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Effects of Salt Supplementation on the Albuminuric Response to Telmisartan With or Without Hydrochlorothiazide Therapy in Hypertensive Patients With Type 2 Diabetes Are Modulated by Habitual Dietary Salt Intake

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OBJECTIVE — This prospective randomized double-blind placebo-controlled crossover study examined the effects of sodium chloride (NaCl) supplementation on the antialbuminuric action of telmisartan with or without hydrochlorothiazide (HCT) in hypertensive patients with type 2 diabetes, increased albumin excretion rate (AER), and habitual low dietary salt intake (LDS; <100 mmol sodium/24 h on two of three consecutive occasions) or high dietary salt intake (HDS; >200 mmol sodium/24 h on two of three consecutive occasions).

RESEARCH DESIGN AND METHODS — Following a washout period, subjects ($n = 32$) received 40 mg/day telmisartan for 4 weeks followed by 40 mg telmisartan plus 12.5 mg/day HCT for 4 weeks. For the last 2 weeks of each treatment period, patients received either 100 mmol/day NaCl or placebo capsules. After a second washout, the regimen was repeated with supplements in reverse order. AER and ambulatory blood pressure were measured at weeks 0, 4, 8, 14, 18, and 22.

RESULTS — In LDS, NaCl supplementation reduced the anti-albuminuric effect of telmisartan with or without HCT from 42.3% (placebo) to 9.5% ($P = 0.004$). By contrast, in HDS, NaCl supplementation did not reduce the AER response to telmisartan with or without HCT (placebo 30.9%, NaCl 28.1%, $P = 0.7$). Changes in AER were independent of changes in blood pressure.

CONCLUSIONS — The AER response to telmisartan with or without HCT under habitual low salt intake can be blunted by NaCl supplementation. By contrast, when there is already a suppressed renin angiotensin aldosterone system under habitual high dietary salt intake, the additional NaCl does not alter the AER response.

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Reducing albumin excretion rate (AER) by blockade of the renin angiotensin aldosterone system (RAAS) and adherence to a low-salt diet are well recognized strategies for renal

protection in people with diabetes (1,2). The antiproteinuric effect of RAAS blockade is magnified by dietary salt restriction in nondiabetic subjects with renal disease (3,4). Furthermore, a low-salt diet poten-

tiates the anti-albuminuric effects of RAAS inhibition in type 2 diabetic patients with microalbuminuria (5).

In hypertensive patients without diabetes, the antiproteinuric effect of ACE inhibitors is diminished by high salt intake but enhanced by low salt intake or concurrent administration of a diuretic (6,7). However, it is not clear whether the combination of a diuretic and the angiotensin receptor blocker (ARB) telmisartan has additive effects on the albuminuric response in diabetes and whether this response is influenced by habitual dietary salt intake and additional NaCl. The present study was therefore designed to determine if NaCl supplementation reduces the anti-albuminuric effects of the ARB telmisartan with or without the addition of the thiazide diuretic hydrochlorothiazide (HCT) in hypertensive patients with type 2 diabetes, elevated AER, and either high or low habitual dietary salt intake.

RESEARCH DESIGN AND METHODS

We studied 32 patients with type 2 diabetes, hypertension, and AER in the range of 10–200 $\mu\text{g}/\text{min}$. Participants were recruited from the diabetes clinics at Austin Health, where at each visit, patients routinely perform a 24-h urine collection for the measurement of AER and sodium excretion. Inclusion criteria were type 2 diabetes, hypertension (blood pressure $>140/90$ mmHg or taking antihypertensive therapy), and AER between 10 and 200 $\mu\text{g}/\text{min}$ (median of three consecutive measurements collected over a 12-month period). Patients were classified as having a habitually high dietary salt intake (HDS) on the basis of a urinary sodium excretion >200 mmol/24 h on two out of three consecutive occasions or habitual low dietary sodium intake (LDS) with urinary sodium excretion of <100 mmol/24 h on two of three consecutive occasions.

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As BMI and urinary sodium excretion are related (8), patients in the HDS and LDS groups were matched for BMI. Exclusion criteria included serum potassium >5.0 mmol/l, serum creatinine >200 μ mol/l, AER >200 μ g/min, A1C $>10.0\%$, and major systemic illness. The study was approved by the human research ethics committee at Austin Health, and all participants gave informed consent before commencement of the study. This trial was registered with the Australian Clinical Trials Registry (ACTRN 012606000128594).

