EDITORIALES

Pharmacologic treatment of early diabetic nephropathy

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INTRODUCTION

Approximately one third of patients with type I diabetes and one fifth of patients with type II diabetes develop clinically overt DN. While the incidence of DN in type I diabetes is declining, the incidence of end-stage renal failure in type II diabetic patients has increased dramatically in the United States in recent years. The functional and structural lesions of DN develop in predisposed patients over 10 to 20 years following diagnosis, and it is not clear if there is a latent period. DN evolves through several stages which generally follow the sequence hyperfiltration, microalbuminuria, raised blood pressure, macroalbuminuria and progressive fall in glomerular filtration rate (GFR) as shown in figure 1. Apart from hyperfiltration, the concomitants of microalbuminuria include increase in serum prorenin levels [1] and apoprotein(a) levels [2]. If it could be shown conclusively that increases in prorenin precede the development of microalbuminuria, it would follow that aggressive intervention would need to be considered in this subgroup of patients. Although these stages represent a continuum, they are often considered separately as incipient and overt DN.

Incipient DN is defined as persistent levels of albumin excretion rate (AER) in the range 20-200 ug/min (established microalbuminuria). It may indicate the presence of renal disease rather than being a marker for its subsequent development. Overt DN occurs when AER persistently exceeds 200 ug/min and when total proteinuria exceeds 0.5 grams/24 hours. This is approximately equivalent to a positive (+) albustix test. In patients with evolving DN, AER usually increases exponentially and averages 30-40 % per year in both type I and type II diabetes [3]. Results of AER measurements over several years are shown in figure 2 for a patient with progressively increasing AER, prior to and after commencement of antihypertensive therapy.

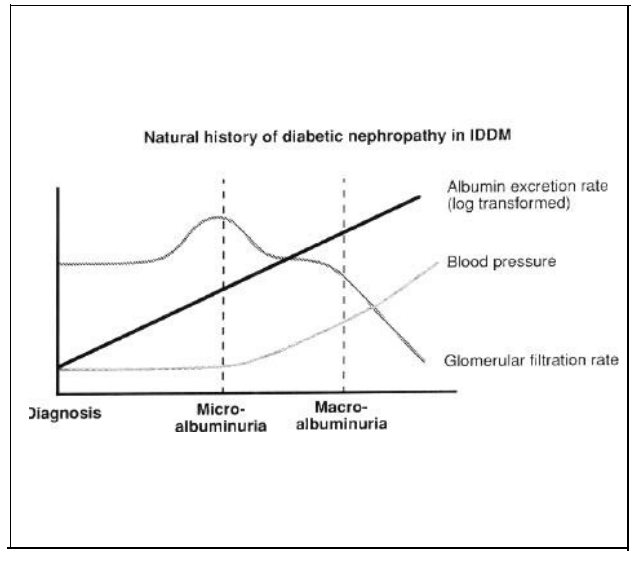

Fig. 1.-Natural history of diabetic nephropathy in IDDM

The increase in AER may be explained by functional changes in renal haemodynamics and by changes in glomerular ultrastructure such as basement membrane thickening and increased mesangial volume leading to a decrease in available filtration surface [4]. In addition, both functional and structural parameters, such as loss of heparan sulphate proteoglycan, may cause alterations in the permselectivity of the glomerular filter. The existence of a functional component in albuminuria is one reason why it is not appropriate to assume that reduction or stabilisation of AER in microalbuminuric patients is necessarily coupled to delay or amelioration of the subsequent decline in renal function [5]. Although an

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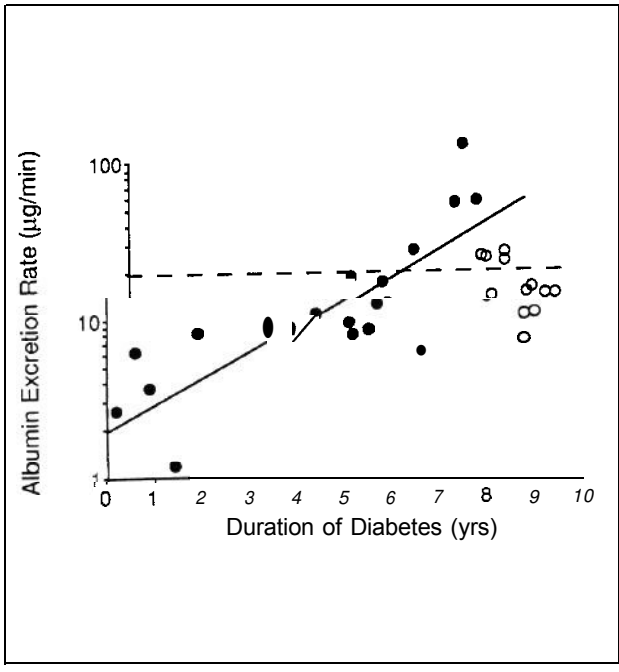


Fig. 2.-Progression of albuminuria before and after intervention with antihypertensive therapy in an individual patient. Solid circles represent no therapy and open circles represent antihypertensive therapy. Solid line represents the regression relationship during no therapy (r = 0.79, p = 0.00011. Dashed line represents the lower limit of microalbuminuria 120 ug/min).

