Effect of a Reduction in Uric Acid on Renal Outcomes During Losartan Treatment

A Post Hoc Analysis of the Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus With the Angiotensin II Antagonist Losartan Trial

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Abstract—Emerging data show that increased serum uric acid (SUA) concentration is an independent risk factor for end-stage renal disease. Treatment with the antihypertensive drug losartan lowers SUA. Whether reductions in SUA during losartan therapy are associated with renoprotection is unclear. We therefore tested this hypothesis. In a post hoc analysis of 1342 patients with type 2 diabetes mellitus and nephropathy participating in the Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus With the Angiotensin II Antagonist Losartan Trial, we determined the relationship between month 6 change in SUA and renal endpoints, defined as a doubling of serum creatinine or end-stage renal disease. Baseline SUA was 6.7 mg/dL in placebo and losartan-treated subjects. During the first 6 months, losartan lowered SUA by −0.16 mg/dL (95% CI: −0.30 to −0.01; P=0.031) as compared with placebo. The risk of renal events was decreased by 6% (95% CI: 10% to 3%) per 0.5-mg/dL decrement in SUA during the first 6 months. This effect was independent of other risk markers, including estimate glomerular filtration rate and albuminuria. Adjustment of the overall treatment effects for SUA attenuated losartan's renoprotective effect from 22% (95% CI: 6% to 35%) to 17% (95% CI: 1% to 31%), suggesting that approximately one fifth of losartan's renoprotective effect could be attributed to its effect on SUA. Losartan lowers SUA levels compared with placebo treatment in patients with type 2 diabetes mellitus and nephropathy. The degree of reduction in SUA is subsequently associated with the degree in long-term renal risk reduction and explains part of losartan's renoprotective effect. These findings support the view that SUA may be a modifiable risk factor for renal disease. **(*Hypertension*. 2011;58:2-7.)**

Key Words: serum uric acid ■ angiotensin receptor blocker ■ losartan ■ diabetic nephropathy ■ type 2 diabetes mellitus

Over the past decades, serum uric acid (SUA) has emerged as a cardiovascular risk marker. Increased SUA has been shown to predict the risk of hypertension, diabetes mellitus, and cardiovascular disease.[1–3] More recent data also point to SUA as a risk marker for progression of chronic kidney disease.[4,5]

These observations raise the question as to whether interventions that lower uric acid could confer cardiovascular or renal protection. In this respect, the angiotensin receptor blocker losartan is of potential interest. The drug has been clearly demonstrated to be renoprotective in patients with diabetic nephropathy, with this effect largely attributed to its effects on blood pressure and/or proteinuria/albuminuria.[6] However, it is unclear whether other off-target effects of the drug could contribute to the ultimate improvement in renal outcome with this agent. Importantly, previous studies have shown that losartan lowers SUA. This hypouricemic effect does not occur with other angiotensin receptor blockers[7] and appears to be largely mediated through reductions in the level of human urate transporter 1 (URAT1) and decreased net urate reabsorption in the proximal tubule.[8–10]

With respect to cardiovascular endpoints, a subanalysis from the Losartan Intervention for Endpoint Reduction in Hypertension Trial showed that the superior effect of losartan could be

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The RENAAL trial has been registered at www.clinicaltrials.gov (identifier NCT 00308347).

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partly explained by its effect on SUA.[11] Whether the same holds true for the long-term renoprotective effect of losartan is unknown but is worth investigating in the context of the increased body of evidence linking uric acid to the progression of chronic kidney disease.[12] The aim of the present study, therefore, was to assess whether losartan-induced changes in uric acid during initial months of therapy are associated with decreased (long-term) risk of readily measurable renal outcomes in patients with type 2 diabetes mellitus and nephropathy.

