



What is the most effective management of hypertension in diabetes?

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Over half of type 2 diabetics, particularly women, are likely to be hypertensive at age 50 using the recently recommended cutoff of 130/85 mm Hg. The cause is multifactorial and includes insulin resistance, which is closely related to obesity, itself a risk factor for hypertension. The first-line treatment is lifestyle modification (exercise, weight loss, and smoking withdrawal). This must almost always be aided by drugs, preferably a long-acting angiotensin-converting enzyme inhibitor on the grounds of hard end points (cardiovascular events), renoprotection, and quality of life (decreased impotence), often combined with a low-dose diuretic or a dihydropyridine calcium channel blocker. Proteinuria warrants even more stringent blood pressure control (125/75 mm Hg). Finally, aggressive use of statins may be beneficial even if initial cholesterol levels are only average.

Keywords: hypertension; diabetes; insulin resistance; nephropathy; lifestyle; ACE inhibitor; diuretic; β -blocker; calcium channel blocker

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The new message, from three large studies, is that vigorous treatment of hypertension in diabetics can markedly reduce hard end points.¹⁻³ This means that more and more cardiologists and physicians treating hypertension will be seeing diabetic patients. The presence of diabetes profoundly increases the cardiovascular risk, largely through the adverse combination of diabetes and hypertension. Thus, the prediction charts of the British Joint Committees and several other bodies, such as the combined European Societies of Cardiology, Hypertension, and Atherosclerosis, are divided into those who have diabetes and those who do not. But, what is diabetes and what is hypertension? And is the type of diabetes of importance? As most diabetics presenting with hyper-

tension will be type 2 (maturity-onset, non-insulin-dependent), this article will concentrate on this group.

DIABETES MELLITUS AND HYPERTENSION: DEFINITIONS

Diabetes mellitus and impaired fasting glucose

Recently, the diagnosis of diabetes has been simplified. In the USA, the new guidelines take a consistently elevated fasting blood glucose of 110 up to 125 mg/dL (6.1 to 6.9 mmol/L) as an impaired fasting glucose, and higher values as diabetes mellitus.⁴ Elsewhere, the new proposals of the World Health Organization expert com-

SELECTED ABBREVIATIONS AND ACRONYMS

ACE	angiotensin-converting enzyme
DHP	dihydropyridine
EUCLID	EURODIAB Controlled trial of Lisinopril in Insulin-dependent Diabetes
HOPE	Heart Outcomes Prevention Evaluation study
HOT	Hypertension Optimal Treatment study
IFG	impaired fasting glycemia
IGT	impaired glucose tolerance
SHEP	Systolic Hypertension in the Elderly Program
SYST-EUR	SYSTolic hypertension in elderly in EUROpe trial
UKPDS	United Kingdom Prospective Diabetes Study

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mittee⁵ will probably be followed, diagnosing diabetes as a fasting plasma glucose of 7 mmol/L or more, with values of 6.1 mmol/L, but, below 7.0 mmol/L, representing impaired fasting glycemia (IFG). If the 2-hour glucose is also abnormal in a glucose tolerance test, being above 11.1 mmol/L, then there is impaired glucose tolerance (IGT). However, the major aim is simplification, and the new reliance is on the fasting glucose values, rather than on the glucose tolerance curve, which becomes less important than before.

Definitions of hypertension

A sustained blood pressure (BP) value of 140/90 mm Hg or above is taken as hypertension by both the American and the international bodies.^{6,7} For diabetics, both recommend that BP be reduced to 130/85 mm Hg or below. This means that any higher pressures are too high and, by definition, indicate hypertension. In reality, trial data show that a diastolic value of 82 mm Hg reduces hard end points,¹ but trial data to support the very low systolic recommendation are not yet available.

Incidence of hypertension in diabetics

Taking the now outdated criteria for hypertension, ie, a BP equal to or exceeding 160/90 mm Hg, 35% of male and 46% of females with type 2 diabetes are hypertensive at a mean age of 52 years.⁸ The incidence with the new lower criteria must therefore be even higher, probably exceeding 50%. Of interest, the higher incidence in females, though related to greater obesity, persists even when corrected for obesity.⁸ As in nondiabetics, hypertension is a risk factor for coronary artery disease.