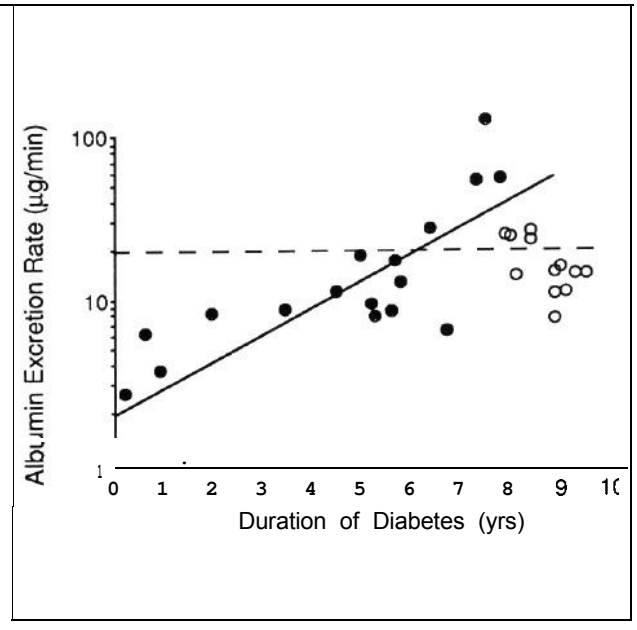


Fig. 3.-Progression of AER despite improving glycaemic control in a patient studied over 16 years.

increased AER is the hallmark of early DN, it should be noted that some female patients with type I diabetes may develop decreased renal function and glomerular ultrastructural changes indistinguishable from DN [6]. It should also be noted that the onset of microalbuminuria may lose most of its prognostic value in type I diabetic patients with disease duration exceeding 15 years [7].

GLYCAEMIC CONTROL AND PREVENTION OF OVERT DN

The respective roles of glycaemic and blood pressure control in evolving DN are shown in figure 3, which emphasise the loss of effectiveness diagrammatically of glycaemic control in the later stages of DN. Glycaemic control has been traditionally listed as a factor in preventing DN, but persuasive human data to support this have been scarce [8]. Recently, two randomised, prospective longterm studies from Sweden and the United States have shown that HbAlc levels of < 7.5 % (normal < 6.1 %) are achievable with multiple insulin injections over periods of 7.5 years [9] and 9 years [10]. These studies also showed that microvascular complications, including overt DN, can be delayed and possibly prevented by intensive glycaemic control. In the Swedish study, half of 102 type I diabetic patients were randomised to intensive glycaemic control and half to standard control. DN, defined as AER > 200 ug/min, developed in 1 patient on intensive treatment compared with 9 patients on standard treatment ($p < 0.01$). A subnormal GFR occurred in no patient in the intensive treatment group compared with 6 patients receiving standard treatment ($p < 0.02$, [9]) Similar results have been found in the much larger DCCT, which studied approximately 1400 patients, half of whom were treated with intensive glycaemic control [10]. This study showed that development of overt DN was reduced by approximately 50 % in the intensive control group, which maintained a mean HbAlc of 7.2 % during the study. Our own studies have shown a significant correlation between the rate of increase in AER and-mean HbAlc levels over intervals of 9 to 14 years in patients with either type I or type II diabetes [3].

Atpresent, no longterm study exists to document the effects of intensified glycaemic control on the evolution of DN in type II diabetes. However, one study has shown that addition of a nocturnal dose of long-acting insulin to oral hypoglycaemic therapy is better tolerated than the multiple insulin injection regimen, and results in comparable glycaemic control [11]. It is important to note that AER may increase despite improving glycaemic control as shown in a patient studied for over 10 years (figure 4). This indicates that