Methods

Study Design

The Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus With the Angiotensin II Antagonist Losartan (RENAAL) Trial was a multinational, randomized, double-blind trial that compared the effects of losartan versus placebo in addition to conventional antihypertensive medication in patients with type 2 diabetes mellitus and nephropathy. Patients had serum creatinine levels between 1.3 and 3.0 mg/dL (1.5 to 3.0 mg/dL for men >60 kg). The study was performed in 250 centers in 28 countries and involved 1513 patients. The study design, the inclusion/exclusion criteria, and the treatment protocol have been reported previously.[13] In short, after a 6-week screening phase, patients were randomly assigned to either losartan (100 mg) or placebo. Additional antihypertensive medications (calcium channel blockers, β-blockers, centrally acting agents, and diuretics, excluding angiotensin-converting enzyme inhibitors or other angiotensin receptor antagonists) were permitted to achieve the blood pressure goal of <140/90 mm Hg (systolic/diastolic). All of the patients signed informed consent before enrollment, and the local institutional review board of each participating center approved the study. The mean duration of follow-up was 3.4 years.

Measures and Outcomes

In this study, we performed a post hoc analysis of all of the subjects with uric acid measurements included in the RENAAL Trial. Blood pressure, SUA, serum creatinine, and albuminuria were measured every 3 months, and hemoglobin A1c was measured every 6 months for the duration of the study. Albuminuria was assessed as the ratio of albumin:creatinine concentrations from a first-morning-void urine sample. The Modification of Diet in Renal Disease formula was used to estimate glomerular filtration rate (eGFR).[14] We assessed the relationship between change in SUA level at month 6 and renal outcomes. The change from baseline to month 6 was chosen because this is the earliest time point at which most variables of interest were available, the treatment effects were considered to be fully manifest, and relatively few renal events occurred before month 6.[15] Changes in SUA, blood pressure, albuminuria, and hemoglobin A1c were calculated as baseline minus month 6.

The primary renal outcome was defined as a composite of a confirmed doubling of serum creatinine or end-stage renal disease. The latter was defined as the need for chronic dialysis or renal transplantation. All of the endpoints were adjudicated by a blinded endpoint committee using rigorous guideline definitions.

Statistical Analysis

Patients with SUA measurements at baseline and month 6 were included in the present analysis. Mean SUA at each visit during follow-up was calculated in both the losartan and placebo groups. Patient characteristics were summarized according to tertiles of month 6 changes in SUA. To identify parameters associated with a change in SUA at month 6, a multivariate logistic regression model was used. Baseline characteristics, as well as month 6 changes in systolic and diastolic blood pressure, hemoglobin A1c, log-transformed albuminuria, and eGFR, were included in the multivariate model. A backward selection procedure was used for selection of covariates for the final model (α=0.1).

The proportion of patients without renal events was estimated using the Kaplan–Meier procedure. Multivariate Cox regression analyses were performed to determine whether changes in SUA were independently associated with renal outcomes. Changes in SUA were included in the Cox model as a continuous variable. All of the analyses were adjusted for risk markers that showed a statistically significant association with month 6 change in uric acid. These included the following: age, sex, treatment assignment (losartan or placebo), eGFR, systolic blood pressure, log-transformed albuminuria, serum albumin, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use at baseline, and changes in log-transformed albuminuria and eGFR. Finally, the contribution of therapy-induced changes in SUA on losartan's renoprotective effect was assessed by time-varying Cox regression models. Relative risk reductions are described in the text as percentage reductions ([1−hazard ratio]×100). Analyses were conducted with SAS (version 9.2; SAS Institute, Cary, NC). A P value <0.05 was considered to indicate statistical significance.

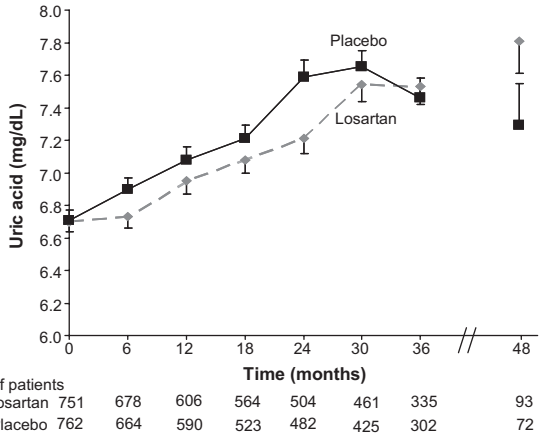

Figure 1. Mean uric acid level during follow-up among patients in the losartan and placebo groups. Bars represent standard errors.

