

Hypertension in Type 2 Diabetes Mellitus

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ABSTRACT

Background: Hypertension and type 2 diabetes mellitus (DM) frequently occur together, and their coexistence markedly enhances the risk for cardiovascular and renal disease. Each plays an important role in the metabolic syndrome, in which insulin resistance and compensatory hyperinsulinemia are features of both diseases.

Objective: This article discusses the loss of hormonal homeostasis due to insulin resistance and the relationships among the triad of hypertension, type 2 DM, and cardiovascular disease.

Methods: An online PubMed database search of articles published from 1994 to 2005 was conducted using search terms that included *hypertension*, *type 2 DM*, and *cardiovascular disease*. Relevant articles were studied and summarized in combination with the existing knowledge and expertise of the authors.

Results: There is increasing evidence that the renin-angiotensin-aldosterone system is activated at the local-tissue level in patients with type 2 DM, as a result of insulin resistance, glucotoxicity, and other metabolic abnormalities. The common fertile soil of insulin resistance and lost hormonal homeostasis (genetic and environmentally driven) links these two entities. Multiple metabolic toxicities contribute to the strong association of an underlying oxidative-redox stress and reactive oxygen species, resulting in endothelial dysfunction and microalbuminuria. Because microalbuminuria is a precursor to cardiovascular disease, stroke, and chronic renal disease, it is important to screen for its presence in each patient with hypertension and type 2 DM.

Conclusions: Renin-angiotensin-aldosterone system blockade is the cornerstone in managing these abnormalities; however, in type 2 DM, the angiotensin-converting enzyme inhibitors and/or the angiotensin receptor blockers seldom control the elevated blood pressure when used as monotherapy. Therefore, combination therapy with ≥ 2 antihypertensive agents, including thiazide diuretics, β -blockers, and calcium channel blockers, is required to reach the established blood pressure goal of $<130/80$ mm Hg. Careful control of hypertension in patients with type 2 DM decreases the morbidity and mortality resulting from cardiovascular and renal disease. (*Insulin*. 2006;1:22–37) Copyright © 2006 Excerpta Medica, Inc.

Key words: insulin resistance, hyperinsulinemia, hyperproinsulinemia, hyperamylinemia, hyperglycemia or glucotoxicity, renin-angiotensin-aldosterone system (RAAS) blockade, angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB).

INTRODUCTION

The association of hypertension (HTN) and type 2 diabetes mellitus (DM) dates back to 1923 when Kylin first described the clinical clustering of HTN, hyperglycemia, and hyperuricemia.¹ In 1988, Reaven brought this clinical clustering syndrome—called Syndrome X—into the limelight for clinicians by explaining the central importance of insulin resistance (IR), hyperinsulinemia (HI), free fatty acids, HTN, and coronary artery disease.² Others have proposed that the clustering comprises HTN, hyperglycemia, hyperlipidemia (hypertriglyceridemia), and upper body obesity.^{3–5}

This clustering syndrome has been called many names over the years, including the cardiometabolic syndrome, the dysmetabolic syndrome, and the IR syndrome.⁵ The metabolic syndrome (MetS)—the term now used to profile these metabolic risk factors for cardiovascular disease (CVD)—affects ~47 million people in the United States alone. IR and HI are now seen to represent the common fertile soil for the development of these diabetes complications.⁶

The goal of the current article was to discuss the loss of hormonal homeostasis due to IR and the relationships among the triad of HTN, type 2 DM, and CVD.

MATERIALS AND METHODS

An online PubMed database search of articles published from 1994 to 2005 was conducted using search terms that included *hypertension*, *type 2 DM*, and *cardiovascular disease*. Relevant articles were studied and summarized in combination with the existing knowledge and expertise of the authors.

FACTORS LINKING TYPE 2 DIABETES MELLITUS AND HYPERTENSION

More than 50% of patients with newly diagnosed type 2 DM will present with coexisting HTN, and ~50% of patients with essential HTN will develop type 2 DM over a 10- to 15-year period.^{7–9} Factors linking clinical findings to the association of HTN and type 2 DM include: family history of DM, HTN, dyslipidemia, and/or premature CVD; ethnic background (eg, Asian, Pacific Islander, Hispanic, black, or Native American); upper body obesity with phenotypic characteristics of abdominal obesity (defined as waist circumference ≥ 102 cm for men and ≥ 88 cm for women); gestational diabetes; multiparity; polycystic ovary syn-

drome; prediabetes with impaired glucose tolerance (140–190 mg/dL) or impaired fasting glucose (100–125 mg/dL); aging; acanthosis nigricans; prehypertension (120–139 mm Hg systolic blood pressure [BP] and 80–89 mm Hg diastolic BP, per guidelines of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [JNC VII], or overt HTN); and dyslipidemia of the lipid triad (increased very low density lipoprotein cholesterol/triglycerides; small, dense low-density lipoprotein [LDL] cholesterol; and decreased high-density lipoprotein [HDL] cholesterol).^{10,11}

The MINER acronym, as described in **Table 1**,¹² may serve as a simple tool to aid clinicians in remembering those end-organ systems affected by the MetS, IR, and type 2 DM. If primary care providers think of the future complications in the real and present time, they are more likely to think of various measures to prevent complications.

PATHOPHYSIOLOGY: LOSS OF β -CELL HORMONAL HOMEOSTASIS

Insulin: Hyperinsulinemia

The intact β -cell–insulin secretory axis resulting in the physiologic secretion of insulin due to nutrient stimuli is recognized for its important role in proper glucose transport, glucose homeostasis, and vasodilation (promoting the endothelial nitric oxide synthase [eNOS] enzyme and endothelial nitric oxide [eNO]), as well as

Table 1. The spectrum of diabetes complications implicating reactive oxygen species (ROS): The MINER acronym of hypertension and type 2 diabetes mellitus.

