choice of antihypertensive agents has a significant effect on metabolic risk factors or progression to T2DM in patients who adopt lifestyle modifications is currently unknown [7].

GLOBAL CARDIOMETABOLIC RISK REDUCTION

To delay or prevent T2DM, an aggressive multifaceted treatment approach for patients with hypertension should be adopted. The RAAS acronym was developed to summarize a program for achieving global risk reduction in patients with the CMS, atherosclerosis, and T2DM, but many of its components are also important for diabetes prevention in patients with hypertension (Table 8) [4,193].

The Hypertension Writing Group recently shared with the clinical community a new definition of hypertension that alludes to global cardiometabolic risk: "Hypertension is a progressive cardiovascular syndrome arising from complex and interrelated etiologies. Early markers of the syndrome are often present before BP elevation is observed; therefore, hypertension cannot be classified solely by discrete BP thresholds. Progression is strongly associated with functional and structural cardiac and vascular abnormalities that damage the heart, kidneys, brain, vasculature, and other organs and lead to premature morbidity and death." "Other organs," as can be ascertained from this review article, certainly include the pancreas in relation to the development of T2DM. This review discusses the multiple metabolic functional changes, as well as structural changes, within the pancreatic islet that contribute to the development of T2DM.

Patient compliance with antihypertensive medication is approximately 64%, and adherence to exercise programs is only about 50% [194]. Table 9 lists approaches that may assist clinicians to increase adherence to a global risk reduction program [4,194].

CONCLUSION

Persons with hypertension have an increased risk for developing T2DM due to IR, compensatory hyperinsulinemia-hyperamylinemia, and related metabolic abnormalities. The formation and deposition of amylin-derived islet amyloid in the pancreas can diminish islet β -cell function and cause β -cell loss by apoptosis, compounding the risk for T2DM.

The various classes of antihypertensive drugs have different metabolic and structural effects that can impact on the development of T2DM. One must not overlook the clear cardiovascular benefits of low-doses of thiazide diuretics, however, high doses of thiazides may lead to the development of T2DM. First- and second-generation β -blockers promote diabetes, whereas newer vasodilating β -blockers may have more neutral, benign, or protective effects. CCBs decrease incident diabetes in patients with CMS and have intermediate effectiveness between the thiazide diuretics and older β -blockers compared with the RAAS inhibitors. α -Adrenergic blockers offer important metabolic benefits, but a problematic adverse effect profile prevents first-line use in most patients. Accumulating evidence suggests that overcoming IR with agents that interrupt the RAAS, including ACE inhibitors and ARBs, may prevent or delay the development of diabetes. In addition, these are the only agents known to attenuate the pancreatic damage caused by islet fibrosis and may be capable of slowing the progression of islet amyloid deposition by reducing islet oxidative stress, which accelerates polymerization of amylin monomers necessary for the formation of mature amylin-derived islet amyloid fibrils. Renin inhibitors, a new class of drugs introduced into clinical practice, exert their effects at a point upstream from ACE inhibitors and ARBs. This characteristic suggests that when clinical outcome trials are conducted, renin inhibitors may have the potential to also delay the onset of T2DM. In addition to determining the best pharmacologic regimen for their patients with hypertension who may be at risk for developing T2DM, clinicians should help patients make beneficial lifestyle modifications, as well as incorporate a global risk reduction strategy into their practice.

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Hypertension Mandala

Figure 1.

The hypertension mandala. Clustering of the cardiometabolic syndrome and cardiometabolic risk factors. IR is central to the development of hypertension and IGT–T2DM, along with multiple metabolic and clinical conditions surrounding the outer portions of this hypertension mandala. Obesity is placed at the top of the mandala because it is believed to be the driving force behind the subsequent clinical end-organ remodeling and disease. The central placement of hypertension was chosen because it represents the central importance regarding its treatment to prevent many of the associated clinical complications and specifically T2DM placed vertically below and opposite obesity. The interconnectedness between IR, hypertension, and T2DM is not to be underestimated.

