MICRO-ALBUMINURIA IN DIABETES MELLITUS — MANAGEMENT

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Annual screening of patients with diabetes for micro-albuminuria will make it possible to identify early nephropathy. Improving glycaemic control, aggressive treatment of hypertension and use of ACE inhibitors will slow the rate of progression of diabetic nephropathy.

S Afr Med J 1999; **89:** 795-797.

An article published early in 1998 outlined the screening and significance of micro-albuminuria in diabetes mellitus.[1] Micro-albuminuria is one of the earliest clinically identifiable signs of diabetic nephropathy, and it is believed that prevention of progression is best achieved at this stage.[2,3]

MANAGEMENT OF MICRO-ALBUMINURIA

In order to understand the rationale behind the current recommendations for management of micro-albuminuria (early nephropathy) to protect renal function in diabetes, it is important to outline the impact of glycaemic and blood pressure control, use of angiotensin-converting enzyme (ACE) inhibitors and other modalities.

Proposed guidelines for management are presented in Fig.1.[2,4]

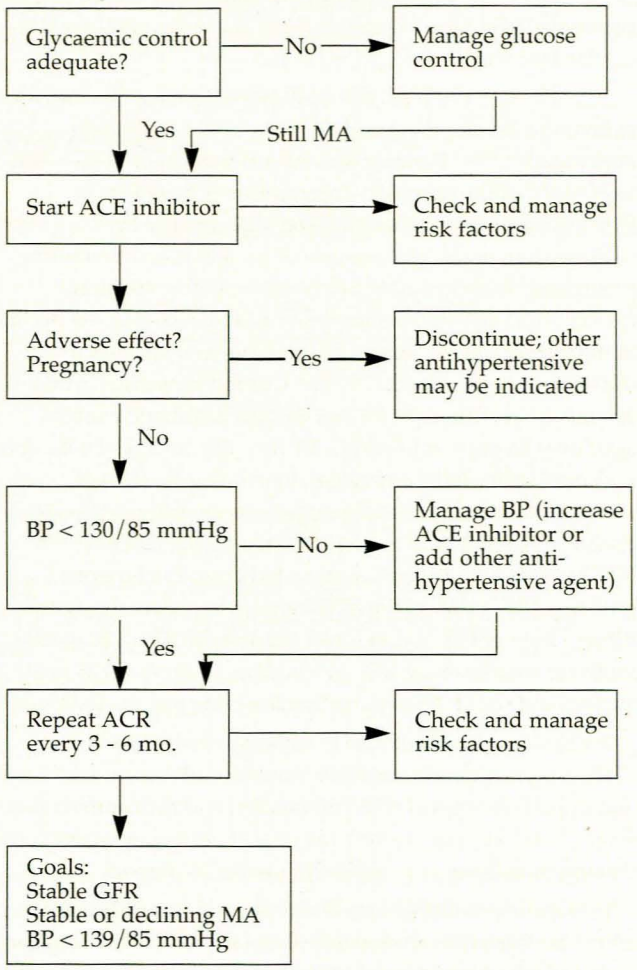

Fig. 1. Management of micro-albuminuria in diabetes mellitus.

Effect of glycaemic control

Several smaller studies and the Diabetes Control and Complications Trial (DCCT) have shown conclusively that intensive glycaemic control prevents the onset of (micro-albuminuria) and delays the progression (micro-albuminuria → proteinuria) of diabetic nephropathy in type 1 diabetes.[5] An earlier prospective study in Japanese with type 2 diabetes, most of whom were of normal weight, suggests a similar benefit of glycaemic control on diabetic nephropathy.[6] More recently the largest clinical study in type 2 diabetes, the United Kingdom Prospective Diabetes Study (UKPDS), has confirmed that intensive blood glucose control decreases the risk of microvascular complications in this group.[7] However, there is little evidence from long-term studies that glycaemic control influences the progression from overt nephropathy (proteinuria) to end-stage renal disease (ESRD).

The best glycaemic control possible should therefore be the goal for every diabetic patient.[2,4,5,8,9]

Blood pressure control

Current consensus recommends that the classification of blood pressure and hypertension in diabetes be based on the Fifth Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (JNC-V).[2,4,8-11] The JNC-V classification for adults (> 18 years) defines hypertension as an average blood pressure (BP) of ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic, based on repeated (≥ 3) measurements. A normal blood pressure is defined as < 130 mmHg systolic and < 85 mmHg diastolic. Micro-albuminuria is associated with a modest increase in blood pressure. Using the recent definition of hypertension

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(BP ≥ 140/90), its prevalence has been shown to exceed 50% in both type 1 and type 2 diabetics with micro-albuminuria in a clinic-based study.[12]