Results

A total of 1342 subjects were involved in the present analysis. In the losartan group, the mean SUA remained 6.7 mg/dL during the first 6 months of therapy. By contrast, in the placebo group, the mean SUA increased from 6.7 mg/dL at baseline to 6.9 mg/dL at month 6, resulting in a mean group difference of −0.16 mg/dL (95% CI −0.30 to −0.01; P=0.031) (Figure 1). The level of SUA in the placebo group continued to increase from month 6 onward. Likewise, the SUA level also started to rise at month 6 in the losartan group. The "apparent" fall observed at 36 months in the placebo group is likely to be linked to "dropout" of patients in the placebo group with high SUA levels. Patients were subsequently classified into tertiles according to the change in SUA at month 6 (Table 1). Relevant baseline characteristics were not different among the tertile groups apart from SUA and albuminuria, which were higher and, respectively, lower in patients who had a decrease in SUA. In addition, these patients had a smaller reduction in systolic blood pressure and albuminuria at month 6.

To investigate the parameters associated with a change in SUA at month 6, a multivariate linear regression was performed in the overall population. Allocation to losartan therapy was independently associated with a larger fall in uric acid at month 6. Furthermore, higher baseline SUA, eGFR, and serum albumin, as well as a larger reduction in eGFR and a smaller reduction in albuminuria, were significantly associated with a larger decrease in SUA at month 6 (Table 2).

Table 1. Characteristics of the Overall Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus With the Angiotensin II Antagonist Losartan Trial Population by Treatment Allocation and by Month 6 Change in Uric Acid

			Tertiles of Change in Uric Acid		
Characteristic	Placebo (n=664)	Losartan (n=678)	Uric Acid Decrease ≥0.5 mg/dL (n=457)	−0.5<ΔUric Acid<0.5 mg/dL (n=435)	Uric Acid Increase ≥0.5 mg/dL (n=450)
Age, y	60.2 (7.6)	60.0 (7.3)	60.3 (7.2)	60.2 (7.6)	59.9 (7.5)
Men, n (%)	421 (63.4)	422 (62.2)	296 (64.5)	270 (62.1)	277 (61.6)
Race, n (%)					
White	327 (49.3)	322 (47.5)	228 (49.9)	212 (48.7)	209 (46.4)
Black	92 (13.9)	109 (16.1)	62 (13.6)	65 (14.9)	74 (16.4)
Hispanic	120 (18.1)	124 (18.3)	90 (19.7)	80 (18.4)	74 (16.4)
Asian	117 (17.6)	114 (16.8)	70 (15.3)	72 (16.6)	89 (19.8)
Other	8 (1.2)	9 (1.3)	7 (1.5)	6 (1.4)	4 (0.9)
Systolic BP, mm Hg	152.9 (20)	152.0 (19)	151.1 (19.1)	152.1 (19.8)	154.2 (19.2)
Diastolic BP, mm Hg	82.3 (10)	82.4 (10)	82.3 (10.5)	82.1 (10.3)	82.7 (10.4)
Total cholesterol, mg/dL	227.9 (56)	225.7 (55)	224.6 (55.1)	226.3 (52.4)	229.5 (58.0)
HbA1C, %	8.4 (1.6)	8.5 (1.6)	8.3 (1.6)	8.5 (1.7)	8.5 (1.6)
Serum uric acid, mg/dL	6.7 (1.7)	6.7 (1.7)	7.4 (1.8)	6.4 (1.5)	6.4 (1.5)*
Hemoglobin, mg/dL	12.4 (1.8)	12.5 (1.8)	12.6 (1.9)	12.5 (1.8)	12.4 (1.8)
Urinary ACR, mg/g	1261 (568 to 2475)	1168 (538 to 2540)	947 (475 to 1964)	1246 (593 to 2682)	1369 (693 to 2831)*
eGFR, mL/min/1.73 m^2	39.8 (12.7)	39.5 (11.8)	39.8 (12.2)	39.9 (12.4)	39.2 (12.2)
Serum creatinine, mg/dL	1.9 (0.5)	1.9 (0.5)	1.9 (0.5)	1.9 (0.5)	1.9 (0.5)
Serum albumin, mg/dL	3.8 (0.4)	3.8 (0.4)	3.7 (0.4)	3.8 (0.4)	3.7 (0.4)
Other treatments, n (%)					
ACEi or ARB	329 (49.6)	368 (54.3)	237 (51.9)	235 (54.0)	225 (50.0)
β-blockers	122 (18.4)	128 (18.9)	102 (22.3)	68 (15.6)	80 (17.8)
Calcium channel blockers	484 (72.9)	488 (72.0)	323 (70.7)	308 (70.8)	341 (75.8)
Diuretics	384 (57.8)	394 (58.1)	282 (61.7)	236 (54.3)	260 (57.8)
Follow-up characteristics					
Change in uric acid, mg/dL	0.2 (1.4)	0.0 (1.3)	−1.3 (0.8)	0.0 (0.2)	+1.5 (0.9)
Change in systolic BP, mm Hg	−0.3 (20)	−5.4 (19)	−0.4 (19)*	−2.3 (19)	−6.0 (21)
Change in diastolic BP, mm Hg	−0.7 (11)	−2.7 (10)	−0.6 (10)	−1.2 (9)	−3.5 (10)
Change in urinary ACR, %	+4.7	−28.8	+2.6	−13.2	−29.7*