ASO, atheroscleropathy; CHF, congestive heart failure; CKD, chronic kidney disease; CVD, cardiovascular disease; Dd, diastolic dysfunction; ; ESRD, end-stage renal disease; IGT, impaired glucose tolerance; IR, insulin resistance; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PCOS, polycystic ovarian syndrome; T2DM, type 2 diabetes mellitus.

Figure 2.

Brief summary of the major metabolic and structural alterations in hypertension [4,5,7].

Ang II, angiotensin II; eNOS, endothelial nitric oxide synthase; Glut, glucose transporter; NO, nitric oxide; PI3(Akt)-MAP, phosphatidylinositol 3-kinase-mitogen activated protein; RAAS, renin angiotensin aldosterone system; SNS, sympathetic nervous system.

Figure 3. Counterregulatory roles of insulin and angiotensin II in glucose utilization: the role of oxidative stress [5].

There is increasing evidence of a strong association between hypertension, insulin resistance, and the development of T2DM.

AT₁-R, angiotensin II type 1 receptor; GLUT, glucose transporter; INS, insulin; IRS, insulin-receptor substrates; NADPH, nicotinamide adenine dinucleotide phosphate; NOS, nitric oxide synthase; NO, nitric oxide; PI3-K, phosphatidylinositol 3-kinase; ROK, Rho kinase; ROS, reactive oxygen species.

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Dysfunction – Damage to the vulnerable β -cell and pancreatic islet β -cell dysfunction and apoptosis

Figure 4.

The role of glucotoxicity in the development of islet redox stress and pancreatic islet structural damage β -cell dysfunction [6].

A-FLIGHT-U, see Table 3 for explanation of this acronym; AGE, advanced glycosylation end products; NAD, nicotinamide adenine dinucleotide; NADH, nicotinamide adenine dinucleotide, (reduced); RNS, reactive nitrogen species; ROS, reactive oxygen species; SOD, super-oxide dismutase.

Adapted from Hayden MR, Tyagi SC. J Pancreas 2002; 3: 86–108. [6].

Figure 5. The primary structure of human amylin (islet amyloid polypeptide) [55]. Reproduced from Hayden MR, et al. *J Pancreas* 2005; **6**: 287–302 [55]).

A correctly folded native protein.

Figure 6.

The progression from unfolded or misfolded amylin to the formation of insoluble amyloid fibrils [55].

ER, endoplasmic reticulum; UPR, unfolded protein response.

Reproduced from Hayden MR, et al. *J Pancreas* 2005; **6**: 287–302 [55].

Figure 7.

Islet structural changes associated with amylin-derived islet amyloid deposition.

Panel 7A: Hematoxylin and eosin staining of a single human islet from a middle-aged patient with T2DM. Note the interbeta and pericapillary hyaline changes associated with islet amyloid deposition. Note the presence of islet amyloid surrounding the islet capillary. This critical location may serve as a barrier to docking of the insulin secretory granules as depicted in the TEM panel 7D. Magnification $\times 80$.

Panel 7B: A hypocellular islet (due to islet amyloid deposition) from the transgenic (Sprague-Dawley transfected with the human amylin gene) novel 8-month-old HIP transgenic rat model of T2DM. This Voerhoff Van Gieson–stained islet demonstrates peri-islet and perivascular fibrosis of the islet (arrows). Magnification $\times 40$.

Panel 7C: This same islet stained with Congo red and under crossed polarized light. Depicts islet amyloid appearing white in this black-and-white image. Note the novel findings of islet amyloid present in the peri-islet vessels. Amylin-derived islet amyloid in the perivascular region has not been previously demonstrated. Magnification $\times 40$.

Panel 7D: Demonstrates a TEM image of an islet from a 4-month-old transgenic HIP rat model of T2DM. It is interesting to note that the ISGs(*) seem to abut the pericapillary islet amyloid deposits (#) and indicate impaired ISG trafficking and docking with the capillary endothelial cell, which helps explain the impaired glucose tolerance and impaired first-phase insulin

secretion. To our knowledge, this is the first image to demonstrate structurally this impaired trafficking and docking of the ISGs. The progressive deposition of islet amyloid seems to parallel the progressive nature of T2DM. Magnification $\times 4000$.

