Prevention of Microalbuminuria in Type 2 Diabetes: Millimeters or Milligrams?

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The phenomenon of albuminuria has been recognized for more than 200 yr, and its association with kidney disease dates to the epochal insights of Richard Bright in 1827 (1). It now is widely appreciated that the excretion of even small amounts of albumin in the urine may portend serious future events, such as elevation of systemic arterial pressure, cardiovascular disease, and progressive renal dysfunction (2,3). Indeed, numerous reports now show clearly that the association of albuminuria with cardiorenal risk is continuous and begins at levels only slightly above the normal (non-diabetic, nonhypertensive) median level of albumin excretion indexed for creatinine excretion (approximately 4 \( \mu g \) albumin/g creatinine in men and 7.5 \( \mu g/g \) creatinine in women) (3,4). The lack of any “threshold effect” for albumin excretion in relationship to cardiorenal risk has led to calls for abandoning the concept of “microalbuminuria” (3,5). This term originally was coined by Viberti et al. (6) and by Svendsen et al. (7) to identify and differentiate albumin excretion rates (20 to 200 \( \mu g/min \)) that were below the usual level of detection by a standard dipstick method (>200 \( \mu g/min \), also termed “macroalbuminuria”) in patients with diabetes.

Increased albumin excretion rates, even in the “high normal range” (e.g., 10 to 19 \( \mu g/min \)) are associated with an increased risk for further progression to distinct “microalbuminuria” and eventually to overt nephropathy in both type 1 and type 2 diabetes (3,4,8). Overt albuminuria or other tightly associated events can contribute to progression of renal disease by promoting “downstream” alterations in glomerular and tubular epithelial cells, leading to glomerulosclerosis and interstitial fibrosis (3,9).

It seems reasonable, therefore, to try to modify the development of albuminuria at an early stage of diabetes to determine whether the evolution of diabetic renal disease can be ameliorated. This was the objective of the Bergamo Nephrological Diabetes Complications Trial (BENEDICT), the results of which first were reported in November 2004 (10). In brief, this randomized, double-blind trial was designed to test the hypothesis that an angiotensin-converting enzyme (ACE) inhibitor (trandolapril), alone or in combination with a nondihydropyridine calcium channel blocker (verapamil), could prevent the development of microalbuminuria (=20 \( \mu g/min \)) in patients who have type 2 diabetes and elevated systemic arterial BP (>130/85 mmHg) and “normal” albumin excretion (<20 \( \mu g/g \)). The treatments resulted in a comparable decline in BP in all groups (from approximately 150/87 mmHg at baseline to approximately 140/81 mmHg at follow-up), but the groups that received trandolapril (with or without verapamil) experienced a substantial decline in the rate of development of microalbuminuria during the 48 mo of follow-up (6% in the trandolapril-treated groups and 17% in the non-trandolapril-treated group). The development of microalbuminuria in the verapamil only–treated group was similar to a placebo. ACE inhibition (with trandolapril) delayed the onset of microalbuminuria in these hypertensive patients who had type 2 diabetes without baseline microalbuminuria. This study was not designed to separate the specific effects of BP control and the effects of ACE inhibition, but it was logical to believe that the observed reduction in progression to microalbuminuria could not be accounted for fully by BP reduction alone. Studies in patients with type 1 and with type 2 diabetes and persistent microalbuminuria or macroalbuminuria also have demonstrated an antiproteinuric effect of angiotensin II (AngII) inhibition (ACE inhibitors or AngII receptor antagonists) (3,11,12).