M	Myocardial redox stress and remodeling	ROS
I	Islet and intimal-vascular redox stress and remodeling	ROS
N	Neural redox stress and remodeling	ROS
E	Endothelial redox stress and remodeling	ROS
R	Renal and retinal redox stress and remodeling	ROS

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its antioxidant, anti-inflammatory, and profibrinolytic properties.¹³ Thus, in physiologic concentrations, insulin is considered to be a vasculoprotective hormone.

Compensatory HI due to underlying IR enhances the body's ability to delay the development of overt type 2 DM. However, this loss of hormonal homeostasis does not come without a price. HI increases the activity of the sympathetic nervous system, increases reabsorption of sodium and water in proximal renal tubules, decreases urinary sodium excretion, activates the renin-angiotensin-aldosterone system (RAAS), raises arterial tone and pressure by increasing the membrane transport of calcium, increases the number of angiotensin type 1 (AT-1) receptors, and stimulates vascular smooth muscle cell proliferation, migration, and vascular extracellular matrix remodeling.^{14,15}

Tables II and III summarize these and other maladaptive effects of endogenous HI when there is loss of hormonal homeostasis.

Amylin: Hyperamylinemia

Amylin, or islet amyloid polypeptide, is the second β -cell-derived hormone important in glucose homeostasis. Amylin, the major component of islet amyloid,

is found in up to 90% of autopsied patients with type 2 DM.^{16,17} Amylin is cosynthesized and cosecreted with insulin in response to glucose or nutrient stimuli. Amylin and insulin—both products of pancreatic β -cells—have distinct amino acid sequences, structures, and functions. Although the insulin story has been evolving since its discovery in 1922, the amylin story has remained a mystery until recently.

Unlike insulin, amylin is amyloidogenic. Type 2 DM is, in part, a conformational disease related to the misfolding properties of the small 37-amino acid protein that results in islet amyloid formation.¹⁸ Amylin-derived islet amyloid deposition appears to be a factor in the progressive nature of type 2 DM. Amylin-derived islet amyloid results in a diffusion barrier, as well as a secretory and an absorptive defect within the islet; its small oligomeric forms are capable of causing apoptosis of islet β -cells, resulting in β -cell loss.¹⁹

Table II. Detrimental effects of hyperinsulinemia (HI).

- HI promotes activation of the sympathetic nervous system
- HI promotes Na^+ and H_2O retention and decreases urinary Na^+ excretion, which increases blood volume and blood pressure
- HI increases membrane cation transport, increasing intracellular Ca^{++} , increasing tone and pressure
- HI stimulates vascular smooth muscle cell proliferation, migration, and remodeling
- HI is associated with hyperproinsulinemia and hyperamylinemia, which independently and synergistically activate the renin-angiotensin-aldosterone system with a subsequent increase in angiotensin II, renin, and aldosterone
- HI increases the number of angiotensin type I receptors

Endogenous insulin is associated with amylin, whereas exogenous insulin is not associated with amylin or proinsulin.

Table III. Hyperinsulinemia promotes a local renin-angiotensin-aldosterone system with resultant detrimental angiotensin II effects.

- Angiotensin II: potent stimulus for production of NADPH oxidase with superoxide production and generation of reactive oxygen species
- Angiotensin II promotes the MAP kinase pathway and remodeling
- PI3K/Akt-MAP kinase shunt; impairs the metabolic (PI3K/Akt) pathway while promoting the MAP kinase remodeling pathway
- Angiotensin II promotes endothelin pathway MAP kinase
- Hyperinsulinemia creates cross talk between the insulin receptors and AT-1 receptors, resulting in more profound angiotensin II effects
- Both hyperinsulinemia and angiotensin II promote plasminogen activator inhibitor-1 activation production and secretion

Endogenous insulin is associated with amylin, whereas exogenous insulin is not associated with amylin or proinsulin.

NADPH = reduced form of nicotinamide adenine dinucleotide phosphate; MAP = mitogen-activated protein; PI3K = phosphatidylinositol 3-kinase; Akt = protein kinase B; AT-1 = angiotensin type 1.

Hyperamylinemia (HA) can also activate the RAAS independently and synergistically with HI, further advancing the link of HTN to IR and type 2 DM. HA acts as a potent marker of risk for the development of HTN, and amylin-derived islet amyloid appears to be an integral component of the MetS, IR, and type 2 DM.^{18,20,21}

Amylin is a potent inhibitor of gastric emptying and is important in controlling and delaying the rate of meal-derived glucose.²² It inhibits hepatic release and the production of glucose in the postprandial period. In addition, amylin has been shown to inhibit glucagon and somatostatin secretion, slowing insulin's secretion. Amylin's synthesis and excretion parallel those of insulin in the β -cell; however, it has biological actions in many tissues. Amylin contributes to the perception of satiety and thirst, indicating that it has actions within the central nervous system. Amylin also has been shown to have binding sites within the renal cortex in the area of the juxtaglomerular apparatus and to activate the RAAS.²² This may help explain, in part, why the angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are important in the drug treatment of type 2 DM.

HA has recently been shown to predict the future development of essential HTN in the normotensive offspring of those patients with essential HTN and thus may become a useful marker for HTN.²³ For those patients with DM who are insulin and amylin deficient, an injectable amylin analogue (pramlintide) is available. Pramlintide replaces the amylin deficiency just as exogenous insulin replaces only the endogenous insulin deficiency in patients with both type 1 and type 2 DM; it has also been shown to lower glycosylated hemoglobin levels and improve the postprandial glucose spikes without causing weight gain.²⁴ Pramlintide does not activate the RAAS during physiologic replacement doses, and the analogue is not amyloidogenic.²⁵ Current estimates indicate that only 20% of patients with IR and HI/HA develop type 2 DM, while the remaining 80% are able to compensate—at least for a period of time—through the process of β -cell expansion, hypertrophy, and hyperplasia (using the replicative pool of periductal cells).^{11,18,20,21}

