Antihypertensive Therapy in Diabetic Patients
BERNHARD N. TROST, PETER WEIDMANN, AND CARLO BERETTA-PICCOLI

SUMMARY Hypertension in diabetic patients is more common than in controls, contributes substantially to their increased cardiovascular morbidity and mortality, and should be treated as accurately as diabetes mellitus itself. After appropriate exclusion of secondary forms, the first therapeutic step consists of reduction of overweight, salt intake, and smoking; the omission of interfering drugs; and adequate instruction. Step 2 has usually been the prescription of a diuretic drug, in spite of its known side effects on carbohydrate and lipid metabolism. A new possible alternative may be a calcium antagonist. Results in 10 hypertensive diabetic persons suggest that at a dose that normalizes blood pressure, neither carbohydrate nor lipid metabolism is altered, uric acid decreases, the exaggerated cardiovascular reactivity toward norepinephrine becomes normal, and the pressor dose for angiotensin II tends to rise. Body weight, blood volume, exchangeable sodium, as well as plasma and urinary sodium, potassium, and creatinine levels were unchanged. The third therapeutic step is the addition of a cardioselective beta blocker in a moderate dose. This avoids the disadvantages of beta2-adrenergic blockade such as decreased insulin output, prolonged hypoglycemia, diminished glucagon secretion, and increased vasosplasticity during hypoglycemic states, as well as aggravation of peripheral vascular disease. Alternatives are other sympatholytics with their known tendency to cause or increase orthostatic and sexual problems or, again, a calcium antagonist. In step 4, a hydralazine-type drug or prazosine is added. The fifth step, which adds minoxidil or captopril to the previous drugs, should only be taken after a specialist reevaluates the overall situation.

KEY WORDS • beta blockers • hypertension • diabetes mellitus • diuretics • calcium antagonists • sympatholytics • vasodilators • stepped care

THE prevalence of hypertension is markedly increased among patients with diabetes mellitus compared to the nondiabetic population. This is at least in part because of the close relationships of type II diabetes with obesity and of overweight with hypertension, whereas patients with the less frequent type I diabetes usually become hypertensive only with onset of nephropathy. Moreover, most diabetic patients eventually die or become disabled from cardiovascular complications. Hypertension per se also seems to promote microvascular damage, and this influence can be separated from the effects of poor diabetic control; retinopathy in those with type II diabetes is twice as common if systolic hypertension is present. Therefore it is deemed necessary that any accompanying risk factors, hypertension in particular, be treated as adequately as the disordered carbohydrate metabolism itself.

Impaired glucose tolerance or frank diabetes sometimes occurs in association with secondary forms of hypertension, such as acromegaly, thyrotoxicosis, pheochromocytoma, Cushing's syndrome, or mineralocorticoid excess. Whenever possible, these should be treated with the usual therapy of the underlying condition. The same applies to arteriosclerotic renal artery stenosis, which is probably at least as common in diabetic patients as in nondiabetic controls.

At this time it is uncertain if diabetes and hypertension are merely two associated symptoms of multifaceted disease(s) or if they are causally connected, and the role of possible common pathophysiological factors is too poorly understood to serve as a solid basis for guidelines of therapy. Nevertheless, treatment of hypertension in diabetic patients is somewhat different from therapy of essential hypertension, since metabolic and other side effects of antihypertensive drugs need special consideration.

We propose a stepped-care approach (Figure 1) with emphasis on the new possible alternative of a calcium antagonist and the cardioselectivity of beta blockers. Since hypertension and diabetes mellitus are not at all homogeneous entities and their sequelae manifold, treatment must be tailored to the individual patient.
ANTIHYPERTENSIVE THERAPY IN DIABETES/Trost et al.

1

Minoxidil or captopril (after reevaluation of the overall situation by a specialist)

2

Vasodilator (hydralazine-type or calcium antagonist)

Cardioselective beta blocker (moderate dose)

or

or

3

prazosin

if taking both step-2 drugs, cardioselective beta blocker

Instruction

Diuretic drug (low to moderate dose), KCl if necessary or calcium antagonist

Food ↓ (NIDDM)

Salt ↓

Smoking

Drugs elevating BP

Stress ↓

压力

FIGURE 1. Proposal of stepped-care antihypertensive therapy in diabetic patients. Each additional step is to be added to the previous one. Continuous control and smoothing of the step as it is reached are mandatory. NIDDM = non-insulin-dependent diabetes mellitus; BP = blood pressure.