BP indicates blood pressure; ACR, albumin:creatinine ratio; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; HbA1C, hemoglobin A1C. Mean (SD) or numbers of patients (%) was provided for normal distributed continuous variables and categorical variables, respectively. Because of the skewed distribution of the albumin:creatinine ratio, urinary albumin:creatinine ratio is presented as median (interquartile range). To convert the values of serum uric acid to micromoles per liter, multiply by 59.48. To convert the values of serum creatinine to micromoles per liter, multiply by 88.4. To convert the values for cholesterol to millimoles per liter, multiply by 0.0259.

*$P<0.05$ is shown for tests for trend among tertiles of month 6 serum uric acid change.

Figure 2 shows the proportion of patients free of renal events during follow-up according to the change in SUA. A total of 463 renal events occurred during follow-up. Those subjects with a decrease in SUA >0.5 mg/dL at month 6 had the lowest risk of developing renal endpoints (Figure 2). Subsequently, hazard ratios were calculated for finer categories of change in uric acid. After controlling for baseline and change in other risk factors, we observed an almost linear relationship between the change in uric acid and renal outcome (Figure 3), so that each 0.5-mg/dL reduction in SUA during the first 6 months was associated with a reduction in the risk of doubling of serum creatinine/end-stage renal disease of 6% (95% CI: 10% to 3%; $P<0.001$). To investigate how much of losartan's renoprotective effect could be attributed to its effect on SUA, we analyzed the impact of a reduction in SUA over time on losartan's renoprotective effect. When the treatment effect was adjusted for the residual SUA (the last measurement before the occurrence of the renal endpoint), the treatment effect of losartan on the doubling of serum creatinine/end-stage renal disease endpoint attenuated from 22% (95% CI: 6% to 35%) to 17% (95% CI: 1% to 30%); that is, ≈4% of 22% (one fifth) of the benefit of losartan could be attributed to its effect on SUA.

