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section 21 Disorders of the kidney and urinary tract 4982 increased albuminuria. Accurate data on GFR are not given in many of these studies, but in type 1 patients, long-term ACE inhibitor therapy appears to stabilize renal function after an initial reduction. Interpretation of all these studies is complicated by the fact that the actively treated patients have nearly always had significantly lower blood pressures than the placebo groups. While statistical correc- tion for these differences has been applied, it is uncertain whether mathematical correction can completely allow for the biological consequences of blood pressure reduction. In addition, there are some data showing a return of albuminuria to pretreatment levels following withdrawal of therapy, calling into question the durability of effect. There are no conclusive long-term data showing a posi- tive benefit on hard endpoints such as mortality or endstage renal disease. Tertiary prevention Studies in the early 1980s established that lowering blood pres- sure in hypertensive type 1 patients with severely elevated albu- minuria resulted in a more than 50% reduction in UAER and a significant slowing of the rate of decline of GFR from 10 to 3 ml/ min per year. The Collaborative Study Group Trial in type 1 dia- betic patients who had a blood pressure below 140/90 mmHg and severely elevated albuminuria showed that the addition of captopril 100 mg a day resulted in a significant reduction in the numbers of patients doubling baseline serum creatinine com- pared to placebo (35% vs 78%; $P < 0.001$). This significance was confined to those with an entry serum creatinine concentration of more than 133 µmol/litre (1.5 mg/dl). There was a similar re- duction in the numbers reaching a combined endpoint of death or the need for renal replacement therapy in the captopril-treated patients. In patients with type 2 diabetes, the results are complicated due to their increased cardiovascular comorbidity. Two large studies using angiotensin II receptor blockers in patients with clinical proteinuria have shown a reduction of 25 to 33% in the rate of doubling of serum creatinine after 2 to 3 years of treatment. This is considerably less than that seen in the captopril trial in type 1 patients, possibly be- cause the type 2 patients had more advanced diabetic nephropathy at entry. The ACCORD blood pressure trial investigated whether a systolic blood pressure of less than 120 mmHg versus less than 140 mmHg would be more renoprotective, but while there were fewer cases of severely elevated albuminuria there was no benefit in terms of GFR. Taken together, the studies in type 1 and 2 patients support the use of drugs which block the renin–angiotensin system as first- line therapy in both moderately and severely elevated albuminuric patients, and are recommended in all national and international guidelines. Nonrenal outcomes Although there are many large studies of the effects of antihypertensive therapy on cardiovascular mortality and morbidity in patient groups that have included sizeable cohorts of diabetic pa- tients, their nephropathic status has rarely been specified. Most have shown that low blood pressure is associated with the reduction in overall mortality and stroke incidence, although the effect on myo- cardial infarction is inconsistent. Diabetic patients on the whole

showed a greater benefit from active treatment. Clinical features Clinical progression is usually defined in terms of changes in UAER, GFR, and blood pressure. Much of our current understanding is based on cross-sectional data, although more long-term prospective studies of individual patients are being reported. Albuminuria is clearly a continuous variable and its separation into stages is arti- ficial, but the distinction between moderately and severely elevated albuminuria has proved to be clinically useful and has been incorp- orated into the latest classification of CKD. There is an increasing realization that an elevated UAER is not an invariable finding in pa- tients with diabetes and CKD. This is a particular feature of older people with type 2 diabetes, but has also been described in type 1. Because of this there has been a huge interest in exploring other biomarkers for diabetic kidney disease and there are promising data using proteomics and metabolomics suggesting improved predictive performance when combined with albuminuria. These methods are not yet available for routine clinical use. UAER UAER may be raised at diagnosis of type 1 diabetes and during acute hyperglycaemia, but usually returns to normal with glycaemic cor- rection. Thereafter most patients (>60%) will have a normal UAER throughout their diabetic life, but the remainder develop persistent mod- erately increased albuminuria at incident rates of between 1 and 2% per annum, usually preceded by intermittently positive tests. Interestingly, an inception cohort of Danish type 1 patients followed from diag- nosis showed that UAER was significantly higher (but well within the normal range) in those subsequently going on to develop moderately increased albuminuria after 15 to 20 years, compared to those who did not (11 vs 8 μg/min; P = 0.002). The rate of increase of UAER in patients with moderately increased albuminuria is historically around 20% per annum, but this is lower in those commencing antihypertensive therapy or intensified insulin regimens (Table 21.10.1.2). It is unusual to develop moderately increased albuminuria within the first 5 years of diabetes onset, but it can develop at any time thereafter, even after 40 years. Many patients with type 1 diabetes and moderately increased albuminuria will progress to severely ele- vated albuminuria unless treated; those with longer durations of diabetes before moderately increased albuminuria tend to progress more slowly. More recent prospective studies have shown that as many as 25% of type 1 moderately increased albuminuric patients may spontaneously regress to normoalbuminuria. Around 12.5% may oscillate between normoalbuminuria and moderately increased albuminuria for many years. The significance of these movements is unclear and is possibly the result of blood pressure-lowering ther- apies and short-term changes in glycaemic control. What seems clear, however, is that these patients are at lower risk of progressing to endstage renal disease. Once UAER exceeds 300 mg/day, there tends to be a relentless increase, occasionally into the nephrotic range. The rate of change varies between patients and is very dependent on systemic blood pressure. Historically, the incidence of severely elevated albumin- uria peaked after 15 to 17 years' duration of diabetes, but more re- cent studies are showing a delay to 25 years or more. As the onset of type 2 diabetes is more difficult to define, the pre- cise incidence of moderately increased albuminuria is harder to

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