E β -C, endothelial beta-cell (representative of endothelial tissue uncoupling); EC, endothelial cell; hIAPP, human islet amyloid polypeptide; HIP, human islet-amyloid polypeptide c; ISG, insulin secretory granule; RBC, red blood cell within the islet capillary; T2DM, type 2 diabetes mellitus; TEM, transmission electron microscope.

Figure 8.

The RAAS cascade.

This image demonstrates the 3 critical steps in the production and blockade of Ang II. The renin enzyme, ACE, and the AT₁ receptor. The current medications in use are the ACE inhibitors and ARBs, and this image portrays the emerging medication aliskiren. The 3 classes of medications will soon be the -rens, the -prils, and the -sartans. It will be interesting to see if the new renin inhibitor aliskiren will delay or prevent the development of T2DM in patients with hypertension compared with placebo or other antihypertensive medications.

ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; RAAS, renin-angiotensin aldosterone system; T2DM, type 2 diabetes mellitus.

Figure 9.

Renin inhibitor-binding pockets on the active site of renin [135,136].

Panel A represents the ribbon and band structure with the medication aliskiren overlying the binding pocket S1/S3 and extension into the hydrophobic S3 subpockets, which allows for the prerequisite higher affinity binding necessary for the desired clinical response.

Panel B represents the model used to portray this binding pocket site within the renin molecule. Reprinted from Chemistry Biology, volume 7, Raheul J et al. Structure-based drug design. Pp 493–504. Copyright 2000, with permission from Elsevier.

Table 1

A simple classification of hypertension

Primary (80% to 90%)	Secondary (10% to 20%)	Others (loosely defined category)
No single identifiable and treatable cause; 80% to 90% of cases	Renal Renal parenchymal Renovascular CKD any cause	Obstructive sleep apnea Becoming almost an epidemic largely due to the obesity epidemic Excess alcohol
	Endocrine Pheochromocytoma Mineralocorticoid excess Primary hyperaldosteronism Glucocorticoid excess Cushing disease Hyperparathyroidism Acromegaly Hyperthyroidism Hypothyroidism	Excess licorice Corticosteroid therapy COX inhibitors, NSAIDs Estrogen Pregnancy Environmental stressors, such as crowding, emotional stress, and environmental deprivation, and sense of loss and despair. HPA axis-related glucocorticoid excess

CKD, chronic kidney disease; COX, cyclooxygenase; HPA, hypothalamic-pituitary-adrenal; NSAIDs, nonsteroidal anti-inflammatory drugs.

Table 2

National Cholesterol Education Program Criteria for Diagnosis* of the metabolic syndrome-cardiometabolic syndrome [10]

Risk Factor	Defining Level
Abdominal obesity [†] (waist circumference) [‡]	
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
Triglycerides	≥150 mg/dL
High-density lipoprotein cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	≥130/≥85 mm Hg
Fasting glucose	≥110 mg/dL

* According to NCEP criteria, the CMS is present when 3 or more risk factors are present.

[†] Overweight and obesity are associated with insulin resistance and the CMS. However, the presence of abdominal obesity correlated more highly with metabolic risk factors than an elevated body mass index. Therefore, the simple measure of waist circumference is recommended to identify the body weight component of the CMS.

[‡] Some men can develop multiple metabolic risk factors when waist circumference is only marginally increased (eg, 94–102 cm [37–40 in]). Such patients may have a strong genetic contribution to insulin resistance and should benefit from changes in life habits, similar to men with categorical increases in waist circumference.

CMS, cardiometabolic syndrome; NCEP, National Cholesterol Education Program.

Reprinted from National Cholesterol Education Program Adult Treatment Panel III. JAMA 2001; **285** 2486–2497 with permission [10].

