Diverse diuretics regimens differentially enhance the antialbuminuric effect of renin–angiotensin blockers in patients with chronic kidney disease

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The addition of spironolactone or hydrochlorothiazide enhances the antialbuminuric effect of renin–angiotensin blockers. However, comparative studies on the effect of different diuretics are lacking. We conducted a prospective randomized crossover study to compare the effects of spironolactone (25 mg/day), hydrochlorothiazide (50 mg/day) without/with amiloride (5 mg/day) on top of enalapril treatment in 21 patients with CKD stages 1–3 and a urinary albumin-to-creatinine ratio (UACR) over 300 mg/g. Treatment periods lasted 4 weeks. The UACR showed a significant reduction with the diuretics: spironolactone, −34% or hydrochlorothiazide without/with amiloride −42% or −56%, respectively. Reduction of the UACR was significantly greater with hydrochlorothiazide without/with amiloride when compared with spironolactone. The percentage of patients who achieved UACR reductions greater than 30% and 50% was greater with hydrochlorothiazide without/with amiloride (81% and 57%, and 81% and 66%, respectively) when compared with spironolactone alone (57% and 28%, respectively). Glomerular filtration rate (GFR), blood pressure, and body weight decreased with the three diuretic regimens. A significant correlation was found between the UACR reduction and GFR and blood pressure changes. Thus, diverse diuretic regimens differentially enhance albuminuria reduction, an effect likely associated with the degree of GFR reduction.

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The most important therapeutic strategies for slowing the progression of chronic kidney disease (CKD) and reducing the disproportionate cardiovascular risk of CKD patients are controlling blood pressure (BP) and reducing albuminuria.[1–7] Renin–angiotensin–aldosterone system (RAAS) blockers (angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs)) are the backbone of these therapies due to their efficacy in controlling BP and their known antialbuminuric effect. The favorable influence of these drugs on the progression of chronic diabetic and nondiabetic nephropathy has been demonstrated in several prospective controlled studies.[3–9] This favorable influence has a close relationship with the reduction of albuminuria; the more intense the reduction in albuminuria the greater the reduction in the risk of progression of CKD.[4,7] However, the antialbuminuric effect of RAAS blockers is mild or negligible in a substantial number of CKD patients. The so-called "residual albuminuria" (i.e., the level of albuminuria that persists after reaching the maximum tolerated dosage of RAAS blockers and proper BP control) is considered one of the most significant factors in the progression of kidney damage.[10–13] Therefore, the search for new alternatives that enhance the antialbuminuric effect of ACEIs and ARBs is of paramount importance.

In recent years, several studies have demonstrated the antialbuminuric potential of aldosterone receptor antagonists (spironolactone (SR) and eplerenone).[14–21] Likewise, observational studies have suggested that this reduction in albuminuria, as occurs with ACEIs and ARBs, is associated with a significant reduction in the risk of progression of CKD.[18,20–23] Nevertheless, prospective controlled studies have not been performed with the duration necessary to demonstrate the renoprotective effect of aldosterone antagonist diuretics. Moreover, the combination of these diuretics with ACEIs or ARBs increases the risk of hyperkalemia, especially in patients with reduced glomerular filtration.[18,20,21,23]

Compared with the extensive experimental and clinical research performed on aldosterone antagonist diuretics, the possible antialbuminuric effect of other diuretics has been scarcely studied. However, several clinical studies have shown

that hydrochlorothiazide (HCT), at dosages of 25–50 mg/day, induces powerful albuminuria reductions in patients with or without diabetes who have residual albuminuria despite maximum dosages of ACEIs or ARBs.[24–26] This antialbuminuric effect was similar to that achieved with a low-sodium diet. The combination of the two measures (HCT plus a low-sodium diet) achieved a very significant reduction in albuminuria, greater than that achieved by each measure in isolation.[24,26] Other studies have shown that furosemide can also boost the antialbuminuric effect of ACEIs and ARBs.[27,28] There is no clinical information available on amiloride concerning its possible antialbuminuric effect, but experimental models have suggested a possible nephroprotective role of this diuretic.[29,30]

To the best of our knowledge, there are no clinical studies that have compared the antialbuminuric efficacy of various types of diuretics. This information would be extremely important for the design of renoprotective clinical strategies, given that the use of various types of diuretics is standard practice for controlling BP and volume overload in CKD patients. Aim of our study was to compare the antialbuminuric effect of SR, HCT, and amiloride. However, amiloride is usually marketed in combination with HCT in most countries, including ours. We therefore designed a prospective, randomized crossover study to compare the antialbuminuric effect of SR, HCT, and HCT+amiloride (A) for patients with CKD and a urinary albumin-to-creatinine ratio (UACR) >300 mg/g.

