Management issues in hypertensive diabetics

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Association between hypertension and diabetes

Diabetes mellitus and hypertension are common clinical conditions that often co-exist. This combination has been called the deadly duet to emphasise the increased cardiovascular risk when the two conditions co-exist. Hypertension occurs more commonly in diabetics than in comparable non-diabetics, as the prevalence of hypertension in diabetics is about two times higher than that of hypertension as observed in the general population. In type 2 diabetes mellitus, hypertension is often present as part of a possible common underlying metabolic abnormality, such as insulin resistance. However, in type 1 diabetes mellitus, hypertension is often due to the onset of diabetic nephropathy.

Hypertensive people are 2.5 times more likely to develop diabetes mellitus within five years. This may be due to the presence of an underlying metabolic syndrome, and made worse by the type of antihypertensive drug used, e.g. high-dose thiazides combined with high-dose beta blockers.

The co-existence of hypertension and diabetes mellitus greatly increases the risk for macrovascular and microvascular diabetes complications. The presence of hypertension causes a 7.2-fold increase and a 37-fold increase in mortality in diabetic patients and in diabetic nephropathy respectively.

Most patients with diabetes and hypertension will die from a cardiovascular cause. Hypertension exacerbates all the vascular complications of diabetes, including coronary artery disease, renal disease, stroke, peripheral artery disease, leg amputations and retinopathy. Diabetes increases the risk of coronary artery disease twofold in men and fourfold in women, putting women in particular, at risk.

Management principles

Intense non-pharmacological measures (lifestyle changes) should be encouraged in all diabetic patients with attention to weight loss and reduction of salt intake, especially in type 2 diabetes. A healthy diet is included in lifestyle management.

Blood pressure control is crucial

Data from clinical trials emphasise the need for vigilant blood pressure control in patients with diabetes and hypertension. In the UK Prospective Diabetes Study (UKPDS), each 10 mmHg decrease in mean systolic blood pressure was associated with risk reductions of 12% for any complication relating to diabetes, 15% for death, 13% for microvascular complications, and 11% for myocardial infarction, respectively. There was no threshold of blood pressure where risk was not observed.

What is the blood pressure goal?

A target blood pressure goal $\leq$ 130/80 mmHg is both reasonable and safe to achieve. Both the UKPDS and Hypertension Optimal Treatment (HOT) trials demonstrated improved outcomes in patients assigned to lower blood pressure targets. Epidemiological analyses show that blood pressure $\geq$ 120/70 mmHg is associated with increased cardiovascular event rates and mortality in patients with diabetes. Achieving lower levels will decrease risk, but can be difficult to achieve and will increase the cost of treatment and the side-effect profile. Control of systolic blood pressure is especially important. The Advance Collaborative Group study demonstrated the benefit of an angiotensin-converting enzyme (ACE) inhibitor and indapamide in a fixed combination, reducing blood pressure in diabetics close to the desired goal. The study strongly suggests that the blood pressure goal (< 130/80 mmHg), as recommended by guidelines, is

correct. The ACCORD trial showed that reducing systolic blood pressure in diabetics below 120 mmHg had no benefit.

The need for multiple-drug therapy

Evidence shows that, to achieve the set goal of ≤ 130/80 mmHg, use of multiple-drug antihypertensive therapy is required. Agents should be used that have been shown to reduce cardiovascular risk, while not worsening concomitant conditions, e.g. new onset diabetes or abnormal lipids. A renin-angiotensin system (RAS) blocker [ACE inhibitor or angiotensin receptor blocker (ARB)] should be a component of any combination treatment in diabetes.

Blockade of the renin-angiotensin system

It is appropriate that an agent that can block RAS, such as an ACE inhibitor or an ARB, should be one of the partner drugs used in combination in hypertensive patients with diabetes or glucose intolerance. These drugs are also important to use if there is microalbuminuria or proteinuria present, even if blood pressure is only in the high normal range, as they reduce progression to end-stage renal disease. Other drugs have also been shown to reduce proteinuria, e.g. indapamide and non-dehidropiridine calcium-channel blockers (e.g. verapamil).

Which drug to use?

Clinical trials with diuretics, beta blockers, ACE inhibitors, ARBs and calcium-channel antagonists have all demonstrated benefit in the treatment of hypertension in type I diabetes mellitus, as well as type 2 diabetes mellitus. This benefit is related to the degree of blood-pressure lowering.