MECHANISMS FOR HYPERTENSION IN DIABETICS

The origin of the hypertension frequently found in diabetics is probably multifactorial. In the more common type 2 diabetes, causes of hypertension may include obesity, insulin resistance, sodium retention, occult renal impairment, increased peripheral vascular resistance, and endothelial dysfunction (*Figure 1*). The latter may, hypothetically, participate in a vicious circle mechanism. Insulin resistance may precede the development of overt type 2 diabetes by more than a decade.⁹ Probably, much or all of the insulin resistance is closely related to obesity, itself a risk factor for hypertension.⁸ The mechanisms for obesity-related hypertension include increased cardiac output and adrenergic activity. The metabolic cardiovascular syndrome describes the association of central obesity, hypertension, and type 2 diabetes and atherosclerotic cardiovascular

disease, in which a key role is played by insulin resistance (*Figure 2*).

Insulin resistance

The basic pathophysiology of the two types of diabetes differs: type 1 diabetes is straightforward insulin deficiency, while type 2 diabetes is associated with hyperinsulinemia and insulin resistance. Insulin resistance has multiple mechanisms of action, including failure to decrease circulating free fatty acid levels to normal values.¹⁰ Free fatty acids may in turn promote vasoconstrictor α_1 -adrenergic activity, at least in normal volunteers. Additionally, insulin resistance reduces skeletal muscle blood flow.

Antihypertensive drugs

Antihypertensive drugs further impair insulin resistance. A mixture of β -blockade, diuretics, and hydralazine, in variable amounts and over 9 years, precipitated diabetes in some subjects who already had

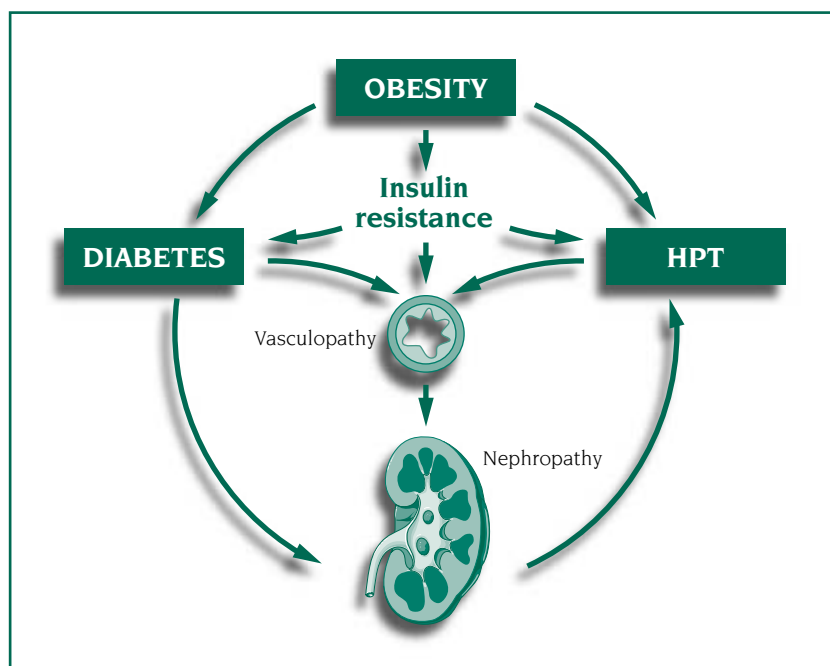


Figure 1. Complex links between diabetes mellitus, hypertension, insulin resistance, and nephropathy. HPT, hypertension. Copyright © L.H. Opie, 1999.