Study protocol

The study was performed in six phases.

Phase 1, washout (–6 to 0 weeks).

There was no change in drug therapy if sitting blood pressure was $<160/95$ mmHg. Drugs known to affect the RAAS were replaced with combinations of verapamil, prazosin, methyldopa, or hydralazine at week –6. Titration to achieve blood pressure $<160/95$ mmHg was performed between weeks –6 and –3, and this regimen was continued until the completion of the trial.

Phase 2, telmisartan, and phase 3, telmisartan plus HCT (0–8 weeks).

All patients commenced 40 mg daily telmisartan for 4 weeks followed by 40 mg telmisartan plus 12.5 mg HCT daily for 4 weeks. HDS and LDS groups received NaCl or placebo capsules, in addition to their usual diet and any of the non-RAAS antihypertensive agents started in phase 2, during the last 2 weeks of telmisartan monotherapy and during last 2 weeks of combined telmisartan and HCT therapy.

Phase 4, second washout (8–14 weeks).

As in phase 1, patients remained on the background non-RAAS blocking antihypertensive agents.

Phases 5 and 6 (14–22 weeks). Phases 2 and 3 were repeated with placebo and NaCl capsules in reverse order.

A total of 100 mmol/day of NaCl supplements were administered daily in five capsules. Identical placebo capsules contained lactose. Patients were instructed to take two capsules with breakfast, one with lunch, and two with their evening meal. The 24-h urinary AER and sodium excretion, fasting plasma glucose, electrolytes, A1C, and 24-h ambulatory blood pressure were measured at 0, 4, 8, 14, 18, and 22 weeks. In each patient, urinary sodium excretion was corrected for completeness of collection by adjusting for av-

Table 1—Baseline characteristics

Habitual salt intake	High dietary salt	Low dietary salt	P
n	14	15	
Age (years)	65 $\pm$ 2.5	60 $\pm$ 1.9	0.16
Male:female ratio	13:1	7:8	0.006
BMI	32.0 $\pm$ 0.8	32.9 $\pm$ 2.0	0.7
A1C (%)	7.4 $\pm$ 0.3	7.4 $\pm$ 0.3	0.97
Smoker:nonsmoker	1:13	4:11	0.06
24-h urinary Na excretion (mmol/24 h)	271 $\pm$ 24	118 $\pm$ 12	<0.0001
Ambulatory mean arterial blood pressure (mmHg)	101 $\pm$ 2.2	98 $\pm$ 2.2	0.24
Mean serum creatinine (μ mol/l)	92.5 $\pm$ 5.4	83.9 $\pm$ 5.4	0.24
Estimated glomerular filtration rate (ml/min per 1.73 m ²)	78.1 $\pm$ 5.5	78.3 $\pm$ 4.2	0.36
Baseline AER* (μ g/min) geometric mean $\times/\div$ tolerance factor	34 $\times/\div$ 1.3	56 $\times/\div$ 1.4	0.3
Number of patients requiring additional antihypertensives to target blood pressure $<160/95$ mmHg	11	8	0.49

erage creatinine excretion in six urine samples.

All blood samples were taken between 0800 h and 1000 h in the morning after an overnight fast and before the administration of study medication. Albumin concentration was measured by a turbidimetric SYNCHRON System. The interassay coefficient of variation was 3.4% for a sample concentration of 112 mg/l. Ambulatory blood pressure was measured with a portable recording machine (Spacelabs 90207; Spacelabs Medical Products, Deerfield, WI) based on an oscillometric method.