General Measures

The first therapeutic step, for hypertension as well as for diabetes mellitus, is by no means a pharmacological approach except for emergency situations. Before adding anything, it makes sense to help to omit all possible contributors to hypertension, essentially (too much) food and (too much) salt; smoking; and drugs that may elevate blood pressure, such as oral contraceptives, anorexants (especially amphetamine-like agents), sympathomimetics, phenylbutazone and related inhibitors of prostaglandin synthetase, and medications with mineralocorticoid activity. Reduction of stress (or education for dealing with it) as well as alleviation of emotional burdens through a good therapeutic relationship between patient and doctor might be of some help.

The most important addition at this level is instruction about hypertension associated with diabetes mellitus. This includes the increased risks and sequelae when the diseases occur together, and how they might be prevented, at least in patients with the usual type II diabetes, by nonpharmacological measures such as reducing overweight (which mostly is also beneficial for associated hyperlipoproteinemia, salt intake, and nicotine. Treatment with antihypertensive drugs is indicated only if such measures fail.

Therapy with Antihypertensive Medications

The goal of antihypertensive drug therapy is to normalize blood pressure with the fewest side effects at a reasonable cost. In younger persons with type I diabetes it seems appropriate to attempt to achieve blood pressure around 120/80 mm Hg, thereby delaying the progress of nephropathy and probably also of retinopathy. In older patients, less aggressive blood pressure lowering is indicated, although no long-term studies exist for this special group to serve as guidelines.

The second therapeutic step has usually been the prescription of a diuretic drug in a moderate dose, in spite of its known untoward metabolic side effects. Thiazides generally are administered as long as renal function is normal; when serum creatinine level rises above 150 μmol/L, more potent substances such as the loop diuretics furosemide or metolazone are used. Since patients with diabetes mellitus, including those without nephropathy, usually have excessive sodium retention, this approach has a sound pathophysiological basis. Moreover, the increased cardiovascular reactivity to norepinephrine may also be normalized by means of diuretic therapy. Other advantages are the simple one-dose-per-day regimen and the low cost.

There are, however, potentially relevant disadvantages. It is possible that these agents impair glucose metabolism, especially in those with type II diabetes, which is partly dependent on potassium depletion but cannot always be reversed by the administration of KCl or even triamterene or spironolactone. Also, if potassium-sparing diuretics are prescribed, there is danger of life-threatening hyperkalemia, particularly when renal failure is present or in patients with hyporeninemic hypoaldosteronism. In addition, the risk of a hyperosmolar or ketoacidotic coma may be increased, especially in...
elderly diabetic patients; the potentially atherogenic low-density and very low-density lipoprotein cholesterol fractions may become elevated; and serum uric acid levels may increase. Finally, there is increased tendency for impotence or orthostatic hypotension. Therefore an alternative type of drug, combining blood pressure-lowering efficiency with few metabolic and functional side effects, would be preferable for beginning antihypertensive pharmacotherapy in diabetic patients.

Calcium antagonists may become the first-line drugs against hypertension in diabetes. Although they alter insulin release in animal models in vitro, in all likelihood they do not impair overall glucose homeostasis in diabetic patients. A continuing study in our outpatient clinic and laboratory is evaluating several aspects of the antihypertensive and metabolic profile of calcium antagonism in patients with diabetes mellitus and mild hypertension.

In the first 10 of these patients (Table 1), mainly with type II diabetes with a mean age of 57 ± 1 (SEM) years and a mean body weight 160 ± 11% of ideal, 6 weeks of monotherapy with nitrendipine, 36 ± 6 mg every morning at the end of the verum phase, reduced supine and upright mean blood pressures by 16 and 25% respectively (p < 0.001) compared to the values at the end of a placebo period of 4 weeks. It normalized the diminished pressor dose of infused norepinephrine: 77 ± 28 ng/kg/min were needed to increase mean blood pressure by 20 mm Hg after placebo and 178 ± 56 after nitrendipine (p < 0.001; paired t test with natural logarithm). When the increase in mean blood pressure between 0 and 20 mm Hg was plotted against the plasma concentration of norepinephrine actually measured, the compared areas under the curve differed significantly (p < 0.02); that is, with therapy with nitrendipine, the norepinephrine blood level had to be higher than with placebo to produce the same elevation of mean blood pressure. Plasma renin activity rose slightly, and the dose of infused angiotensin II to elevate the diastolic blood pressure by 20 mm Hg was increased from 10 ± 2 to 49 ± 21 ng/kg/min (p < 0.02). The plot of the increase in diastolic blood pressure and plasma levels of angiotensin II showed the same tendency as the one with norepinephrine mentioned above; the difference between the placebo and nitrendipine phases just reached significance (p < 0.05). Body weight; exchangeable sodium; blood and plasma volumes; basal blood levels of norepinephrine, epinephrine, angiotensin II, and aldosterone; as well as plasma and urine sodium, potassium, and creatinine values were all statistically unchanged, whereas the plasma levels of uric acid were significantly diminished. Most important in diabetics, glucose homeostasis was unaltered as determined by means of glycosylated hemoglobin (HbA1c) levels, plasma glucose, and insulin profiles before and after a standard breakfast (analyzed as incremental areas under the curve) as well as 72-hour glucose excretion in the urine and several fasting blood glucose values. Moreover, detailed analysis of lipids and lipoproteins did not yield any alteration whatsoever. Side effects as compared with the placebo period were minimal; there were no dropouts.