Leptin: Hyperleptinemia and Selective Leptin Resistance

The MetS and IR (playing a central role with compensatory HI and HA) are also associated with hyper-

leptinemia. As humans become obese, leptin levels increase due to adipocyte accumulation. This adipose-derived hormone is responsible for acting on the hypothalamus to decrease appetite and increase energy expenditure and sympathoneuronal outflow. It has been proposed that a selective leptin resistance exists in humans, whereby leptin's metabolic ability to suppress appetite and promote weight loss is lost and the sympathetic stimuli and increased sodium reabsorption ability are preserved. This selective leptin resistance may be a crucial mechanism linking adiposity and HTN.²⁶

METABOLIC TOXICITIES AND PRODUCTION OF REACTIVE OXYGEN SPECIES

Numerous metabolic toxicities are associated with HTN and type 2 DM as a result of IR and the MetS, summarized with another useful acronym, A-FLIGHT-U (**Table IV**).²⁷ These toxicities are characterized by excessive tissue generation of reactive oxygen species (ROS), resulting in endothelial dysfunction and detrimental tissue remodeling. The elevation of free fatty acids is not only important as a source of ROS but also is responsible for promoting IR in skeletal muscle, as well as in hepatic, cardiovascular, and renal tissue. Multiple reviews have discussed each of these metabolic toxicities in detail.^{11,21,25,28,29}

Angiotensin II Renin Paradox

At first it may appear paradoxical to have a systemic low-to-normal plasma renin state in type 2 DM with coexisting HTN.³⁰ However, on examination of the local-tissue RAAS, it becomes evident that this enzyme system is activated and may be largely due to the associated IR with the ensuing compensatory HI and HA. IR is not caused by HTN; IR, due to genetic and environmental causes, is a major contributor to the development of HTN in patients with type 2 DM.³¹

Insulin Resistance in Essential Hypertension

Impaired insulin signaling occurs in essential HTN; patients with essential HTN who are drug naive have higher fasting and postprandial insulin levels than age- and sex-matched normotensive individuals, regardless of body mass.³¹ In addition, a direct relationship exists between plasma insulin levels and BP. IR and HTN have been demonstrated to coexist in rodents with genetic HTN.^{32,33} Furthermore, the relationship between plasma insulin levels and HTN does not occur with secondary

Table IV. Multiple metabolic toxicities in diabetes complications: The A-FLIGHT-U acronym.²⁷

A	Angiotensin II: activates membrane-bound NADPH, producing reactive oxygen species and TGF- β Amylin: activates renin-angiotensin-aldosterone system (angiotensin II) Antioxidant-oxidant imbalance Advanced glycation end products Advanced fructosylation end products Advanced lipoxidation end products Atherosclerotic nephropathy Accelerated atherosclerosis-atheroscleropathy \rightarrow cardiovascular disease Aging Albuminuria: requires early detection and treatment
F	Free fatty acid toxicity
L	Lipototoxicity
I	Insulin resistance/insulin toxicity (hyperinsulinemia/hyperproinsulinemia) Ingested or dietary advanced glycation end products
G	Glucotoxicity
H	Hypertension toxicity Homocysteine toxicity
T	Triglyceride toxicity
U	Uric acid toxicity via xanthine oxidase

NADPH = reduced form of nicotinamide adenine dinucleotide phosphate; TGF- β = transforming growth factor- β .

HTN. IR and HI are not consequences of HTN but instead constitute a genetic predisposition that may contribute to both disorders.³¹ This idea is given additional support by the observation that children of hypertensive parents have abnormal glucose metabolism.³¹

Patients with essential HTN are more prone than normotensive individuals to develop DM, a propensity that may reflect a decreased ability of insulin to promote relaxation and glucose transport in vascular and skeletal muscle tissue, respectively. Accumulating data suggest that angiotensin II, acting through its AT-1 receptors, inhibits the action of insulin in vascular and skeletal muscle tissue, in part, by interfering with insulin signaling through phosphatidylinositol 3-kinase (PI3K) and its downstream protein kinase B (Akt) signaling pathways.³¹ The effect of angiotensin II is partially mediated through stimulation of RhoA (the small G protein family-guanosine triphosphatase) activity and oxidative stress (superoxide is the primary ROS generated; peroxynitrite is the primary reactive nitrogen species). RhoA and increased ROS inhibition of PI3K/Akt signaling result in decreased endothelial cell production of the naturally occurring nitric oxide, increased myosin light chain activation with vasoconstriction, and reduced skeletal mus-

cle glucose transport. More details are known about the complex nature of angiotensin II and insulin-like growth factor-1 counterregulatory actions in endothelial cells, vascular smooth muscle cells, and skeletal muscle. This shunting mechanism also promotes vascular and extracellular matrix remodeling due to impairment of the metabolic PI3K/Akt pathway while promoting the mitogen-activated protein (MAP kinase) remodeling pathway. This remodeling shift has been termed the "PI3(Akt)-MAP kinase" shunt.³¹

MANAGEMENT OF HYPERTENSION IN TYPE 2 DIABETES MELLITUS

BP <130/80 mm Hg is recommended by the JNC VII, the National Kidney Foundation (NKF), and the American Diabetes Association (ADA) guidelines.²⁹⁻³² Reduction of BP in people with DM decreases the incidence of associated complications such as renal disease progression and cardiovascular mortality.³⁴⁻³⁷

Nonpharmacologic Intervention

Therapeutic lifestyle changes are paramount, along with medical therapy at the earliest detection of elevated BP in patients with type 2 DM. Weight reduction and

increased aerobic activity are essential in treating patients who have the MetS; both strategies have been shown to improve HTN, IR, and dyslipidemia.³⁸ Strong consideration for daily caloric reduction and adoption of a dietary approach to prevent HTN (eg, an eating plan such as the Dietary Approaches to Stop Hypertension intervention that consists of low sodium, high potassium, and high fiber) should be a definite part of the therapeutic strategy.³⁸ Diet coupled with increased physical activity—such as walking or any reduction in sedentary activity—are also helpful; up to 30 to 45 minutes of walking 3 to 5 days per week may help improve BP, IR, dyslipidemia, and glycemic control.