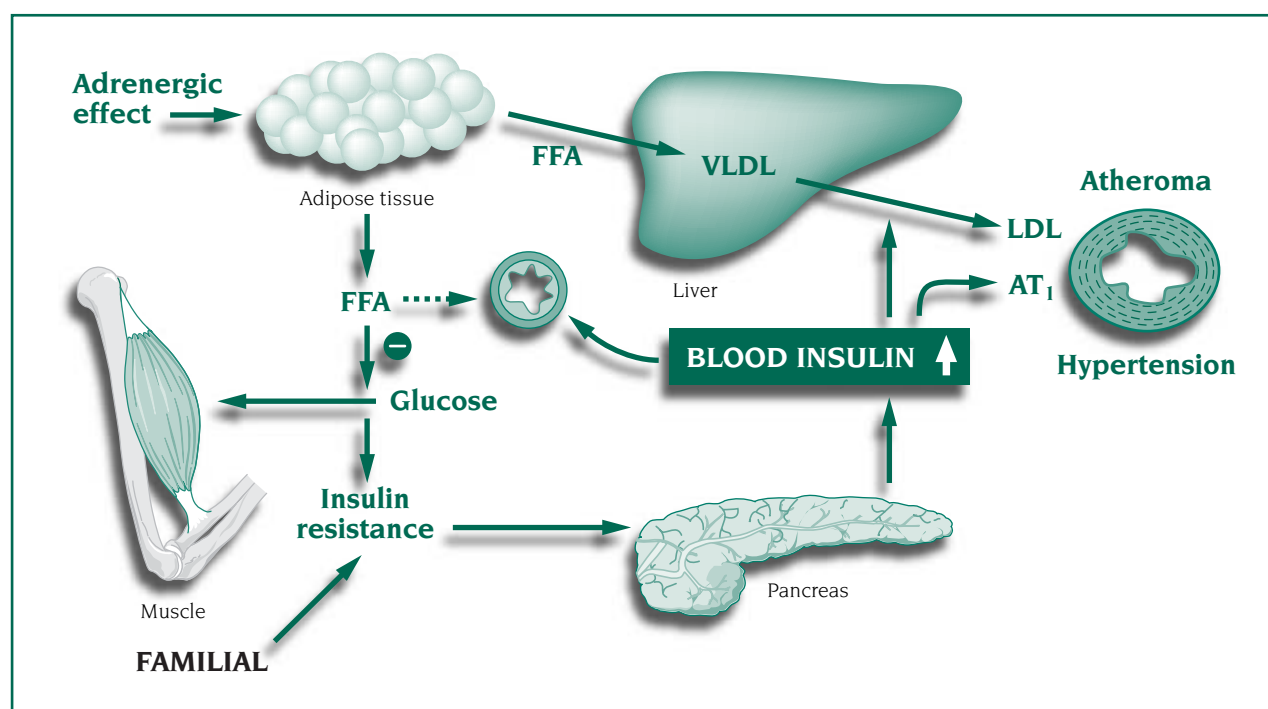


Figure 2. Mechanisms proposed to explain insulin resistance and its vascular complications. AT_1 , angiotensin II receptor, subtype 1; FFA, free fatty acids; LDL, low-density lipoproteins; VLDL, very-low-density lipoproteins. Copyright © L.H. Opie, 1999.

insulin resistance at the start.¹¹ Conversely, changing from a β -blocker to an angiotensin-converting enzyme (ACE) inhibitor may improve insulin resistance in a subset of hypertensives with marked insulin resistance.¹²

Diabetic nephropathy

Diabetic nephropathy is the most common cause of hypertension in the less common type 1 insulin-deficient diabetic.¹³ Yet it also contributes variably to the hypertension of type 2 diabetics.

NONDRUG TREATMENT FOR ALL

Lifestyle modification

A total revolution in the lifestyle of most obese type 2 diabetics is often required. The concept of insulin resistance has implications for the

treatment of hypertension, because nonpharmacological treatment potentially improves insulin sensitivity.

- **Exercise.** Exercise training improves insulin sensitivity.¹⁴ Muscular work enhances the transport of glucose into liver cells.¹⁴ Exercise training is known to reduce BP in nondiabetics. Lack of exercise is now an established risk factor for coronary heart disease, which is known to be a serious complication of diabetes. Physical inactivity may be a risk factor for premature death in diabetics. Therefore, exercise (regular, aerobic) becomes doubly important. A simple recommendation would be running for 15 minutes or walking briskly for 30 minutes every day. In a multifactorial intervention trial, the aim was light-to-moderate exercise for at least 30 minutes, 3 to 5 times per week.¹⁵

- **Smoking.** Type 1 diabetic smokers have higher 24-hour BP values than

nonsmokers, but data for type 2 diabetes are lacking. Both smoking and diabetes cause endothelial dysfunction, so that smoking should stop even in the absence of specific trial data.