Another aspect that could favor calcium antagonists is their greater blood pressure-lowering effect in patients with low renin type of hypertension, which is common among diabetics. Thus although more experience and long-term studies are clearly needed, antihypertensive treatment in diabetics with a calcium antagonist seems a reasonable alternative to a diuretic regimen.

The third therapeutic step is usually the addition of a beta-blocking agent. Its cardioprotective potential is highly desired in many patients with diabetes mellitus. There are, however, some unwanted effects, most of which can be avoided or minimized by prescribing a cardioselective beta blocker in a moderate dosage.

Since insulin secretion is stimulated through beta2-
TABLE 1 (Continued).

<table>
<thead>
<tr>
<th>Variable</th>
<th>After 4 weeks of placebo</th>
<th>After 6 weeks of nitrendipine</th>
<th>p (paired t test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma sodium (mmol/L)</td>
<td>138.7±0.8</td>
<td>139.2±0.9</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma potassium (mmol/L)</td>
<td>3.9±0.1</td>
<td>4.0±0.1</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma creatinine (µmol/L)</td>
<td>95.9±5.1</td>
<td>94.7±4.8</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma uric acid (µmol/L)</td>
<td>303.0±27.7</td>
<td>246.6±30.6</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>Plasma renin activity (ng/ml/hr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine*</td>
<td>1.8±0.3</td>
<td>2.9±0.6</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Upright†</td>
<td>2.4±0.3</td>
<td>4.4±0.9</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Plasma aldosterone (nmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine*</td>
<td>0.27±0.05</td>
<td>0.16±0.02</td>
<td>NS</td>
</tr>
<tr>
<td>Upright†</td>
<td>0.60±0.10</td>
<td>0.77±0.15</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma norepinephrine (nmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine*</td>
<td>1.8±0.2</td>
<td>2.5±0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Upright†</td>
<td>3.0±0.4</td>
<td>6.7±1.5</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>Plasma epinephrine (nmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine*</td>
<td>0.16±0.02</td>
<td>0.18±0.04</td>
<td>NS</td>
</tr>
<tr>
<td>Upright†</td>
<td>0.18±0.02</td>
<td>0.50±0.11</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Urinary sodium (mmol/72 hr)</td>
<td>545±78</td>
<td>570±66</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary potassium (mmol/72 hr)</td>
<td>221±25</td>
<td>235±21</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary creatinine (mmol/72 hr)</td>
<td>30048±3053</td>
<td>30401±3042</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary glucose (mmol/96 hr)</td>
<td>627±309</td>
<td>546±214</td>
<td>NS</td>
</tr>
<tr>
<td>AUC glucose §</td>
<td>6.4±1.4</td>
<td>6.9±1.9</td>
<td>NS</td>
</tr>
<tr>
<td>AUC insulin§</td>
<td>28.3±12.2</td>
<td>9.6±27.6</td>
<td>NS</td>
</tr>
<tr>
<td>HbA1c %</td>
<td>10.5±0.9</td>
<td>10.1±0.7</td>
<td>NS</td>
</tr>
<tr>
<td>Serum triglycerides (mmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1.6±0.3</td>
<td>1.5±0.3</td>
<td>NS</td>
</tr>
<tr>
<td>VLDL</td>
<td>0.9±0.2</td>
<td>0.9±0.2</td>
<td>NS</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>5.5±0.2</td>
<td>5.6±0.2</td>
<td>NS</td>
</tr>
<tr>
<td>LDL</td>
<td>3.4±0.2</td>
<td>3.5±0.1</td>
<td>NS</td>
</tr>
<tr>
<td>HDL</td>
<td>1.2±0.1</td>
<td>1.3±0.1</td>
<td>NS</td>
</tr>
<tr>
<td>Apoproteins (g/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>0.8±0.03</td>
<td>0.9±0.04</td>
<td>NS</td>
</tr>
<tr>
<td>A-I</td>
<td>1.2±0.04</td>
<td>1.2±0.04</td>
<td>NS</td>
</tr>
<tr>
<td>A-II</td>
<td>0.4±0.02</td>
<td>0.4±0.02</td>
<td>NS</td>
</tr>
</tbody>
</table>