Diet and exercise, along with oral antidiabetic medications and insulin use, have been shown to improve glycemic control, as demonstrated by the Diabetes Control and Complications Trial in type 1 DM and the United Kingdom Prospective Diabetes Study (UKPDS) in type 2 DM.^{39,40} Tight BP control should be as important as tight control of blood sugar.⁴⁰ Not only do these measures reduce the morbidity/mortality complications, but they also are quite cost-effective in this high-risk group of patients.⁴¹

Pharmacologic Intervention

RAAS blockade with an ACE inhibitor or an ARB combined with a thiazide diuretic as initial therapy is generally warranted and serves as the cornerstone of combination therapy.⁴² Combination therapy of ≥ 2 classes of antihypertensive medications is usually required to achieve the goal BP of $<130/80$ mm Hg. Because RAAS blockade with ACE inhibitors and/or ARBs seldom bring BP in line with current guideline levels, additional antihypertensive medication is frequently required. Poor BP control may lead to excessive systemic mechanical stress and stretch at the vascular level, despite adequate inhibition of angiotensin II effects.

Angiotensin-Converting Enzyme Inhibitors

ACE inhibitors are cardioprotective, vasculoprotective, and renoprotective in DM; they also improve IR and delay the onset of overt type 2 DM.⁴¹ ACE inhibitors have demonstrated the ability to slow progression of nephropathy in microalbuminuric, normotensive patients with type 2 DM when compared with other antihypertensive agents. In addition to the antihypertensive effects of ACE inhibitors, pleiotropic positive effects exist in preventing renal remodeling within

the glomerulus and tubular interstitium. ACE inhibitors decrease mesangial and interstitial extracellular matrix expansion, glomerular basement membrane permeability to albumin, and intraglomerular pressure. ACE inhibitors also may have an effect on the adipose tissue and the adipocyte in obesity, with resulting improvements in insulin sensitivity and reduced production of detrimental adipocytokines.^{41,43}

Monitoring of renal function and potassium levels is important when using ACE inhibitors. A slight rise in serum creatinine may be expected. Withdrawal of an ACE inhibitor in such patients should occur only when the increase in creatinine exceeds 30% above baseline values within the first 2 months of ACE inhibitor initiation or when hyperkalemia develops (serum potassium level ≥ 5.6 mEq/L).^{41,44} Analyses of many ACE inhibitor-based trials demonstrate the greatest slowing of renal disease progression in patients with the highest degree of renal insufficiency at study initiation.^{41,44} If abnormalities develop, then bilateral renal artery stenosis or chronic volume depletion should be excluded. Most cases of inordinate increases in creatinine are due to volume depletion and can often be corrected by normalizing volume status. If excessive cough or fatigue develops, then switching to an ARB may be an effective alternative.

Angiotensin Receptor Blockers

With an antihypertensive efficacy roughly equivalent to ACE inhibitors, ARBs have been shown to have an improved adverse-effect profile compared with ACE inhibitors.⁴¹ ARBs block the AT-1 receptor that is responsible for the effect of angiotensin II. In patients with type 2 DM, ARBs have been shown to reduce albuminuria and time to creatinine doubling.^{45,46} One study did find a reduction in the progression of nephropathy but not a slowing in the rate of decline in creatinine clearance.⁴⁶ The BP-independent effects of the ARBs were further confirmed by the Microalbuminuria Reduction with Valsartan Study.⁴⁷ Based on the current evidence and because of their tolerability, ARBs are recommended as first-line therapy for patients with DM, HTN, and significant proteinuria.⁴⁸

Our laboratory has recently observed the prevention of podocyte cellular structural remodeling and preservation of filtration slits in an animal model that overexpressed angiotensin II (Ren-2 model with transfection of the mouse renin gene) with the use of an ARB.⁴⁹ The

combined prevention of these structural changes, prevention of microalbuminuria, the abrogation of oxidative stress, and improved insulin sensitivity in this Ren-2 model all point to the importance of renoprotection with the use of this class of medication.⁵⁰

Diuretics: Thiazides

Thiazide diuretics have been shown to reduce cardiovascular events and slow renal disease progression. In the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT), the thiazide diuretic chlorthalidone comparably reduced all-cause mortality such as stroke, coronary artery disease, and heart failure similar to the use of an ACE inhibitor (lisinopril) and a calcium channel blocker (CCB) (amlodipine).⁵¹ A dose of chlorthalidone equivalent to 50-mg hydrochlorothiazide was utilized, leading to an increase in new onset of DM. However, the BP-lowering effect with this high dose of chlorthalidone was superior to the lowering of BP with ACE inhibitors or CCBs, which may have accounted for an improvement in the observed decrease in cardiac events. Thus, the results of ALLHAT lend considerable weight to the concept of using thiazide diuretics as first-line therapy for many hypertensive patients. Even though diuretics have been shown to worsen IR and thus may promote HI with associated salt retention and volume expansion, they have also been shown to consistently improve cardiovascular outcomes, even in those with DM, which points to the overall importance of BP reduction.⁵¹ Diuretics can potentiate the antihypertensive effects of ACE inhibitors and ARBs, decrease volume expansion, and be an effective first-line combination therapy.