Table 3

A-FLIGHT-U acronym: multiple metabolic abnormalities associated with hypertension are responsible for the generation of ROS

A	Ang II production of ROS via AT ₁ receptor activation of membranous NAD(P)H oxidase enzyme Amylin activation of RAAS Antioxidant-oxidant imbalance Advanced glycosylation end product formation and ROS generation Aging
F	Free fatty acid toxicity
L	Lipotoxicity via obesity
I	Insulin resistance Impaired glucose tolerance and utilization
G	Glucotoxicity
H	Hyperinsulinemia-hyperproinsulinemia Hyperamylinemia
T	Triglyceride toxicity
U	Uric acid toxicity via xanthine oxidase enzyme. Uric acid in normal physiologic range is considered to be an antioxidant; however, in an acidic or oxidant milieu or when levels are increased, uric acid can become pro-oxidant via a urate redox shuttle and contribute to ROS generation

Ang II, angiotensin II, AT₁, angiotensin II type 1; NAD(P)H, nicotinamide dinucleotide phosphate; RAAS, renin-angiotensin aldosterone system; ROS, reactive oxygen species.

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Table 4
Results of major clinical trials that investigated the link between antihypertensive drug therapy and the development of type 2 diabetes

Antihypertensive Class/Clinical Trial	No. of Patients	Patient Characteristics	Treatment		Incidence of New-Onset Diabetes (%)		Absolute Risk Reduction (%)	Relative Risk Reduction (%)
			Active	Control	Treated Group	Control Group		
CCB-based therapy								
ASCOT-BPLA [63]	14,112	M/W 40–79 y with HTN and ≥3 CVD risk factors	Amlodipine ± perindopril ± other agents	Atenolol ± bendro-flumethiazide	8.0	11.3	3.3	29
INVEST [64]	16,176	M/W ≥50 y with HTN and CAD	Verapamil SR + trandolapril, hydrochlorothiazide	Atenolol + hydrochlorothiazide, trandolapril	7.0	8.2	1.2	15
ACE-inhibitor-based therapy								
CAPP [67]	10,985	M/W 25–66 y with diastolic HTN	Captopril	β-Blocker, diuretic, or both	6.1	6.9	0.8	12
HOPE [65]	9297	M/W ≥55 y with CVD	Ramipril	Placebo	3.6	5.4	1.8	33
ALLHAT [70]	5637*	M/W ≥55 y with HTN and risk for CVD	Lisinopril	Chlorthalidone or amlodipine	8.1	11.6, 9.8	3.5, 1.7	30, 17
SOLVD [66]	291	M/W ≤80 y with LV dysfunction	Enalapril	Placebo	5.9	22.4	16.5	74
PEACE [69]	6904	M/W ≥50 y with stable CAD and normal or slightly reduced LV function	Trandolapril	Placebo	9.8	11.5	1.7	15
AASK [68]	1017	AA M/W 18–70 y without DM, with HTN, and decreased renal function	Ramipril	Metoprolol or amlodipine	2.8	4.5, 4.4	1.7, 1.6	38, 36
ARB-based therapy								
LIFE [74]	7998	M/W 55–80 y with HTN and LV hypertrophy	Losartan	Atenolol	6.0	8.0	2.0	25
CHARM [71,72]	5436	M/W ≥18 y with HF grade II–IV	Candesartan	Placebo	6.0	7.4	1.4	19
ALPINE [73]	392	Mostly W 18–75 y with newly detected HTN	Candesartan	Hydrochlorothiazide Atenolol	0.5	4.1	3.6	88
VALUE [75] [†]	15,245	M/W ≥50 y with HTN and high risk for CVD	Valsartan	Amlodipine	13.1	16.4	3.3	20
VALUE [76] [‡]	4933	M/W ≥50 y with HTN and high risk for CVD	Valsartan	Amlodipine	7.8	9.9	2.1	21

AA, African American; AASK, African American Study of Kidney Disease and Hypertension; ACE, angiotensin-converting enzyme; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attacks Trial; ALPINE, Antihypertensive Treatment and Lipid Profile in a North of Sweden Efficacy Evaluation; ARB, angiotensin receptor blocker; ASCOT-BPLA, Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm; CAD, coronary artery disease; CAPP, Captopril Prevention Project; CCB, calcium channel blocker; CHARM, Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity; CVD, cardiovascular disease; DM, diabetes mellitus; HF, heart failure; HOPE, Heart Outcomes Prevention Evaluation; HTN, hypertension; INVEST, International Verapamil-Trandolapril Study; LIFE, Losartan Intervention for Endpoint Reduction in Hypertension; LV, left ventricular; M, men; PEACE, Prevention of Events With Angiotensin Converting Enzyme Inhibition; SOLVD, Studies of Left Ventricular Dysfunction; SR, sustained release; VALUE, Valsartan Antihypertensive Long-term Use Evaluation; W, women.