*After 1 hour of bedrest in a warm and quiet room.
†Related to body surface area and sex. 30
‡After 1 hour in the upright position.
§Incremental area under the curve 0–120 minutes after a standard breakfast.
NS = not significant (p > 0.05); VLDL = very low-density lipoprotein; LDL = low-density lipoprotein; HDL = high-density lipoprotein.
adrenergic receptors, nonselective blockade of both beta, and beta, receptors could lead to impaired glucose metabolism by a decreased insulin output in patients with type II diabetes.5, 32-35, however, this theory could not be substantiated by trials in such patients treated with propranolol.36 In patients who need oral antidiabetic agents or insulin injections to maintain glucose homeostasis, three problems may arise in connection with hypoglycemia. First, beta, blockade can prolong the hypoglycemic state by compromising peripheral glycogenolysis in muscle and lipolysis in adipose tissue, thereby reducing the substrates for gluconeogenesis (glycerol and lactate) and ketogenesis (free fatty acids).1, 3, 5, 32, 34, 35 Moreover, since glucagon secretion is stimulated through beta, receptors, its output in hypoglycemia could be throttled at least theoretically even more than is already the case in diabetics with neuropathy.32, 34 These problems most likely can be prevented by using cardioselective beta blockade.1, 3, 32, 34, 35 Second, perception of hypoglycemic symptoms may be impaired or at least altered by nonselective beta blockers.1, 2, 3, 32, 34, 35 Whereas beta, blockade in a moderate dose only dampens tachycardia and palpitations. This point probably has been overestimated1, 2, 3, 35 in prospective long-term studies in diabetics, problems of this kind were exceptional.39 Nevertheless, patients receiving beta blockers should be informed about this possibility. Third, beta, blockade can induce hypertensive crises during a hypoglycemic episode, because overstimulated alpha-receptor-dominated arteriolar constriction is not opposed by beta,-mediated dilation. This complication again can be avoided by the use of a cardioselective beta blocker.1, 3, 32-35 In addition, nonselective beta blockade in diabetic patients may aggravate peripheral microvascular disease and even cause gangrene, the frequency of which was lower during treatment with selective beta, blockers.5, 32-35

In summary, several theoretical and practical reasons favored cardioselective agents in diabetic patients, whereas arguments against them could not be found. Nevertheless, in elderly diabetic patients who have minimal cardiac reserve or overt heart failure, caution is appropriate with beta, blockers, too. These drugs seem to have the same potential as nonselective agents in elevating serum triglycerides and lowering the antiatherogenic high-density lipoprotein cholesterol.27; however, the significance of these findings on a long-term basis is uncertain.

