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Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: lessons from RENAAL.

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BACKGROUND: Proteinuria or albuminuria is an established risk marker for progressive renal function loss. Albuminuria can be effectively lowered with antihypertensive drugs that interrupt the renin-angiotensin system (RAS). We investigated whether albuminuria could not only serve as a marker of renal disease, but also function as a monitor of the renoprotective efficacy of RAS intervention by the angiotensin II (Ang II) antagonist, losartan, in patients with diabetic nephropathy. METHODS: The data from the RENAAL (Reduction in End Points in Noninsulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan) study, a double-blind, randomized trial, were used to examine the effects of losartan on the renal outcome [i.e., the primary composite end point of doubling of serum creatinine, end-stage renal disease (ESRD) or death] in 1513 type 2 diabetic patients with nephropathy. We examined the effect of the degree of albuminuria at baseline, initial antiproteinuric response to therapy, and the degree of remaining (residual) albuminuria on renal outcome (either the primary composite end point of RENAAL or ESRD). We also evaluated the contribution to renal protection of the antiproteinuric effect of losartan independently of changes in blood pressure. RESULTS: Baseline albuminuria is almost linearly related to renal outcome, and is the strongest predictor among all measured well-known baseline risk parameters. After adjusting for baseline risk markers of age, gender, race, weight, smoking, sitting diastolic blood pressure, sitting systolic blood pressure, total cholesterol, serum creatinine, albuminuria, hemoglobin, and hemoglobin A(1c) (HbA(1c)) patients with high baseline albuminuria (> or =3.0 g/g creatinine) showed a 5.2-fold (95% CI 4.3-6.3) increased risk for reaching a renal end point, and a 8.1-fold (95% CI 6.1-10.8) increased risk for progressing to ESRD, compared to the low albuminuria group (<1.5 g/g). The changes in albuminuria in the first 6 months of therapy are roughly linearly related to the degree of long-term renal protection: every 50% reduction in albuminuria in the first 6 months was associated with a reduction in risk of 36% for renal end point and 45% for ESRD during later follow-up. Albuminuria at month 6, designated residual albuminuria, showed a linear relationship with renal outcome, almost identical to the relationship between baseline albuminuria and renal risk. Losartan reduced albuminuria by 28% (95% CI -25% to -36%), while placebo increased albuminuria by 4% (95% CI +8% to -1%) in the first 6 months of therapy. The specific (beyond blood pressure lowering) renoprotective effect of the Ang II antagonist, losartan, in this study is for the major part explained by its antialbuminuric effect (approximately 100% for the renal end point, and 50% for ESRD end point). CONCLUSION: Albuminuria is

the predominant renal risk marker in patients with type 2 diabetic nephropathy on conventional treatment; the higher the albuminuria, the greater the renal risk. Reduction in albuminuria is associated with a proportional effect on renal protection, the greater the reduction the greater the renal protection. The residual albuminuria on therapy (month 6) is as strong a marker of renal outcome as is baseline albuminuria. The antiproteinuric effect of losartan explains a major component of its specific renoprotective effect. In conclusion, albuminuria should be considered a risk marker for progressive loss of renal function in type 2 diabetes with nephropathy, as well as a target for therapy. Reduction of residual albuminuria to the lowest achievable level should be viewed as a goal for future renoprotective treatments.

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