The question of which drug is superior has not clearly been answered, but an answer is probably not necessary, because the hypertensive diabetic will require two or more drugs to reach the lower blood pressure target. It is also important to evaluate patients for either known complications, e.g. coronary artery disease, or other concomitant disease, to decide on the best combination of drugs.

The Blood Pressure Lowering Treatment Trialist collaboration published a meta-analysis of 27 randomised trials with 158 709 patients to evaluate the effect of blood-pressure lowering on major cardiovascular events in patients with and without diabetes mellitus. The results from this meta-analysis demonstrated that major cardiovascular events were reduced to a comparable extent in individuals with and without diabetes, by regimens based on ACE inhibitors, calcium antagonists, ARBs and diuretic-beta blocker combinations. This effect was for short-to-medium term duration. There are no data for long-term event reduction. The data also did not evaluate specific indications for specific drug groups. The implications of this meta-analysis clearly demonstrate that there is no one particular drug that is superior in diabetes and that the majority of patients will require two or more drugs to achieve the blood pressure goal. Recently, the combination of an ACE inhibitor combined with a calcium-channel blocker (amlodipine) was shown to be superior to a combination of the same ACE inhibitor plus a diuretic in a large group of hypertensive patients, and in a sizeable group of diabetic patients.

New-onset diabetes and the use of antihypertensive drugs

People with elevated blood pressure levels are 2.5 times more likely to develop diabetes mellitus within five years than those with normal levels. This phenomenon is made worse by the chronic administration of diuretics and beta blockers, especially when administered in combinations with one another, and in high doses when compared to other antihypertensive drugs.

The exact mechanism and long-term clinical implications of new-onset diabetes is currently being debated. The dismetabolic effects of diuretics and beta blockers could be dose dependent. There is indirect trial evidence that diuretics (thiazide type), in doses from 25-50 mg and higher, are associated with increased incidence of new-onset DM, particularly when combined with high doses of beta blockers, e.g. 100 mg of atenolol. A recent meta-analysis of seven studies in almost 60 000 patients showed that, compared to beta blockers and diuretics, RAS blockers decreased the occurrence of new- onset diabetes by 20% ($p < 0.001$), while calcium antagonists decreased the onset of diabetes by 16% ($p < 0.001$).

A comparison was made in a 16-year follow-up of almost 800 initially untreated hypertensive patients, of whom 6.5% had diabetes at the onset, and 5.8% developed new-onset diabetes following treatment. The risk of cardiovascular disease was similar in the group with pre-existing diabetes to that of the group who developed new-onset diabetes following treatment for hypertension. This suggests that the development of diabetes while on antihypertensive treatment increases cardiovascular risk. It could be that the combination of a low-dose diuretic with a blocker of the RAS or a calcium-channel blocker may prevent the metabolic deleterious effects of a thiazide diuretic.

Hypertension treatment as part of a global cardiovascular risk reduction

Cardiovascular risk factors tend to cluster and insulin resistance, type 2 diabetes mellitus, obesity and hypertension can be common in the same patient. Metformin, used to lower glucose, reduces cardiovascular risk in type 2 diabetes mellitus and also reduces the risk of a cardiovascular events in established macrovascular disease.

The British guidelines suggest a reduction of low-density lipoprotein (LDL) cholesterol to < 2 mmol/L in type 2 diabetes mellitus patients using a statin. A meta-analysis of 12 randomised control clinical trials demonstrated that in both primary and secondary prevention, diabetics had similar cardiovascular risk reductions to non-diabetics when using a statin. Thus, the vast majority, if not all, of type 2 diabetes mellitus patients should receive a statin.

The aim of therapy is to reduce overall cardiovascular risk by targeting blood pressure reduction, blood sugar reduction, smoking cessation and adding a statin in all diabetics.

Summary of treatment

- The blood pressure goal is 130/80 mmHg.
- Multiple drugs are best to achieve target blood pressure.
- ACE inhibitors or ARBs should be part of the regimen.
- In type 1 diabetes mellitus with any degree of albuminuria, an ACE inhibitor/ARB is necessary.
- In type 2 diabetes mellitus with any degree of albuminuria, an ACE inhibitor/ARB is necessary, especially with renal insufficiency.
- Start with ACE inhibitors or ARBs. If systolic blood pressure is > 20 mmHg higher than the goal of 130 mmHg, add a diuret
- ic or calcium-channel blocker. If still uncontrolled, add an ACE-I or ARB, plus diuretic, plus calcium channel blocker. If still uncontrolled, add an aldosterone-receptor blocker.
- Add a statin to reduce macrovascular risk.

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