Discussion

This study demonstrates that losartan treatment in patients with type 2 diabetes mellitus and nephropathy lower SUA levels compared with placebo. Although SUA increased in the placebo group, this effect was attenuated with losartan in the treated group. A significant lower risk for renal events was observed per

Table 2. Covariates Associated With a Change in Serum Uric Acid at Month 6

Risk Markers	β	χ^2	P
Baseline uric acid	0.253	191.6	<0.001
Change urinary ACR	0.526	148.4	<0.001
Treatment assignment (losartan or placebo)	0.477	57.6	<0.001
Change eGFR	−0.032	41.5	<0.001
Baseline eGFR	0.010	13.1	0.002
Baseline serum albumin	0.263	12.6	0.003
Baseline ACEi or ARB use	−0.143	5.5	0.049
Baseline systolic blood pressure	−0.004	4.8	0.067
Sex	0.134	4.1	0.090

eGFR indicates estimated glomerular filtration rate; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ACR, albumin:creatinine ratio. Covariates that showed a P value <0.1 in the multivariate analysis are presented in the table. Covariates are ordered by decreasing significance based on the χ^2 statistics. The natural log-transformed value of urinary ACR and change in natural log-transformed urinary ACR were used in all of the regression analyses.

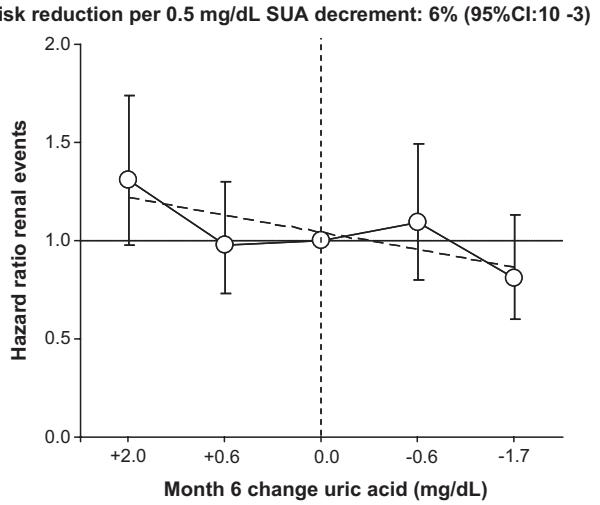

Figure 3. Hazard ratios for incident renal outcomes (doubling of serum creatinine or end-stage renal disease) as function of month 6 change in serum uric acid (SUA). The relation is corrected for baseline and change in other risk markers.

decrement in SUA during the first 6 months, and the association remained statistically significant (and unchanged) after adjustment for a broad range of known risk factors. The effect of losartan on SUA explained ≈20% of its renoprotective effect.

This is the first study that directly shows that the effect of losartan on SUA is associated with renal risk reduction. Thus, the effect on uric acid by losartan appears not only relevant for cardiovascular outcomes as reported in the Losartan Intervention for Endpoint Reduction in Hypertension Study[11] but also for the renal outcome. The estimated contribution of SUA to losartan cardiovascular protective treatment effects was calculated to be 29% in the Losartan Intervention for Endpoint Reduction in Hypertension Trial. In the present population, the contribution of SUA to losartan's renoprotective effect was estimated to be 22%.

The mechanisms through which losartan exerts its hypouricemic effect are well described. The proximal tubule has been identified as the primary location of uric acid secretion and reabsorption. A central role in proximal tubule urate reabsorption has been ascribed to URAT1. URAT1 is located in the lumen of proximal tubule cells and reabsorbs uric acid (as urate) in exchange for intracellular anorganic anions. Losartan increases urate excretion by inhibition URAT1-mediated renal tubule urate reabsorption. Early studies in the healthy population demonstrated that the peak uricosuric effect was already observed 2 to 4 hours after administration.[16,17] The time course of this effect suggests that it is losartan itself rather than its active metabolite that blocks URAT1 and causes the reduction in SUA. Theoretically, the distinct uricosuric effect of losartan could lead to increases in urinary uric acid concentration, which could lead to supersaturation of uric acid and, in the extreme case, precipitate uric acid nephropathy. However, the risk of development of uric acid crystals during losartan therapy is reduced because of the drug's urinary alkalinizing effects. Treatment with losartan raises urinary pH, which is attributed to the blockade of angiotensin II–induced stimulation of bicarbonate reabsorption. This increase in urinary pH offsets the formation of uric acid crystals and reduces the risk of acute uric acid nephropathy.[18]

