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Albuminuria in Hypertensive Patients: Where the Choice of Antihypertensive Medications Matters: Commentary on "Several Conventional Risk Markers Suggesting Presence of Albuminuria Are Weak Among Rural Africans With Hypertension"

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Albuminuria, including microalbuminuria (dipstick-negative albuminuria), is an independent predictor of future cardiovascular (CV) events, CV mortality, and all-cause mortality in patients with and without type 2 diabetes.[1] It has been estimated that for every 0.4-mg/mmol increase in albumin-creatinine ratio (ACR), the hazard ratio for major CV events increases by about 6%. Although a common feature in patients with diabetes, albuminuria also occurs in 5% to 10% of nondiabetic individuals.[2] Albuminuria has been associated with dyslipidemia and metabolic syndrome traits, including obesity, impaired glucose tolerance, insulin resistance, and elevated uric acid levels, and especially with essential hypertension.[3]

The prevalence of albuminuria is about 40% in the untreated hypertensive population and about 25% among hypertensive patients treated with diuretics and β-blockers. The prevalence increases with age and with the duration and severity of hypertension. The severity of albuminuria correlates with blood pressure (BP) levels and responds to lowering of BP.[4] Presence of albuminuria, however, has predictive values independent of BP. Target organ damage is more common in microalbuminuric patients with hypertension. For instance, patients with albuminuria have higher left ventricular mass, higher prevalence of hypertensive retinopathy, and risk of myocardial infarction.[5] The association of albuminuria with cardiovascular mortality is poorly understood. It is proposed that albuminuria represents the renal manifestation of a generalized vascular endothelial dysfunction that underlies its association with CV diseases.[6]

In this issue of *The Journal of Clinical Hypertension*, Rasmussen and colleagues[7] from the University of Copenhagen present their investigation on risk markers for albuminuria in patients with hypertension in rural sub-Saharan Africa (SSA). Exclusion criteria included a positive urine dipstick for nitrites, leukocytes, blood, or fever. BP was measured in the ambulatory setting in both arms, with the highest level taken as the reference. The majority of the participants were women (n=110, 68.8%) and more than 40% of the study participants had an established diagnosis of type 2 diabetes. In their cross-sectional study of 160 SSA

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hypertensive patients, they identified 35.6% with albuminuria, with the majority having microalbuminuria (n=43). A multivariate logistic regression model identified age, glycated hemoglobin (HbA_{1c}) levels, and treatment with dihydropyridine (DHP) calcium channel blockers (CCBs) as the variables significantly associated with albuminuria. The study has several serious limitations. The small size of the study population, which mainly consisted of women with diabetes, is the major limitation. The HIV status of most participants was also not known, a factor that seriously complicates the analysis in a population at high risk for HIV nephropathy.

Remarkably, obesity, BP level, and duration since diagnosis were not associated with albuminuria. These results are in contrast to earlier published data, even in patients of African origin. It is possible that several undetected risk factors were overshadowed by the strong effect of diabetes on the trait, given the small size study population. The unique lifestyle and environmental conditions of rural SSA, in terms of physical activity and nutrition may have influenced the results and, hence, the findings may be unique to this population and not generalizable. Nonetheless, the findings should not be simply discounted, as they are thought-provoking and hypothesis-generating. In fact, a careful scrutiny of the published data suggests that the study may have merits that should be acknowledged and taken into consideration in designing future therapeutic trials for hypertension.

The most striking finding of the study is the association of DHP CCBs with albuminuria. Most studies have shown that BP control results in a decrease in urine albumin levels. Several studies have suggested that all types of antihypertensive therapies are able to lower albuminuria in patients with essential hypertension, simply by lowering BP.[8] Recent studies, however, have shown that angiotensin-converting enzyme (ACE) inhibitors exhibit a higher capability in reducing albuminuria in hypertensive patients, an effect that is independent of their capacity to decrease renal perfusion pressure.[9] Angiotensin II receptor blockers may also have a similar capacity in reducing albuminuria, almost matching those of ACE inhibitors.[10] While drugs that block the renin-angiotensin system have shown a capacity to lower BP as well as urinary albumin excretion, their effects on albuminuria appears to be independent of their ability to lower BP.

DHP calcium antagonists (DHPCAs) on the other hand have failed to reduce proteinuria in patients with type II diabetes. In fact, a handful of studies have suggested that the use of DHPCAs may be associated with increased albuminuria, particularly in treatment-resistant hypertension.[11] The failure to reduce albuminuria occurs despite their adequate control of BP reduction and an effort at dietary sodium restriction.[12] This issue remains controversial, with some studies showing rather favorable effects. Large randomized trials are necessary to address this question.

In contrast, the non-DHP CCBs has been consistently shown to reduce or at least blunt the rise in proteinuria in patients with type II diabetes and low to moderate sodium intake.[13] It is suggested that that non-DHP CCBs may reduce efferent arteriolar tone and intraglomerular pressure. In contrast, DHPCAs have failed to show any beneficial effects on intrarenal hemodynamics.

Whether a decrease in urinary albumin excretion is accompanied by improved renal and cardiovascular prognosis in hypertensive patients remains to be elucidated. The Captopril Study in individuals with type 1 diabetes and nephrotic-range proteinuria demonstrated that BP reduction results in remission of renal disease.[14] Reductions of proteinuria in patients with diabetic nephropathy may also be associated with a reduction in nephropathy progression.[13]

Overall, the consensus among all hypertension specialists is that BP control without improvement of proteinuria has inadequate effect in slowing the progression of nephropathy. Whether reducing albuminuria with ACE inhibitors will also reduce cardiovascular morbidity and mortality should await large pharmacotherapy trials of hypertension.

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