In patients with type 1 or 2 diabetes and macroalbuminuria, inhibition of AngII also has been shown to slow the rate of progressive loss of GFR (3,12–14). However, the BP-independent effects of inhibition of AngII have become controversial recently since a large meta-analysis failed to show such an effect in terms of renoprotection (15). This meta-analysis has been criticized for its inclusion of trials that were not designed to examine renoprotection end points and that did not randomly assign patients with proteinuria in addition to hypertension (16). In trials of overt (macroalbuminuric) diabetic nephropathy, both BP control and the use of inhibitors of AngII have independent and additive protective effects on both renal progression and cardiovascular events (3,17). In overt nephropathy in type 2 diabetes, a target level of systolic BP (SBP) between 120 and 130 mmHg has been suggested by the post hoc analysis of the Irbesartan Diabetic Nephropathy Trial (IDNT) (17). Reduction of the SBP to <120 mmHg or the diastolic BP (DBP) to approximately <75 to 80 mmHg can be associated with an increase in cardiovascular mortality in patients with diabetes, especially with concomitant coronary artery disease (17,18).
These findings set the stage for the post hoc analysis of BENEDICTION reported in this issue of *JASN* by Ruggenenti et al. (19). They examined the relationships of baseline BP and postrandomization BP (absolute and reduction from baseline) with the development of persistent microalbuminuria among the 1180 hypertensive, “normoalbuminuric” participants with type 2 diabetes in BENEDICTION. Importantly, baseline BP did not predict the subsequent development of microalbuminuria. Among all randomly assigned patients the (casual, office-based) BP levels decreased by approximately 10 mmHg SBP and 6 mmHg DBP from baseline to follow-up. Higher SBP levels (of approximately 3 mmHg) were found among patients who developed microalbuminuria at any time after randomization compared with those who did not even after adjustment for baseline covariates and assignment to trandolapril or verapamil therapy. The post hoc nature of the analysis prohibits drawing any causal inferences for this association. It is possible that the development of microalbuminuria is a marker for pathophysiologic events that aggravate BP or impair the response to the BP-lowering effects of antihypertensive drugs or, alternatively, that the increasing systemic arterial BP transmits a higher pressure to the glomerular and peritubular capillaries (in the presence of afferent arteriolar dilation), thereby promoting abnormal glomerular permselectivity or changes in tubular albumin processing. However, patients whose SBP levels were above the median during follow-up and who also were receiving trandolapril had a lower risk for developing microalbuminuria compared with patients who had elevated SBP levels during follow-up and who were treated with non–trandolapril-containing regimens. At SBP levels below the median during follow-up, there was no clear-cut difference in the risk for development of microalbuminuria regardless of treatment randomization stratum. On the surface, this suggests that events that were responsible for transition to microalbuminuria in patients with higher-than-median BP are more amenable to trandolapril therapy. The development of microalbuminuria also was strongly associated with a lesser reduction in SBP levels from baseline, even after adjustment for baseline covariates, except that higher baseline BP was associated with a greater fall in postrandomization BP (not surprising). Patients with a greater-than-median decline in BP after randomization also more frequently were receiving trandolapril (alone or in combination with verapamil), but the incidence of microalbuminuria events was comparable in the trandolapril and non-trandolapril-containing regimens. The trandolapril plus verapamil combination was more likely to result in a greater fall in BP from baseline. Taken together, these findings from a post hoc analysis suggest that lowering BP itself, at least within the ranges observed in this study and regardless of the agents used, has a salutary effect on the risk for development of microalbuminuria in type 2 diabetes. The use of an ACE inhibitor (trandolapril) seems to have a further risk-reducing effect, particularly when the BP is not very well controlled. Adequate control of SBP (below the median for all patients) was associated with a low risk for development of microalbuminuria, regardless of treatment assignment. Reverse causality may rear its ugly head as an issue in the interpretation of these results from a post hoc analysis, because factors that are involved in the generation of microalbuminuria could contribute to the worsening of BP and have an impact on its response to treatment. Nevertheless, from the clinical standpoint, these studies seem to suggest that the management of hypertension (BP >130/85 mmHg) in patients with type 2 diabetes and normoalbuminuria can be undertaken safely without initial recourse to an AngII inhibitor, provided that BP subsequently is maintained at a satisfactory level (probably between 120 and 130 mmHg SBP). It is noteworthy that despite multiple antihypertensive drugs, only 14% of the patients in the BENEDICTION achieved SBP of <130 mmHg, perhaps due in part to adverse effects or to limitations imposed by marked reduction of DBP (18; Ruggenenti P, Clinical Research Center for Rare Diseases “Aldo & Cele Dacco,” Mario Negri Institute for Pharmacological Research, Bergamo, Italy, personal communication, October 18, 2006). It also is noteworthy that only 19% of all patients and only 31% of those who required concomitant therapy in BENEDICTION were receiving a diuretic (Ruggenenti P, personal communication, October 18, 2006). The protocol contained no specification for a low-salt diet, but it is likely that the participants were consuming a “Mediterranean diet.” Salt intake was not assessed during the conduct of the trial. The use of potassium-sparing diuretics was precluded per protocol. One can only speculate regarding the possible influence that a higher utilization of diuretics and/or a lower salt intake might have had on the outcomes that were observed in this study.

This post hoc analysis of a landmark clinical trial adds greatly to the knowledge base that is required for our continuing efforts to reduce the burden of progressive renal disease in the ever-growing population of patients with type 2 diabetes worldwide. The hypothesis that was generated by this study that more effective BP control with an ACE inhibitor–containing regimen can reduce the risk for development of microalbuminuria is a reasonable one that could be proved true or false by another prospective trial using an ACE inhibitor at two different levels of BP control, as suggested by the authors. It is important to point out that even with rigorous attention to BP control and the use of multiple agents that only approximately one in seven patients with type 2 diabetes and hypertension can achieve target BP of <130/80 mmHg consistently without dosage-limiting adverse effects.

If (and this is a very big if) one can achieve consistently target levels of BP control that approach 120/80 mmHg, then perhaps by the aggressive use of diuretics, salt restriction, and other antihypertensive agents, a marked reduction in the risk for developing microalbuminuria and progression of renal disease might be achieved without necessarily resorting to AngII inhibition. However, for the majority of patients who cannot achieve this level of BP control, an ACE inhibitor alone or combined with a nondihydropyridine calcium channel blocker definitely would be indicated, as shown by this study.

As with most good clinical trial research, this post hoc analysis generates as many questions as it resolves. Some of the new questions raised include the following: (1) What would be the effect of escalating doses of an ACE inhibitor alone or combined with an AngII receptor antagonist on the risk for development...
of microalbuminuria? (2) What would be the benefit and the risk of adding a small dose of an aldosterone inhibitor on the risk for development of microalbuminuria? (3) Would more aggressive salt restriction and/or more extensive use of diuretics further promote the microalbuminuria-preventing effects of AngII inhibition? The answers to these and other questions must remain for future studies, but for now, we must be content with the added knowledge that has been provided by the pioneering studies of Ruggenenti and colleagues. They have given us many new insights into this extremely important clinical problem.

References