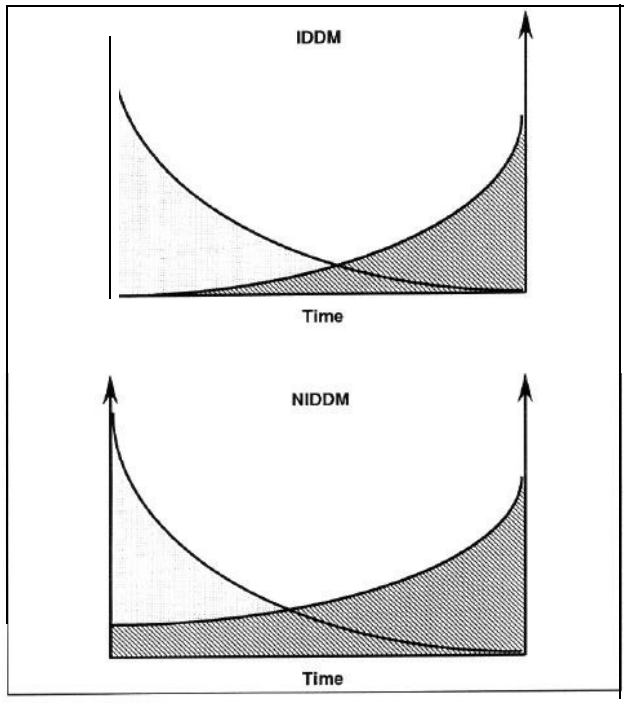


Fig. 4.-Relative effectiveness of intervention in diabetic nephropathy. Y-axis represents increasing effectiveness. Grey area represents glycaemic control and hatched area represents blood pressure control.

blood sugar levels are only one of a number of pathogenetic factors contributing to DN.

ANTIHYPERTENSIVE THERAPY IN **THE NORMOTENSIVE, MICROALBUMINURIC PATIENT**

The case for a specific protective effect of ACE inhibitors on the kidney is based on studies of experimental DN [12], which suggested that these agents lower intraglomerular pressure and also partially restore glomerular permselectivity towards normal. Short-term studies in man support the latter action of ACE inhibitors. The calcium channel blocker, diltiazem, has also been reported to exert a beneficial effect on glomerular heparan sulphate content and on albuminuria in diabetic rats [13]. However, no studies of the effects of calcium channel blockade on glomerular permselectivity appear to have been done Several studies have examined the effects of antihypertensive therapy, usually with ACE inhibitors, in normotensive, microalbuminuric patients with type I diabetes for intervals of 1 to 4 years [14-17]. These studies showed a reduction or stabilisation of microalbuminuria in association with a slight decrease in blood pressure [14] or without any decrease in blood pressure.

The Melbourne Diabetic Nephropathy Study Group (MDNSG) has also addressed the question [18] of antihypertensive treatment in normotensive and hypertensive microalbuminuric patients. In this study, 43 type I and type II diabetic patients with persistent microalbuminuria were randomised to treatment with the ACE inhibitor, perindopril, or the calcium channel blocker, nifedipine, for a period of 12 months, aiming for a reduction in diastolic blood pressure of 4 mmHg in normotensive patients and a target diastolic blood pressure of 90 mmHg in hypertensive patients. In this study hypertension was defined as > 160/95 [19]. A significant correlation was found between the change in mean blood pressure and the change in AER in individual patients (r = 0.37, p = 0.02), but there was no clear evidence that perindopril was superior to nifedipine in reducing AER. Both drugs prevented increases in AER in normotensive patients and decreased AER in hypertensive patients. It should be noted that there has been a recent trend to use a lower threshold for the definition of hypertension in diabetic patients, such as 140/90 or less [20]. It is important to note that one month after cessation of antihypertensive treatment, there was a rebound of AER in the total cohort, with no significant difference between those receiving perindopril and those receiving nifedipine. Analysis of the rebound of AER in a subgroup of patients with a total follow-up exceeding 9 years indicated that, while both drugs stabilised AER, subsequent rates of increase in AER while off treatment were approximately parallel to pretreatment values [21].

A second study by the MDNSG is in progress. This is examining the effects of perindopril, nifedipine and placebo on AER and renal function in normotensive diabetic patients with microalbuminuria. Preliminary results show that both active drugs prevent increases in AER but no effects on GFR are yet evident. The effects of antihypertensive intervention in microalbuminuric diabetic patients have been the subject of two recent editorials [22,23]. Both conclude that AER may be favourably influenced by ACE inhibitors in normotensive patients. However, it should be pointed out that no longterm (> 5 yr) intervention studies exist in normotensive type I microalbuminuric patients to show that ACE inhibition preserves GFR. By contrast, a recent study of ACE inhibition, using enalapril 5mg twice daily, in normotensive microalbuminuric patients with type II diabetes has demonstrated stabilisation of AER and plasma creatinine levels over 5 years [24]. Placebo treated patients showed an increase in AER and a rise in serum creatinine levels starting from the second year of the study. However, the enalapril effect on changes in serum creatinine levels was small, although statistically significant. Further longterm studies with isotopic measurements of GFR and/or glomerular ultrastructure are needed to strengthen the case for ACE inhibition in normotensive microalbuminuric patients.