* Patients without diabetes at baseline with fasting glucose data at 4 years [70].

[†] Entire patient population receiving valsartan-based or amlodipine-based therapy in VALUE [75].

[‡] Patients who received valsartan or amlodipine monotherapy in VALUE [76].

Adapted from Stump CS, Hamilton MT, Sowers JR. Effect of antihypertensive agents on the development of type 2 diabetes mellitus. *Mayo Clin Proc* 2006; **81**: 796–906 with permission [7].

Table 5
Effects of the major classes of antihypertensive agents related to the development of diabetes

Effects*	Thiazide Diuretics	Older β -Blockers	Vasodilating β -Blockers	CCBs	α -Adrenergic Blockers	RAAS Inhibitors		
						ACE Inhibitors	ARBs	Renin Inhibitors
Prevent or delay development of diabetes	-	-	?	+	?	+	?	?
Other actions								
Improve insulin sensitivity	-	-	0/+	+	+	+	+	?
Improve glycemic control	-	-	0/+	0/+	+	+	+	?
Improve lipid parameters	-	-	0/+	0	+	+	0	?
Exert antioxidant effects	+	+	+	+	+	+	+	?
Protect the pancreas	?	?	?	?	?	+	+	?
Counteract pancreatic effects of anylin	?	?	?	?	?	+	+	?
Have an acceptable safety/tolerability profile	+	+	+	+	-	-	+	+

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; RAAS, renin-angiotensin aldosterone system.

* Effects: +, known to be present; -, known to be absent; 0, neutral effect; ?, effect unknown or not reported.

Table 6

Treatment recommendations based on the effects of antihypertensive agents on new-onset diabetes

Class of Agent	Treatment Recommendations
Thiazide diuretics	<ul style="list-style-type: none"> • Use the lowest effective dose [77] • Increase diabetes surveillance in treated patients [78] • Avoid routine combination use of a thiazide diuretic and β-blocker in the early management of hypertension, especially in patients at increased risk for diabetes [81] • Consider early combination therapy with a thiazide diuretic and ACE inhibitor or ARB [79–81]
β -Blockers	<ul style="list-style-type: none"> • Increase surveillance for diabetes in patients treated with first- or second-generation agents [78] • Use a vasodilating agent (eg, carvedilol) for patients with the CMS [82]
CCBs	<ul style="list-style-type: none"> • Consider prescribing a CCB with an RAAS inhibitor for patients requiring combination therapy
α -Adrenergic blockers	<ul style="list-style-type: none"> • Avoid first-line therapy with an α-adrenergic blocker, even for patients with the CMS [7] • Consider prescribing an α-adrenergic blocker as adjunctive therapy for patients with treatment-resistant hypertension and impaired glucose metabolism [83]
RAAS inhibitors	<ul style="list-style-type: none"> • Choose an ACE inhibitor or ARB as the primary agent for patients with the CMS, especially when impaired glucose tolerance is present [84]
ACE inhibitors	<ul style="list-style-type: none"> • Weigh the demonstrated effectiveness of the ACE inhibitors in decreasing the incidence of diabetes against their less-than-ideal safety/tolerability profile
ARBs	<ul style="list-style-type: none"> • Consider both the proven effectiveness of the ARBs in preventing or delaying diabetes and their excellent safety/tolerability profile when prescribing an antihypertensive agent
Renin inhibitors	<ul style="list-style-type: none"> • Consider prescribing combination therapy with a renin inhibitor and ARB if outcome data support this approach [85]

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; CMS, cardiometabolic syndrome; RAAS, renin-angiotensin aldosterone system.