- **Diet.** In diabetics, a diet high in complex carbohydrates, including fruit, vegetables, and fiber, helps to control blood sugar.¹³

- **Sodium restriction.** This step appears logical. There is increased sodium retention in diabetics. Elderly hypertensives, as a group, tend to retain sodium, even if they are not diabetic, so that sodium reduction may afford specific benefit in elderly diabetics (but this recommendation lacks supporting data).

- **Weight loss.** Important for nondiabetic hypertensives, weight loss is doubly important for diabetics, in whom it is part of diabetic control. Obesity and physical inactivity are

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part of the picture of type 2 diabetes.⁸ In diabetics, even modest weight reduction can improve blood pressure and control of blood sugar.¹³ Overambitious aims on the part of the attending doctor may be counterproductive.

• **Multifactorial intervention.** Ideally, the above measures should be applied simultaneously and together with tight control of the diabetic status as monitored by fasting blood sugar or hemoglobin A_{1c} status.¹⁵

BLOOD PRESSURE LOWERING BY DRUGS

Aims and means.

Does it matter how the desired low level is reached?

The first aim must be to reduce the BP vigorously to a diastolic value of below 85 mm Hg, ideally to 82 mm Hg. This value comes from trial data,¹ and so can be regarded as reliable, but does not exclude the possibility that even lower BP levels might give greater benefit. Regarding systolic values, common sense and a variety of guidelines suggest that values of about 130 to 135 mm Hg are desirable, but, in the United Kingdom Prospective Diabetes Study (UKPDS), the attained systolic value was 144 mm Hg. To obtain such strict control would almost certainly require more than one agent in most diabetic hypertensives—up to three were used in UKPDS and more in the Hypertension Optimal Treatment (HOT) study.² But which is the best one to start with?

Arguments for an ACE inhibitor as first choice

There are several good arguments for using ACE inhibitors first (together with lifestyle changes) in diabetic

hypertensives, including: (i) the powerful preventive capacity of these agents in high-risk cardiovascular patients, including hypertensive diabetics, as shown in the still unpublished Heart Outcomes Prevention Evaluation (HOPE) study, in which the primary combined end point of cardiovascular death, myocardial infarction, and stroke was reduced by 25% in diabetic hypertensives; (ii) the extensive documentation of renoprotection by ACE inhibitors, in both diabetics with macroproteinuria and those with microalbuminuria, as well as in nondiabetic nephropathy; (iii) the better quality of life with ACE inhibitors than with other agents, including less erectile dysfunction (although not specifically reported in diabetics); and (iv) the possibility of protection from diabetic neuropathy or advancing retinopathy. Conversely, hypertensives treated without ACE inhibitors for an average of 9 years by “older” therapy, such as β -blockade, thiazide, or hydralazine, or combinations thereof, had a severalfold increase in the incidence of diabetes.¹¹

For the above reasons, the present author argues that an ACE inhibitor should be the drug of first choice in diabetic hypertensives. ACE inhibitors are among the first-line drugs for diabetic hypertensives recommended by the American National High Blood Pressure Education Program Working Group.¹³ Even in the absence of overt hypertension (initial BP about 145-150/85-86 mm Hg), strict multifactorial intervention, including the use of ACE inhibitors in about 70% of the subjects, helps to prevent complications such as nephropathy, retinopathy, and autonomic neuropathy, as well as cardiovascular events, as shown by Parving's group.¹⁵

However, it must again be stated that to achieve the new low BP

levels demanded by the international bodies and by trial data, combination therapy will often be required. There are powerful data favoring combination therapy. An ACE inhibitor should be an early (possibly the first) component of such combination therapy. In the view of the present author, the ideal combinations with an ACE inhibitor are low-dose diuretics and calcium channel blockers. Although these combinations have been used both in UKPDS¹⁶ and in the HOT study,² yet formal proof of their efficacy compared with other combinations is awaited.