ANTIHYPERTENSIVE THERAPY IN OVERT DN

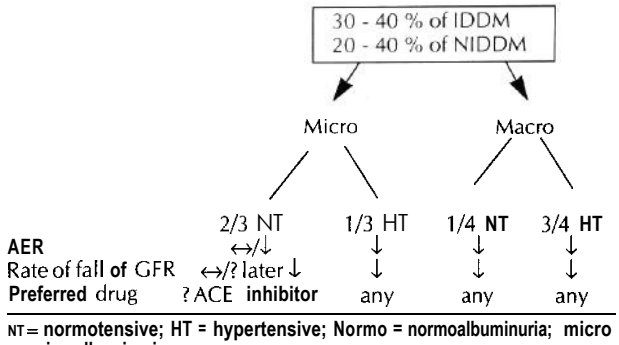
In contrast to the lack of a clear consensus on the choice of and threshold for antihypertensive treatment in the normotensive microalbuminuric patient, the situation in patients with overt DN is much clearer (see table I). Several studies have shown that both conventional antihypertensive agents and the newer ACE inhibitors and calcium channel blockers all have beneficial effects on AER and the rate of fall in GFR, in proportion to their lowering of systemic blood pressure [25-27].

A meta analysis has recently compared the effects of ACE inhibitors, calcium channel blockers and other agents on proteinuria and renal function in diabetic patients [28]. This study concluded that ACE inhibitors can decrease proteinuria and preserve GFR. However, the analysis used pooled data from studies in microalbuminuric and macroalbuminuric patients. Furthermore, of the 12 randomised controlled trials that were analysed, 11 examined the effects of ACE inhibition. In the absence of comparable data on calcium channel blockers and other agents, it may be premature to conclude that ACE inhibitors are the preferred therapy of incipient and overt DN.

TREATMENT OF DYSLIPIDAEMIA IN PATIENTS WITH DN

Apart from hyperglycaemia and raised blood pressure, a further possible explanation for the excess cardiovascular mortality associated with overt DN is

Table I. Effect of antihypertensive therapy on diabetic neohrooathv



NT = normotensive; HT = hypertensive; Normo = normoalbuminuria; micro = microalbuminuria.

dyslipidaemia[29]. Experimental evidence indicates that dyslipidaemia may damage the kidney but few human studies support a causative role for lipid disorders in DN. One study of the rate of decline in renal function in type I diabetic patients has shown a correlation with serum cholesterol levels [30].

Combined hyperlipidaemia with low HDL cholesterol is the commonest type of diabetic dyslipidaemia, and occurs particularly in patients with type II diabetes. This can be treated with lipid modifying drugs such as gemfibroril if high triglycerides and low HDL cholesterol are the main abnormalities, or with HMC CoA reductase inhibitors if raised LDL cholesterol is the predominant abnormality. No data exist to allow assessment of the effects of lipid modifying therapy on AER or other aspects of DN in man. Proteinuric patients with type I diabetes have been shown to have lower HDL cholesterol levels than age and sex matched control subjects [31]. Serial studies in our own laboratory have shown that increasing AER is associated with concomitant increases in apoprotein(a) levels, especially in type II diabetic patients [2]. Unfortunately, no effective methods for lowering apoprotein(a) levels are available. It has been recently shown that treatment with the ACE inhibitor, fosinopril, improves lipid abnormalities in type II diabetic patients with overt DN, in association with a partial reduction in proteinuria [32].

In summary, the above evidence supports aggressive pharmacological intervention is warranted in patients with DN. Before the development of microalbuminuria, emphasis should be on excellent glycaemic control. In practice, this refers to all diabetic patients since identification of DN in the pre-microalbuminuric phase remains controversial. Intensive blood pressure control becomes important after AER has risen to the microalbuminuric stage. Since the usual nocturnal fall in blood pressure may be reduced in diabetic patients, it is possible that the best way of assessing blood pressure may be to use 24 hour ambulatory records [33]. Lipid lowering drugs are also indicated, although the exact role of lipid disorders in the pathogenesis of DN remains to be determined.

Although DN is usually considered to be irreversible in its later stages, after overt DN has developed, it is possible that early intervention with the above pharmacological agents will prevent progression to the point of irreversibility.

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