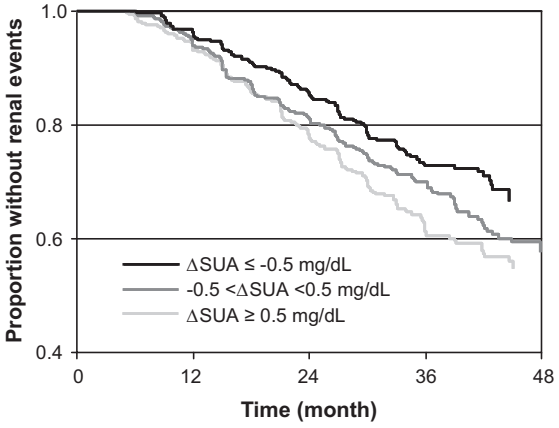

Figure 2. Kaplan–Meier curves for renal outcomes (doubling of serum creatinine or end-stage renal disease). The renal event rates in subjects with a month 6 reduction in SUA ≥0.5 mg/dL, serum uric acid (SUA) change between and 0.5 mg/dL, or an SUA increase ≥0.5 mg/dL were, respectively, 9.5, 12.3, and 14.3 events per 100 patient-years.

Emerging evidence demonstrates an association between SUA and adverse renal outcomes.[12] Whether this relationship is causal is unclear. Indeed, whether SUA is a marker of renal function decline or a risk factor for progressive renal function loss remains a matter of ongoing debate. In the kidney, SUA is filtered, secreted, and reabsorbed. As glomerular filtration rate (GFR) declines, the fractional excretion of uric acid increases. However, this process does not completely counterbalance the fall in GFR. Consequently, SUA levels start to rise. It is therefore reasonable to suggest that changes in SUA are a result of renal disease and have no direct pathogenic role. However, a series of experimental and epidemiological studies have challenged this view. Recent experimental studies have shown that increased uric acid levels increase activity of the renin-angiotensin-aldosterone system,[19] stimulate renal inflammation,[20] enhance endothelial dysfunc-

tion,[21] and impair renal autoregulation resulting in glomerular (and systemic) hypertension.[22] Each of these effects contributes to the initiation and progression of renal disease. In addition, epidemiological studies consistently show that increased SUA levels predict renal function decline, independent of other renal or cardiovascular risk factors. For example, Hovind et al[1] showed recently that increased uric acid is independently associated with development of nephropathy, although that study was performed in a cohort with type 1 diabetes mellitus. These experimental and clinical studies support the view that uric acid may be involved in the pathogenesis of renal disease.

The most compelling way to evaluate whether uric acid is a marker or risk factor for renal disease is to evaluate whether "direct" therapy that lowers uric acid confers renoprotection. A couple of studies have highlighted the relevance for renal outcomes of manipulating SUA concentrations. It appears that reductions in SUA conferred by allopurinol slow down progressive renal function loss in diabetic and nondiabetic patients with chronic kidney disease.[23,24] In addition, treatment of asymptomatic hyperuricemia has been reported to improve renal function even in subjects with normal renal function.[25] The results of our analysis showing that one fifth of losartan's renoprotective effect could be attributed to SUA provide further support for the postulate that treatment-induced reductions in SUA are associated with renoprotection, independent of baseline or changes in renal function. Furthermore, our study indicates that it is reduction of uric acid per se that is important rather than the specific treatment strategy used.