β -Blockers: a surprise result

These agents are often regarded as less desirable in the treatment of diabetic hypertensives, because of the risks of increased glucose intolerance and increased hypoglycemia. However, in the very long-term UKPDS follow-up on type 2 diabetics, both captopril and atenolol achieved equally powerful antihypertensive effects and equal reduction in hard end points.¹⁶ It needs to be recalled that β -blockers are powerful suppressors of the renin-angiotensin system, which would reduce the differences with ACE inhibitors. However: (i) there was decreased control of blood sugar in the atenolol groups, as shown by the need for greater doses of oral anti-diabetic therapy; (ii) there were more dropouts in the atenolol groups ($P < 0.0001$), with probably a greater incidence of impotence; and (iii) there was more weight gain in the atenolol groups.

The ACE inhibitor used in UKPDS was captopril, which is known to have a short duration of action with the risk of rebound activation of the renin-angiotensin system between doses, and without a good record in the management of nondiabetic



hypertension when given once or twice daily.¹⁷ Therefore, the present author proposes that ACE inhibitors, preferably long-acting ones, should be agents of first choice in the therapy of hypertensive diabetics, even though this recommendation is only inferentially supported by the totality of data rather than by specific comparative trial data.

Diuretics

In nondiabetic hypertensives, only low-dose, not high-dose, diuretics improve coronary heart disease and reduce total mortality.⁶ In hypertensive whites treated with diuretics or diuretics and β -blockers, plasma glucose and insulin were higher after a glucose load,¹⁸ particularly after the combination therapy. These findings may explain why treatment involving these drugs is associated with an increased incidence of diabetes mellitus.¹¹ Of note, however, is the fact that the diuretic doses used in those days were often high and very high, and these excessive doses were associated with increased mortality in an observational study. That low-dose diuretic treatment could be the basis of antihypertensive treatment in diabetics with systolic hypertension was shown in the Systolic Hypertension in the Elderly Program (SHEP) substudy, in which a low-dose diuretic was used as initial treatment, combined, if necessary, with atenolol or reserpine.¹⁹

Calcium channel blockers

In mild hypertension in diabetics, an ACE inhibitor is preferred to a calcium blocker of the dihydropyridine (DHP) type.²⁰ In severe hypertension, it is often difficult to achieve adequate BP control without a calcium blocker. Combination therapy with at least two and often three or four drugs

is usually needed. Two studies suggest that therapy starting with a DHP-type calcium blocker is highly effective in diabetic hypertensives.^{2,21} Of note are the remarkable results of the SYSTolic hypertension in elderly in EUROpe trial (SYST-EUR) diabetic substudy, in which total mortality in the elderly with systolic hypertension was decreased by the agent nitrendipine.³ A reservation is that this result reflects the adjusted relative risk of a rather small number of patients.

DIABETIC NEPHROPATHY

ACE inhibitor therapy in hypertensive type 1 diabetics with nephropathy

Hypertension usually reflects diabetic nephropathy, and "almost all patients with type 1 diabetes and overt nephropathy ... are hypertensive."²² Here, nephropathy is defined by the British Joint Committees as dipstick proteinuria or urine protein loss >200 mg per 24 hours.²² BP increases as the urinary albumin loss increases. Are there specific advantages for ACE inhibition? Three persuasive studies show that ACE inhibition can fundamentally change the course of type 1 diabetic renal disease. There should be strict control of BP, to values of below 130/80 mm Hg, or even 125/75 mm Hg if there is proteinuria.²² To achieve such low values, multiple drug therapy—which should include an ACE inhibitor titrated to maximal doses—will almost certainly be needed.