Alternatives to beta blockers at this stage are other sympatholytics and calcium antagonists. Antiadrenergic agents such as methyldopa and guanethidine and also reserpine, clonidine, guanfacine, and debrisoquine may all aggravate problems of orthostatic hypotension33 and sexual dysfunction,7 which commonly occur in diabetic patients even with minor neuropathy.1, 3 Postural hypotension is also promoted by the diuretic regimen already initiated in the previous step, but this therapy is usually needed because of the sodium-retaining tendency of the sympatholytics mentioned. It is mandatory therefore to ask patients carefully about orthostatic and/or sexual disturbance before and after initiating such treatment. The literature about metabolic side effects of these agents in diabetic patients is scarce; methyldopa does not seem to alter glucose homeostasis41 but possibly elevates triglycerides,41 whereas clonidine in hypertensive diabetics increased serum growth hormone levels in short-term trials only,42 but slightly impaired glucose tolerance after a glucose load during longer therapy.43 The fourth therapeutic step consists of the additional prescription of a vasodilating drug of the hydralazine group (in a regimen without calcium antagonist until now; it may then also be added as an alternative to hydralazines). A possible inconvenience of such treatment is the high prevalence of coronary artery disease and angina pectoris among diabetics, because, at least if administered without beta-blocking or sympathetic agent, tachycardia and increased cardiac output may ensue and aggravate problems with myocardial oxygenation.33 On the other hand, these agents have no known metabolic side effects, and orthostatic hypotension and sexual dysfunction seem to be uncommon.7, 33 An alternative would be the administration of prazosin, a postsynaptic alpha,-adrenergic-blocking agent with less tendency for tachycardia than conventional alpha blockers or vasodilators of the hydralazine type, and no increase in cardiac output; therefore there is less risk in patients with coronary artery disease. Because of its sodium-retaining tendency, a diuretic should usually be given in combination with prazosin. Glucose tolerance in noninsulin-dependent hypertensive patients was impaired by this agent, but such was not the case in hypertensive patients with non-insulin-dependent diabetes.44 The lipid profile is unchanged or even ameliorated.27 A disadvantage of prazosin in diabetics is the fact that it can cause or aggravate orthostatic hypotension, and not after the first dose only; therefore it should not be prescribed together with sympatholytics except beta blockers. On the other hand, impaired sexual function with this drug seems to be quite rare.7 If a diuretic and a calcium antagonist have been used for steps 2 and 3, step 4 should be a cardioselective beta blocker.

We feel the fifth therapeutic step should not be routinely undertaken without consulting a specialist with more than average experience in the fields of hypertension and diabetes mellitus. The overall situation must be reevaluated. Is the diagnosis of hypertension correct under standard conditions? Could a profile of registered semiautomatic self-measurements of blood pressure over several days add valuable information? Is the patient compliant? If not, why (too many tablets several times a day; forgetful patient without family member who could take responsibility; side effects such as orthostatic problems or sexual dysfunction in particular being kept secret, etc.)? Are other drugs interfering? Have all secondary forms of hypertension, especially those with a potential for diabetes mellitus, been adequately excluded? Has renal artery stenosis been ruled out?

Only if all these problems have been checked and
hypertension persists with appropriate step-4 therapy, can captopril or minoxidil be added to the present regimen. Because of its sodium-retaining effect and its tendency to cause tachycardia, the potent vasodilator minoxidil should only be prescribed together with a diuretic and a beta blocker. Metabolic side effects on blood glucose or lipids are not known, and the same is true for orthostatic and sexual problems. In women, hypertrichosis usually develops and can become troublesome and often limiting. Captopril is not known to alter glucose homeostasis and can be used in patients with diabetes mellitus. The rare occurrence of renal side effects such as proteinuria and acute renal failure in severe hypertension with renal artery stenosis must be kept in mind, especially in diabetic patients. Furthermore, with progressing nephropathy or hyperreninemic hypoaldosteronism, both by no means rarities in diabetics, such as orthostatic hypotension, sexual dysfunction, or hypokalemia necessitate a change of drugs? Can or prolonged action or tablets containing the necessary agents as it can be, or could once-a-day preparations with side effects such as orthostatic hypotension, sexual dysfunction, or hypokalemia necessitate a change of drugs? Can or should pharmacotherapy be reduced if weight loss has been successful or symptoms of (orthostatic) hypotension or diminished cerebral blood flow occur? On the whole, does the patient understand and accept our intentions? Since knowledge of the underlying pathophysiology is all but perfect and the ideal regimen against hypertension in diabetic patients has not been found, it is necessary to remain open-minded (but not uncritical) about new and perhaps better understanding of both conditions and subsequently new and better treatment in the future.

Finally, smoothing of the respective step at which adequate blood pressure control has been reached and usually lifelong control of diabetes and hypertension are mandatory. Is the antihypertensive regimen as simple as it can be, or could once-a-day preparations with prolonged action or tablets containing the necessary drugs in combination be substituted? Do side effects such as orthostatic hypotension, sexual dysfunction, or hypokalemia necessitate a change of drugs? Can or should pharmacotherapy be reduced if weight loss has been successful or symptoms of (orthostatic) hypotension or diminished cerebral blood flow occur? On the whole, does the patient understand and accept our intentions? Since knowledge of the underlying pathophysiology is all but perfect and the ideal regimen against hypertension in diabetic patients has not been found, it is necessary to remain open-minded (but not uncritical) about new and perhaps better understanding of both conditions and subsequently new and better treatment in the future.

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