Hypertension (both systolic and diastolic) increases the risk of both the development and the progression of diabetic nephropathy.[2,8,10-13] Randomised clinical trials have shown that aggressive antihypertensive intervention is beneficial in slowing the progression of diabetic nephropathy by: (*i*) decreasing micro-albuminuria or proteinuria; (*ii*) retarding progression from incipient (micro-albuminuria) to overt (proteinuria) diabetic nephropathy; and (*iii*) slowing the decline in the glomerular filtration rate (GFR) in patients with overt (established) nephropathy.[2,4,8-10,13-16] Current consensus is that the primary goal of therapy for non-pregnant diabetic patients aged over 18 years is to reduce BP to < 130 mmHg systolic and < 85 mmHg diastolic, and maintain it at that level, and moreover that the BP may be reduced even further if this is done with caution and is well tolerated by the patient.[2,4,8-10,13] (For patients with isolated systolic hypertension (systolic pressure ≥ 180 mmHg) the initial goal is to reduce the systolic BP to < 160 mmHg, and to lower the systolic BP by 20 mmHg for those with levels of 160 - 179 mmHg. (If these initial goals are met and well tolerated, further lowering may be indicated).

In the recent JNC-VI Report,[17] although there have been slight modifications in the classification of BP (i.e. an additional 'optimal BP' category (< 120/80 mmHg) and the combining of stages 3 and 4 hypertension), the goal of antihypertensive therapy in diabetes is as set out in the JNC-V Report.

Therapeutic modalities for blood pressure control should follow the currently recommended guidelines.[2,4,8-11,13,17] A major aspect of initial treatment is lifestyle modifications, e.g. weight loss, reduction of salt and alcohol intake, and exercise.

In patients with underlying nephropathy (micro-albuminuria), treatment with angiotensin-converting enzyme (ACE) inhibitors is also indicated as part of initial therapy (*vide infra*). If, after 4 - 6 weeks, sufficient blood pressure reduction has not occurred, additional pharmacological therapy is indicated in a stepwise fashion.[10,11,17]

Use of ACE inhibitors

Earlier studies have confirmed that aggressive antihypertensive therapy with conventional drugs (ß-blockers, diuretics and hydralazine) was able to decrease albumin excretion and the speed of decline in the GFR in type 1 patients with diabetic nephropathy.[10]

Subsequently animal studies provided evidence that ACE inhibitors were superior to other antihypertensive agents in retarding the progression of renal disease. ACE inhibitors, but not other agents, decrease and can normalise intraglomerular capillary pressure (glomerular hypertension) by preferential dilatation of efferent glomerular arterioles.

This observation was confirmed in human studies. Many studies have shown that in hypertensive patients with type 1 diabetes, ACE inhibitors can reduce the level of albuminuria and can reduce the rate of progression of renal disease to a greater extent than any other antihypertensive that lowered blood pressure to an equal degree.[18,19] It has also been demonstrated that ACE inhibitors are beneficial in reducing the progression of micro-albuminuria in both normotensive patients with type 1 diabetes[20] and in normotensive and hypertensive patients with type 2 diabetes.[21]

In light of the above, the following recommendations can be made:

1. Because of their efficacy as antihypertensive agents and their selective benefit in retarding progression of diabetic nephropathy, ACE inhibitors are recommended as the primary treatment of all hypertensive, albuminuric diabetic patients.[2,4,10,17]

2. Because of the high proportion of patients who progress from micro-albuminuria to overt nephropathy and ESRD, ACE inhibitors are recommended for all type 1 patients with micro-albuminuria, even if they are normotensive.[2,4,10,17]

3. However, because of the more variable rate of progression from micro-albuminuria to overt nephropathy and ESRD in patients with type 2 diabetes, the use of ACE inhibitors is optional.[2,4,17] Should such a patient show progression of albuminuria or develop hypertension, an ACE inhibitor would clearly be indicated.[2]

The new angiotensin receptor blocker losartin has not been studied in humans with regard to renal protective effects.

Use of calcium channel blockers

Studies have shown that the benzothiazepene and phenylakylamine classes of calcium blockers can reduce the level of albuminuria, but no study to date has demonstrated a reduction in the rate of decline of the GFR with their use. Nonetheless, in patients who do not tolerate ACE inhibitors these agents may prove useful.[10]

Other modalities

Animal studies and several small studies in humans with diabetic nephropathy have shown that a protein-restricted diet moderately retards the rate of decline in the GFR. However, there are inadequate data to evaluate the long-term consequences in micro-albuminuric patients.[2] It has been proposed that in such patients protein intake should be limited to 0.8 g/kg/day[8] and to 0.6 g/kg/day once the GFR begins to fall.[22]

Where indicated, lipid-lowering interventions, sodium and phosphate restriction, phosphate binders and agents preventing early renal osteodystrophy may be used.

ECONOMIC IMPACT

In a cost-benefit analysis of management of micro-albuminuria in type 1 diabetes, early intervention was shown to have considerable cost benefits.[4]

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