In type 2 diabetics, the Steno 2 trial has shown that BP reduction, usually by an ACE inhibitor, and as part of multifactorial intervention, can delay progression to nephropathy.¹⁵ Also in type 2 diabetic hypertensives, the ACE inhibitor lisinopril was able to reduce albuminuria more than

the equipotent and hypotensive dose of the β -blocker atenolol.²³

Renoprotective effect in the absence of hypertension

ACE inhibition specifically decreases the glomerular permeability to proteins by lessening the size of the selective pores. Here, the data of the recent EURODIAB Controlled trial of Lisinopril in Insulin-dependent Diabetes (EUCLID) study are of interest. Lisinopril was given over 24 months to type 1 diabetics with microalbuminuria, defined as a urinary albumin excretion of at least 20 μ g/min (about 30 mg per day).²⁴ The final treatment difference, versus placebo, was 38.5 μ g/min less protein loss in the lisinopril group. There was even a decrease in those with normal urine albumin values at the start.

OTHER ASSOCIATED CONDITIONS THAT INFLUENCE THERAPY

Ischemic heart disease

Diabetes predisposes to coronary heart disease, as does hypertension. Both cause coronary endothelial dysfunction. Hyperinsulinemia itself is an independent risk factor for ischemic heart disease. Even impaired fasting glucose, without overt diabetes, predisposes to recurrent ischemic events in survivors of myocardial infarction. If there is previous myocardial infarction, then β -blockers become the agents of choice in view of their proven effect in reduction in postinfarct mortality, also found in diabetics.¹³

Isolated systolic hypertension with diabetes

Diuretics¹⁹ and a DHP-type calcium blocker, nitrendipine,³ have been

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used with success in diabetics with isolated systolic hypertension (systolic BP >160 mm Hg, diastolic BP <90 mm Hg). These agents reduced stroke in their respective studies, but only the DHP-type calcium blocker was able to reduce overall mortality.³ However, it must be emphasized that there has been no direct comparison between a diuretic and any calcium blocker in elderly diabetics with systolic hypertension, so that dogmatic recommendations cannot be made.

Lipidemias: statins

Aggressive use of statins is now being advocated for diabetic hypercholesterolemia. This has relevance to hypertension from two points of view. First, hypercholesterolemia predisposes to endothelial dysfunction, which in turn may exaggerate or perpetuate hypertension. Second, hypertension predisposes to coronary heart disease. Postinfarct diabetic patients are more often hypertensive than nondiabetics, and the use of a statin such as pravastatin reduces cardiovascular events even if the initial cholesterol levels are only average.

Congestive heart failure

The combination of ACE inhibitors, β -blockers, and diuretics will often be used, although this has not specifically been validated for diabetics.

Impotence

ACE inhibitors are generally thought not to cause erectile problems, whereas β -blockers are often suspect. In nondiabetics, lisinopril (20 mg daily) and atenolol (100 mg daily) were compared in a crossover study, with the incidence of successful sexual intercourse as the end point. At first, both agents had

inhibitory effects, but with prolonged therapy, near-normal function was restored in patients on lisinopril.²⁵ Thus, atenolol caused chronic and lisinopril only temporary sexual problems. These studies are relevant because of the known higher incidence of impotence in the diabetic population.¹³

CONCLUSIONS

Diabetics have a number of important reasons for the increased incidence and seriousness of hypertension. Recent trials show that vigorous treatment of hypertension is able to reduce hard end points in type 2 diabetics. Treatment should be based on lifestyle modification, almost always supplemented by drugs. Each of the major categories of antihypertensives has been used in controlled trials as a first-line agent in diabetic hypertensives, with apparent success. Therefore, depending on the characteristics of the individual patient, therapy could be started with any of: (i) an ACE inhibitor; (ii) a cardioselective β -blocker; (iii) a low-dose diuretic; or (iv) a calcium channel blocker. Reasons are convincing for recommending ACE inhibitors as agents of first choice. However, in order to achieve the new low BP goals for diabetic hypertensives, which are low enough to reduce hard end points, combination therapy with two or three or even four drugs, of which one should be an ACE inhibitor, will often be required.

I wish to acknowledge those of my mentors who earlier carried out pioneering work in diabetes, including Sir Hans Krebs and Sir Ernst Chain. A complete list of references (restricted by the Editors) is available from the author.

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