Table 7

Lifestyle modifications for managing hypertension recommended in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (The JNC 7 Report) [1]^{*}

Modification	Recommendation	Approximate Systolic BP Decrease, Range
Weight reduction	Maintain normal body weight (BMI, 18.5–24.9)	5–20 mm Hg/10-kg weight loss
Adopt DASH eating plan	Consume a diet rich in fruits, vegetables, and low-fat dairy products with reduced content of saturated and total fat	8–14 mm Hg
Dietary sodium reduction	Reduce dietary sodium intake to no more than 100 mEq/L (2.4 g sodium or 6 g sodium chloride)	2–8 mm Hg
Physical activity	Engage in regular aerobic physical activity, such as brisk walking (at least 30 minutes per day most days of the week)	4–9 mm Hg
Moderation of alcohol consumption	Limit consumption to no more than 2 drinks per day (1 oz or 30 mL ethanol [eg, 24 oz beer, 10 oz wine, or 3 oz 80-proof whiskey]) in most men and no more than 1 drink per day in women and lighter weight men	2–4 mm Hg

BMI, body mass index calculated as weight in kilograms divided by the square of the height in meters; BP, blood pressure; DASH, Dietary Approaches to Stop Hypertension.

^{*} For overall cardiovascular risk reduction, stop smoking. The effects of implementing these modifications are dose and time dependent and could be higher for some individuals.

Reproduced from Chobanian AV et al. JAMA 2003; **289** 2560–2572 [1] with permission.

Table 8

A treatment strategy for global risk reduction in patients with hypertension: the RAAS acronym [4,193]

Letter	Treatment	Rationale and Comments
R	RAAS blockade Renin inhibition	Prevent or delay diabetes (clinical outcome trial data) Antihypertensive effects
	Reductase inhibitors (HMG-CoA)	Improve triglyceride, LDL-C, and HDL-C levels Reduce oxidative stress
A	ACE inhibitors and ARBs	Have potent antihypertensive effects Inhibit local and systemic angiotensin II effects Reduce injurious stimuli for ROS production Decrease A-FLIGHT* toxicities Exhibit antioxidant effects Attenuate pancreatic structural damage caused by amylin
	Amlodipine (and other CCBs)	Prevent or delay diabetes (clinical outcome trial data) Have mainly neutral metabolic effects Exhibit antioxidant effects
	Adrenergic blockade	Newer nonspecific β -blockers have neutral or positive effects regarding insulin resistance. Also, β -blockers are known to decrease renal renin release
	Acetylsalicylic acid	Antiplatelet anti-inflammatory effect on hyperactive platelets
A	Aggressive BP control	Follow guidelines in JNC 7 Report Prescribe combination therapy when needed
	Aggressive lifestyle modification	Follow JNC 7 recommendations
	Adherence	Adopt strategies shown to increase patient adherence
S	Smoking cessation	Encourage patients to stop smoking
	Statins	Pleiotropic effects (antioxidant–anti-inflammatory effects)

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; HDL-C, high-density lipoprotein cholesterol; JNC 7, Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [1]; LDL-C, low-density lipoprotein cholesterol; RAAS, renin-angiotensin aldosterone system; ROS, reactive oxygen species.

* See Table 3.

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Table 9

Strategies for increasing patient adherence to a global risk reduction plan for preventing diabetes [4,194]

-
- Communicate frequently with patients by telephone, mail, and/or e-mail.
 - Be persuasive in all communications with patients; educate your own front office staff on the importance of patient adherence.
 - Encourage support from the patients' spouse, family, and friends.
 - Establish signed agreements/contracts.
 - Encourage self-monitoring.
 - Provide training in behavioral skills.
 - Educate patients to enhance self-efficacy perceptions.
 - Simplify medication regimens.
 - Increase the number of visits for patients unable to achieve treatment goal.
 - Involve patients in their care through self-monitoring.
 - Develop a standardized treatment plan protocol.
 - Reinforce and reward adherence.
 - Use office computer programs that generate reminders of appointments and track missed appointments.
 - Flag or mark charts, using the RAAS acronym* or your own system.
-

* See Table 8.

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