SUA increased in the placebo group during the trial and started to increase after 6 months in the losartan group. A similar trend of changes in SUA over time has been observed in the Losartan Intervention for Endpoint Reduction in Hypertension Trial.[11] In the RENAAL Trial, eGFR fell in the placebo and losartan groups, a decline of 5.2 and 4.4 mL/min per 1.73 m^2/y, respectively. We cannot exclude that the longitudinal increase in SUA reflects, at least in part, a reduction in GFR over time. An alternative possibility is the possible interference of other drugs influencing SUA. The proportion of patients receiving a diuretic increased from 58% at baseline to 71% at month 6 and to 84% at the time of the primary renal endpoint. The increasing use of concomitant diuretic therapy, which increases SUA, could be an alternative explanation for the increase in SUA observed during the trial. Because the proportion of patients receiving diuretics was similar between the placebo and losartan groups at baseline, month 6, and at the end of the trial, it is unlikely that concomitant diuretic use has confounded our findings. A final explanation may relate to the effects of losartan on uric acid handling during prolonged therapy. In a previous study, the acute effects of losartan on uric acid excretion after 3 weeks of losartan therapy were less pronounced compared with the effects after the first dose was administered.[18] This suggests that the effects of losartan on uric acid excretion wane off over time once a new steady state has been achieved.

The data from our study suggest that losartan, registered as a blood pressure–lowering drug, confers additional renal protection partly through its effect on SUA. Other drugs used in renal and cardiovascular risk management appear to lower SUA as well. Fenofibrate, registered as a lipid-lowering drug, has been shown to decrease SUA. These effects were independent of changes in lipid parameters, indicating that the drug itself exerts uricosuria.[26] Furthermore, fenofibrate has been reported to have certain renal benefits, including benefits on albuminuria.[27] Another lipid-lowering drug, atorvastatin, has been shown to have hypouricemic effects as well, irrespective of the drug's effect on lipid parameters.[28] Whether the effects of these drugs on uric acid excretion contribute to their long-term renal and/or cardiovascular protective effects are uncertain. On the contrary, drugs that increase SUA may adversely influence renal and cardiovascular risk. It is known that diuretics, also registered as blood pressure–lowering drugs, increase SUA. In this respect, a post hoc analysis of the Systolic Hypertension in the Elderly Program Trial demonstrated that the cardiovascular protective effect of diuretic therapy was restricted to those individuals in whom SUA increased <1 mg/dL after 1 year of therapy.[29] Thus, when estimating the effects of a drug on renal or cardiovascular endpoints using risk markers, the effect of the drug on all of the risk markers including SUA should be taken into account rather than focusing on the marker that the drug is registered for.

Limitations of this study include the post hoc nature of the analyses. Although our data are derived from a double-blind, placebo-controlled, randomized trial, the analyses according to change in SUA are no longer randomized. Although we adjusted for all of the available baseline covariates and changes in covariates, residual confounding cannot be completely excluded. Unfortunately, 24-hour urate excretion was not measured in RENAAL participants. This precludes the possibility of determining the fractional excretion of uric acid during losartan therapy. The reduction in uric acid in subjects with the highest baseline uric acid level could indicate a regression to the mean phenomenon. However, the fact that we adjusted our multivariate analyses for baseline uric acid and the fact that the month 6 uric acid level (residual uric acid) remained an independent predictor for the primary renal outcome makes this assumption as an explanation for our findings less likely. Finally, the results of this study can only be generalized to the, admittedly large, population of patients with type 2 diabetes mellitus and nephropathy.

In conclusion, losartan lowers SUA levels when compared with placebo treatment in patients with type 2 diabetes mellitus and nephropathy. This change in SUA is independently associated with a lower risk of doubling of serum creatinine or end-stage renal disease such that approximately one fifth of losartan's renoprotective effect could be attributed to SUA. These data indicate that a reduction in SUA observed during the initial months after starting losartan contributes to its renoprotective effect.

Perspectives

Increasing data suggest that uric acid may be a risk factor for renal disease progression. The results of the current study indicate that the effect of losartan on SUA explains part of its renoprotective effect. These findings support the postulate that uric acid–lowering therapy slows the progression of chronic kidney disease. Prospective randomized, controlled trials on

hard endpoints are needed to confirm that uric acid–lowering therapy delays the progression of renal disease.

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Disclosures

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