β -Blockers

β -Blockers are effective agents for the hypertensive patient with type 2 DM. As demonstrated in the UKPDS, atenolol was comparable to captopril in the reduction of cardiovascular outcomes.^{40,41} A newer β -blocker (carvedilol) has recently been shown to induce vasodilation and improve insulin sensitivity.⁵² Atenolol and carvedilol have been demonstrated to reduce albuminuria, especially in combination with RAAS blockade. Some concerns still exist regarding the use of β -blockers in patients who have both DM and HTN; however, the current position is that these agents are safe and often necessary to obtain established BP guidelines. They are regarded as an important part of the therapeutic regi-

men with coexisting ischemic heart disease or heart failure, unless otherwise contraindicated. Two excellent discussions regarding the use of β -blockers in the hypertensive diabetic patient have recently been published, providing a more in-depth view of these agents.^{53,54}

Calcium Antagonists (Calcium Channel Blockers)

CCBs are potent antihypertensive medications. Nondihydropyridine calcium antagonists (NDHPCAs), such as verapamil and diltiazem, confer an important degree of renal protection. This degree of renoprotection is not comparable to ACE inhibitors or ARBs as monotherapy; however, in combination therapy, NDHPCAs have been shown to have additive effects on reducing albuminuria. When used in conjunction with RAAS blockade, evidence from the ALLHAT and Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) studies indicate that NDHPCAs are renoprotective.^{51,55} Thus, calcium antagonists are often useful as third-line therapy in addition to ACE inhibitors, ARBs, and diuretics.

Calcium antagonists were required to obtain lower BP goals in 78% of the patients in the RENAAL study.⁵⁵ One frequently asked question is, "Do the dihydropyridine calcium antagonists maintain the beneficial cardiovascular effects of RAAS blockade?" According to a post hoc analysis by the RENAAL investigators, the answer is that simultaneous therapy with a CCB did not detract from the beneficial effects of losartan.⁵² Thus, driving down BP to the goal of <130/80 mm Hg with the most commonly used long-acting dihydropyridine (amlodipine) allowed retention of all the beneficial effects of RAAS blockade. BP control to a goal of <130/80 mm Hg may be more important than the initial drug selection in preventing cardiovascular and renal protection in type 2 DM.

α -Antagonists (α -Blockers)

α -Antagonists have been noted to be, at the very least, either neutral or to actually improve the glucose and lipid profiles relative to the other classes of antihypertensive agents, such as β -blockers and thiazide diuretics, and may lower IR due to vasodilation.⁵⁵ They can be used in the regimen to treat HTN in type 2 DM to meet the current BP guidelines; however, they are not to be used as first- or second-line therapy.

Aldosterone Antagonists

Both spironolactone (an older aldosterone antagonist) and eplerenone (a newer and more specific mineralocorticoid receptor antagonist) have recently come into use for the treatment of congestive heart failure. Because sodium retention and volume expansion, mediated in part by aldosterone, are prominent features in low-renin hypertension, the use of these agents in hypertensive diabetic patients is just starting to unfold. They may be considered in the combination therapeutic management as second-line RAAS blockade in the treatment of HTN in type 2 DM.⁵⁶ Hyperkalemia is a concern when using this class of medications; potassium levels should therefore be monitored.

The development of gynecomastia is considerably less with eplerenone compared with spironolactone.⁵⁶

Emerging Therapy: Renin Inhibition

The first-in-class oral renin inhibitor SPP100 (aliskiren) is under development for the treatment of HTN. This inhibition occurs upstream from ACE inhibitors and ARBs; it may be used in combination therapy with an ACE inhibitor and/or ARB in a more complete RAAS blockade. Phase III studies with SPP100 were started in 2004; this new medication may add to the armamentarium for both primary and combination therapy in the treatment of HTN and the end-organ remodeling changes associated with HTN in type 2 DM. Although it could take some time before this new medication proves itself in the management of HTN in type 2 DM, its upstream RAAS effects may prove to offer an additional tool in the repertoire of RAAS blockade.⁵⁷

Peroxisome Proliferator–Activated Receptor Agonists

Peroxisome proliferator–activated receptors (PPARs) are members of the nuclear hormone receptor superfamily and bind to DNA to regulate transcription. They are lipid activated or induced by various pharmaceutical ligands, which exert several functions in development and metabolism. There are 3 PPAR subtypes, which are commonly designated as PPAR- γ , PPAR- α , and PPAR- β/Δ . Although PPAR- γ agonists are considered to be primarily insulin sensitizers and not anti-hypertensive agents, they do alleviate many of the multiple metabolic toxicities (**Table IV**) associated with the vasculopathy of the MetS, HTN, and type 2 DM.

The PPAR- γ agonists—the thiazolidinediones (TZDs), including rosiglitazone and pioglitazone—have been shown to decrease BP in humans and in rodent models of IR and to improve the metabolic, vasoactive, inflammatory, and thrombotic conditions to potentially retard the atherosclerotic process.^{58–64}

TZDs are specific PPAR- γ agonists and improve a number of metabolic abnormalities associated with IR and the MetS. They improve insulin sensitivity in skeletal muscle, adipose tissue, and hepatocytes by increasing the expression of glucose transporters 1 and 4, thereby reducing hyperglycemia and HI. Additionally, they influence lipid metabolism and result in a decrease in free fatty acids and LDL cholesterol levels, and an increase in HDL cholesterol concentrations. Although TZDs are considered insulin sensitizers, they do improve the secretory response of the β -cells to insulin secretagogues. TZDs are known to be anti-inflammatory, decreasing tumor necrosis factor- α via its suppression of nuclear factor κ B. They are known to modulate cardiovascular function and morphology independently of their insulin-sensitizing effects. TZDs have been demonstrated to decrease BP in various animal models of HTN, as well as hypertensive insulin-resistant patients, and are known to inhibit proliferation, hypertrophy, and migration of vascular smooth muscle cells induced by growth factors. Additionally, they induce vasodilation by blockade of calcium mobilization from intracellular stores and by inhibition of extracellular calcium uptake via L-type channels. Furthermore, TZDs interfere with pressor systems (catecholamines, renin-angiotensin system) and enhance endothelium-dependent vasodilation. A key role of the TZDs' effects in vascular remodeling is played by inhibition of the MAP kinase pathway.^{58–62}

The PPAR- α agonists include polyunsaturated fatty acids and the fibrate class of medications, including fenofibrate and gemfibrozil. PPAR- α activation increases HDL cholesterol synthesis, stimulates reverse cholesterol transport, and reduces triglycerides. The fibrates are used in monotherapy and are being increasingly utilized in combination therapy with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) to bring lipids to goal levels.^{54–62}