RESULTS

Of the 29 initially selected patients, 21 patients provided their informed consent and started the study. Three patients were excluded for presenting UACR <300 mg/g, three patients were excluded because of lack of motivation to continue with the study, and two patients were excluded for other causes (Figure 1).

Table 1 reflects baseline clinical and biochemical characteristics at the end of the run-in period for the 21 randomized patients. Almost half of the patients had diabetes and the other half had various glomerular conditions. In all, 3 patients had stage 1 CKD, 10 patients stage 2 CKD, and 8 patients stage 3 CKD. During the study, there was very good treatment adherence to the various types of diuretics in all patients ($>90\%$ of SR, HCT, and HCT+A pills during the three treatment periods). Two patients had to reduce the enalapril dosage (20 mg/day) because of excessive BP control in the HCT+A group.

Main objective

As can be seen in Table 2, UACR showed a significant reduction with the three types of diuretics: SR, -34% (95% confidence interval (CI) $=-21$ to -47; $P=0.001$); HCT, -42% (95% CI $=-28$ to -56; $P=0.001$); and HCT+A, -56% (95% CI $=-44$ to -67; $P=0.001$). UACR reduction was significantly greater with HCT and HCT+A when compared with SR.

Secondary objectives

The percentage of patients who achieved UACR reductions >30 and $>50\%$ was also greater with HCT and HCT+A when compared with SR, although these differences did not reach statistical significance (Table 2). There was a $>30\%$ reduction in UACR in 12 patients (57%) treated with SR and in 17 patients (81%) treated with HCT or HCT+A. The percentage of patients with $>50\%$ UACR reduction was greater in the HCT+A group (14 patients (66%)) compared with the HCT group (12 patients (57%)) and SR group (6 patients (28%)). 24-h proteinuria and 24-h albuminuria also showed significant reductions with the three types of diuretics, without significant between-group differences (Table 2).

Tertiary objectives

Estimated glomerular filtration rate (eGFR) was reduced with the three types of diuretics, as shown in Table 3. This reduction was statistically significant with HCT (-8.5% (95% CI $=-3.8$ to -13.3; $P=0.002$)) and with HCT+A (-12% (95% CI $=-5.9$ to -18.1; $P=0.001$)), whereas it did not reach statistical significance with SR (-6% (95% CI $=-0.9$ to -11.9)). There were no statistically significant between-group differences. As shown in Table 3, BP (systolic BP, diastolic BP, and mean arterial pressure) decreased with the three types of diuretic treatment. This decrease achieved statistical significance with SR and with HCT+A. Body weight also decreased with the three types of diuretics (Table 3), reaching statistical significance with SR and HCT+A. There were no significant between-group differences regarding BP and body weight changes.

Other parameters

There were no significant changes in plasma sodium levels with any of the diuretics, whereas serum potassium levels experienced a significant increase with SR and HCT+A (Table 4). Urinary excretions of sodium and potassium showed no significant changes (Table 4). Uric acid levels increased significantly with all study diuretics, with no between-group differences (Table 4). As expected, renin and aldosterone levels showed an increase with all types of diuretics, which was significant in all cases except for the increase in aldosterone levels in patients treated with HCT (Table 4). No significant between-group differences were found.

Correlations and multivariate analysis

As shown in Figure 2, we found a significant correlation between changes in UACR and eGFR when analyzing all treatment periods ($r=0.50$, $P=0.002$) and in each of the three types of diuretics separately. Changes in UACR also showed a significant correlation with BP changes when analyzing all treatment periods (Figure 3), although it did not reach statistical significance when the various diuretics were analyzed separately. No significant correlation between UACR and weight changes was found.