The dual PPAR agonists (commonly referred to as the glitazars and represented by muraglitazar and tesaglitazar) may be clinically available in the very near

future (2006). They combine the lipid effects of a PPAR- α agonist with the insulin-sensitizing effects of a PPAR- γ agonist. Clinicians await the approval of this new class of medications with great anticipation, as these agents may provide a synergistic effect with regard to improving the metabolic, vasoactive, inflammatory, and thrombotic milieu associated with the increased CVD risk of the MetS and type 2 DM.⁶³

The biological role of PPAR- β/Δ receptors has been unclear until recently. The treatment of obese animals using specific PPAR- Δ agonists results in normalization of metabolic parameters and reduction of adiposity.⁶⁴ The pharmaceutical industry is in the process of developing PPAR- Δ agonists. Currently, the roles of a pan-PPAR agonist are evolving and may further add to our existing and evolving treatment of the metabolic, vasoactive, inflammatory, and thrombotic milieu associated with the MetS, IR, and the various complications associated with type 2 DM.

ENDOTHELIAL DYSFUNCTION IN HYPERTENSION AND TYPE 2 DIABETES MELLITUS

Central to each DM complication is the presence of vascular abnormalities of the endothelium and its associated endothelial dysfunction (ED), the production of ROS, and microvascular and macrovascular complications.

IR leads to the loss of hormonal homeostasis. Subsequent HI, hyperproinsulinemia, and HA individually and synergistically activate the local-tissue RAAS, leading to increased angiotensin II, which is the most potent activator of the membranous reduced form of nicotinamide adenine dinucleotide phosphate oxidase. This then progresses to the generation of reactive species (eg, superoxide and peroxynitrite, an outcome resulting in eNOS uncoupling) (**Figure**).

eNOS is required for the production of eNO. The eNOS enzyme reaction is of critical importance to the normal functioning of the endothelium and the arterial

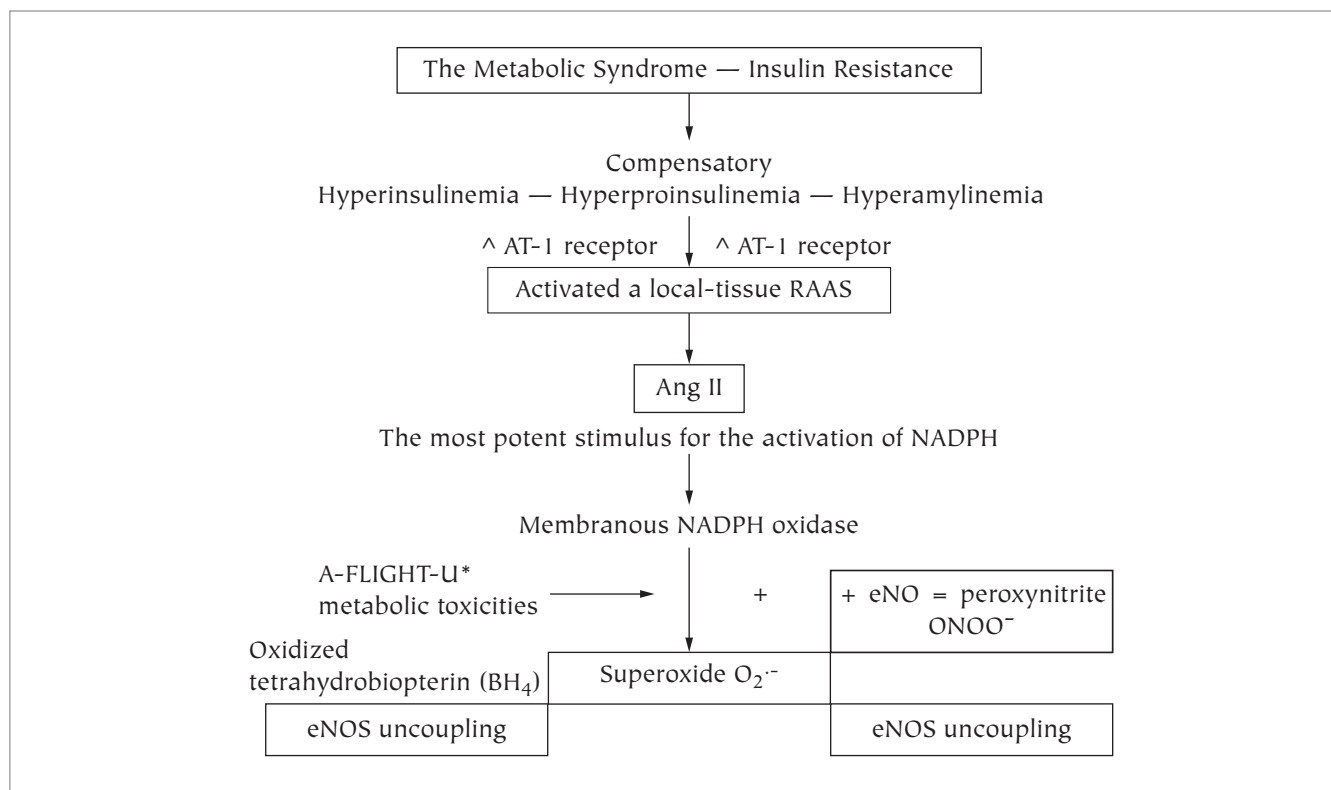


Figure. Insulin resistance leads to the loss of hormonal homeostasis. This figure demonstrates the origin of vascular reactive oxygen–nitrogen species due to endothelial nitric oxide synthase (eNOS) enzyme uncoupling, which results in the net vascular production of superoxide and peroxynitrite instead of the vasculoprotective endothelial nitric oxide (eNO). AT-1 = angiotensin type I; RAAS = renin-angiotensin-aldosterone system; Ang II = angiotensin II; NADPH = reduced form of nicotinamide adenine dinucleotide phosphate. *See Table IV.

vessel wall. In healthy individuals, the endothelium is a net producer of eNO. However, in patients with type 2 DM and HTN, the eNOS enzyme uncouples, and the endothelium becomes a net producer of superoxide and reactive oxygen–nitrogen species, instead of eNO, which has protective antioxidant properties.^{21,28}

Uncoupling of the eNOS enzyme system results in an endotheliopathy and ED (resulting in a leaky endothelium in the glomerulus and systemically). ED plays a major role in the development of microalbuminuria (MAU), which is related not only to diabetic nephropathy but also to an increased risk of cardiovascular events. These findings highlight the importance of early detection and the need to take clinical action to lower the elevated levels of MAU.

MICROALBUMINURIA IN HYPERTENSION AND TYPE 2 DIABETES MELLITUS: EARLY DETECTION AND TAKING ACTION

MAU (defined as 30–300 mg albumin/g creatinine) is an important clinical tool to assess and detect those patients with type 2 DM and HTN who are at increased risk for the development of CVD events and diabetic nephropathy. The ADA and NKF have recommended measurement of the albumin-to-creatinine ratio in either a first-morning voided urine specimen or a random-spot urine collection using the dipstick method due to its simplicity.^{65,66} Levels exceeding the defined parameters of MAU are considered macroalbuminuria (the collection of 24-hour urine samples for creatinine clearance can still be used for measuring total urinary albumin excretion). They further recommend that 2 of 3 specimens be positive before making a diagnosis of MAU.

Various epidemiologic and cross-sectional studies have reported marked variation in the prevalence of MAU, which appears to be associated with ethnic populations and varies from 7% to 9% in United Kingdom whites, 31% in Mexican Americans, 26% in Pima Indians, 42% in Nauruans, 35% in Hispanic Americans, and 36% in individuals from southern India.⁶⁷

A recent study of 2969 patients with DM receiving primary care through a large regional health maintenance organization found that the unadjusted prevalence of MAU or macroalbuminuria was 30.9%, which was similar among the various racial/ethnic groups.⁶⁸ In 1999, a study of >1000 primary care physicians

revealed that 80% screened more than half of their patients with diabetes (both type 1 and type 2 DM) for overt macroalbuminuria, generally by the dipstick method.⁶⁹ In this same study, only 17% conducted screening for MAU in patients with type 1 DM, and only 12% conducted this screening for patients with type 2 DM.

In a preliminary report from the Baylor University Department of Family Practice (Houston, Texas), Champion et al⁷⁰ reported that only approximately one third of patients with type 2 DM were being screened for MAU in the year 2000. Furthermore, of the 1247 patients with type 2 DM who were identified as at high risk for HTN, only 26.7% met the target BP of 130/85 mm Hg.

In a chart review study of 1372 active clinic patients with DM (1247 [90.9%] of whom had type 2 DM), McFarlane et al⁷¹ found that only 26.7% met the target BP level of 130/85 mm Hg. Applying the current recommended guidelines to reach the goal BP of <130/80 mm Hg, these findings would suggest an even lower percentage of patients capable of obtaining the newer, current recommended guidelines.

Elevated BP and poor glycemic control are the 2 causal risk factors for MAU that stand out in type 2 DM, along with the various parameters of the MetS and the A-FLIGHT-U metabolic toxicities. Clinicians need to take more aggressive action with respect to early detection and intervention to protect these patients.

FUTURE DIRECTIONS Global Risk Reduction

The need for a global risk reduction team approach is evident since it is difficult for the primary care provider to balance all of the known guidelines at each visit. Therefore, a team approach—which includes the patient, the DM management staff (including certified DM educators, nutritionists, and medical office staff), and the patient's family, as well as the support of relevant multispecialty colleagues and the utilization of modern-day computer technology—is necessary to reach the accepted current guidelines.

The RAAS acronym (**Table V**)⁷² summarizes treatments for global risk reduction in patients with the MetS and the combination of HTN and type 2 DM. The local-tissue RAAS generates the autocrine, paracrine,

Table V. The RAAS acronym: Treatments for global risk reduction.⁷²

The following treatments individually and synergistically contribute to redox stress reduction:

R	Reductase inhibitors (HMG-CoA)	Decrease LDL-C and triglycerides Increase HDL-C Improve endothelial cell dysfunction Restore abnormal lipoprotein fractions Decrease redox and oxidative stress to arterial vessel wall and myocardium
	RAAS blockade	RAAS blockade
A	ACE inhibitors and ARBs (“prils” and “sartans”)	Both inhibit local and systemic effects of angiotensin II Antihypertensive effects Inhibit deleterious effects of angiotensin II on cells at local levels by decreasing injurious stimuli for ROS production Decrease A-FLIGHT-U* toxicities Positive effects on microalbuminuria; delay progression to end-stage renal disease Direct/indirect antioxidant effect within arterial vessel wall and capillary Antioxidant effects
	Acetylsalicylic acid	Antiplatelet, anti-inflammatory effect on diabetic, hyperactive platelets
	Adrenergic blockade (nonselective)	Blockade of prorenin → renin conversion
	Amlodipine-felodipine	Calcium channel blocking antihypertensive effect Direct antioxidant effects
A	Aggressive control of diabetes mellitus	Target A1C <7.0%: usually requires combination therapy with insulin secretagogues, insulin sensitizers (PPAR-γ agonists), biguanides, α-glucosidase inhibitors, exogenous insulin Decrease LDL-C Improve endothelial cell dysfunction Decrease glucotoxicity and oxidative-redox stress to intima and pancreatic islet
	Aggressive control of blood pressure	Usually requires combination therapy Compelling indications: ACE inhibitors, ARBs, diuretics, β-blockers, CCBs, JNC VII
	Aggressive control of homocysteine with folic acid	Positive effect on recoupling of eNOS enzyme reaction by restoring activity of BH ₄ cofactor eNOS reaction runs via a folate shuttle mechanism and once again produces eNO
	Aggressive control of uric acid levels	Xanthine oxidase inhibitors (allopurinol, oxypurinol, febuxostat) Should be strongly considered in view of prevailing literature to achieve more complete global risk reduction

(continued)

Table V. (Continued)

S	Statins	Improve plaque stability (pleiotropic effects) independent of cholesterol lowering Improve endothelial cell dysfunction Direct/indirect antioxidant, anti-inflammatory effects within the islet and arterial vessel wall, promoting stabilization of the unstable, vulnerable islet, and arterial vessel wall
	Style	Lifestyle modification: weight loss, exercise, and change eating habits
	Stop smoking	

HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; RAAS = renin-angiotensin-aldosterone system; ACE = angiotensin-converting enzyme; ARBs = angiotensin receptor blockers; ROS = reactive oxygen species; A1C = glycosylated hemoglobin; PPAR = peroxisome proliferator-activated receptor; CCBs = calcium channel blockers; JNC VII = Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; eNOS = endothelial nitric oxide synthase; eNO = endothelial nitric oxide.

*See Table IV.

and endocrine molecule angiotensin II, which is activated by the compensatory HI, hyperproinsulinemia, and HA due to a loss of hormonal homeostasis via IR; this is further complicated by excessive redox stress and ROS in each of the component DM and hypertensive complications.

What can we expect if we follow the multifaceted RAAS acronym? The Steno-2 Study demonstrated that if a global risk reduction approach was undertaken in an aggressive fashion, a significant reduction in DM complications could be expected.⁷³ This study (which included patients with type 2 DM plus MAU) showed that intensive intervention for an average of 7.8 years reduced the incidence of cardiovascular events, nephropathy, retinopathy, and autonomic neuropathy by about half as compared with a conventional multifactorial treatment.

As clinicians, a key challenge is to now ensure that these trial experiences are widely adopted in daily clinical practice. In terms of the polygenic multifactorial disease of HTN and type 2 DM, clinicians should try to identify and eliminate treatment barriers to this aggressive, multipronged/multifaceted therapeutic approach.⁷³ The certified diabetic educator can play a very important role in the patient's adherence to a multidisciplinary team approach, as can the local pharmacist. As shown in **Table VI**, clinicians can take specific actions to increase patient adherence, in addition to face-to-face meetings in the office and hospital.⁷⁴

A New Definition of Hypertension

The American Society of Hypertension at its annual meeting held in May 2005 proposed a new definition of HTN and how it fits in global risk reduction. The new definition states: "Hypertension is a progressive cardiovascular syndrome arising from complex and interrelated variables. Early markers of the syndrome are omnipresent before BP elevation is sustained; therefore, hypertension cannot be classified solely by BP thresholds. Progression is strongly associated with function and structure of cardiac and vascular abnormalities that damage the heart, kidneys, brain, and vasculature, and lead to premature morbidity and death."⁷⁵ Use of the A-FLIGHT-U toxicities (**Table IV**) and the RAAS acronym (**Table V**) for the prevention and treatment of HTN and type 2 DM will assist the primary care provider in this task.

Early detection of MAU and effective intervention are the keys to halt the morbidity and mortality associated with HTN and type 2 DM. Identification and treatment of the multiple A-FLIGHT-U toxicities can make a huge difference in the development of complications relating to HTN and type 2 DM. Clinicians are strongly encouraged to adopt the global risk reduction team approach to help patients reach established guideline goals. Utilizing the combination global risk reduction RAAS strategy earlier—rather than later—may help change the outcomes for patients with HTN and type 2 DM.

Table VI. Suggested guidelines for clinicians to increase patient adherence.

- | | |
|---|--|
| <ul style="list-style-type: none"> ● 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 patient's spouse, family, and friends ● Establish signed agreements/contracts ● Encourage self-monitoring ● Provide training in behavioral skills ● Educate patients to enhance self-efficacy perceptions | <ul style="list-style-type: none"> ● 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 V.

DISCUSSION AND CONCLUSIONS

A closer look at the complexities of HTN in patients with type 2 DM is revealing. Insulin is recognized for its important role in proper glucose transport and vasodilation (promoting the eNOS enzyme and eNO), as well as its antioxidant, anti-inflammatory, and profibrinolytic properties. Clinicians are now in a position to understand that IR is accompanied by a compensatory loss of hormonal homeostasis through HI, hyperproinsulinemia, and HA, and that activation of a local-tissue RAAS is responsible for many of the complications associated with the MetS, including HTN and type 2 DM.

Without effective intervention, HTN and type 2 DM can result in multiple DM complications as well as lead to increases in the incidence of cardiovascular events and end-stage renal disease requiring renal replacement therapy. The clinical perception of insulin derangements can be seen as a complicated mosaic, with contributions by ROS due to the interrelated A-FLIGHT-U multiple metabolic toxicities—all leading to the development of DM complications.

The triumvirate— β -cell, muscle, and liver tissues—described by DeFronzo in 1987,⁷⁶ along with the presence of adipose tissue described by Reaven in 1995,⁷⁷ merge to form the complicated mosaic of IR, MetS, and type 2 DM; these conditions result in a loss of hormonal homeostasis. This compensatory hypersecretion by the β -cell in the MetS and prediabetes state plays a major role in the development of HTN through activation

of a local-tissue RAAS. HTN in type 2 DM can be partially explained as a form of secondary HTN involving the β -cell with loss of insulin hormonal homeostasis.^{76–78}

It is important for the reader to keep in mind the following two points regarding the management of the MetS, as set forth by the American Heart Association and the National Heart, Lung, and Blood Institute. First, the MetS is a secondary target for reducing cardiovascular events. Smoking cessation, lowering the levels of LDL cholesterol, and BP management are primary targets for risk reduction. Second, lifestyle interventions are the initial therapies recommended for treatment of the MetS. If lifestyle change is not sufficient, then drug therapies for abnormalities in the individual risk factors may be indicated.⁷⁹

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