Statistical analysis

AERs are shown as medians with 95% CI. A logarithmic transformation was applied to the AER data at baseline and at treatment. The difference, log (AER) during treatment minus log (AER) at baseline, was modeled with a three-way ANOVA using one between-group factor (habitual dietary sodium intake) and two within-subject factors (NaCl versus placebo and telmisartan with or without HCT). ANOVA was performed using GenStat 10th Edition for Windows. The means from the three-way ANOVA model were back-transformed to give an estimate of the median ratio of treatment/baseline {the difference of two logarithms [$\log(a) - \log(b)$] is equal to the logarithm of the ratio [$\log(a/b)$]; hence a backtransformation gives the ratio a/b }; from this, the median percentage reduction in AER from baseline was estimated. For example, if the mean of log AER treatment – log AER

baseline in LDS group receiving telmisartan + placebo was -0.365 , a back transformation of -0.365 produces the number 0.694 (i.e., $e^{-0.365} = 0.694$). Hence, the median AER treatment to baseline ratio was calculated to be 0.694, and the corresponding percentage reduction from baseline is 30.6%.

Urinary sodium excretion was also analyzed using the three-way ANOVA model. Independent-sample *t* tests were used to assess the difference in baseline characteristics in HDS and LDS groups.

RESULTS

Participants

Of the 32 participants, 17 were recruited to the HDS group and 15 to the LDS group over 9 months. Three subjects were withdrawn from the HDS group. One required surgery for bowel obstruction, one was unable to complete the requirements of the study, and one was unable to tolerate NaCl capsules because of nausea. Although other patients complained of nausea and vomiting, this was not sufficient to interfere with the study protocol.

Baseline characteristics of study participants are outlined in Table 1. There were no significant differences in age, BMI, A1C, AER, mean arterial blood pressure (MAP), smoking status, or use of additional antihypertensive agents to achieve the target blood pressure. There was also no significant difference in AER assessed at the start of phase 2 and phase 5, indicating absence of an order effect.

Table 2—Attained AER, blood pressure, and urinary sodium excretion according to treatment group and habitual dietary salt intake

	AER ($\mu\text{g}/\text{min}$)	HDS	Urinary Na (mmol/24 h)	AER ($\mu\text{g}/\text{min}$)	LDS	Urinary Na (mmol/24 h)
		MAP (mmHg)			MAP (mmHg)	
Telmisartan + placebo	28.3 (16–55)	96 (89–102)	263 (212–315)	42.3 (24–96)	89 (85–94)	121 (106–137)
Telmisartan + NaCl	25.8 (15–78)	98 (94–103)	314 (260–367)	68.6 (26–124)	93 (89–97)	179 (144–214)
Telmisartan + HCT + placebo	16.1 (11–44)	91 (85–97)	249 (217–281)	36.9 (15–67)	88 (85–91)	126 (98–154)
Telmisartan + HCT + NaCl	19.3 (11–67)	96 (91–102)	323 (267–378)	54.1 (22–117)	91 (88–94)	173 (140–207)

Data are means (95% CI). AER, blood pressure, and urinary sodium excretion were measured after 4 weeks of treatment with 40 mg telmisartan daily $\pm$ 12.5 mg HCT daily. Supplementation with 100 mmol/day salt (NaCl) or placebo was given for the last 2 weeks of treatment with telmisartan with or without HCT.

However, there were a greater number of men in the HDS group.

Urinary sodium excretion

Attained urinary sodium excretion values are outlined in Table 2. Throughout the study, the mean difference in urinary sodium excretion between HDS and LDS groups was 136 mmol/24 h ($P < 0.001$, 95% CI 99–174 mmol/24 h). The mean difference in urinary sodium excretion between NaCl supplemented and placebo groups was 56 mmol/24 h ($P < 0.001$, 95% CI 34–78 mmol/24 h). Treatment with telmisartan plus HCT was not associated with an increase in urinary sodium excretion in excess of that seen during treatment with telmisartan alone ($P = 0.8$).

Blood pressure response

NaCl supplementation was associated with a statistically significant blunting of antihypertensive effects of telmisartan and telmisartan plus HCT in both HDS and LDS groups (Table 2). The change in MAP during each study period was included in the three-way ANOVA statistical model as a covariate. However, the change in MAP was not associated with a significant effect on AER ($P = 0.2$).

Albuminuria response

There was no significant difference in baseline AER between the HDS and LDS groups. Attained AER values throughout the study are outlined in Table 2. The major findings in this study were

that in the presence of NaCl supplementation, the AER response to telmisartan with or without HCT was reduced by $\sim 75\%$ in the LDS group and that the addition of HCT to telmisartan led to an $\sim 45\%$ increase in AER response in both the HDS and the LDS groups (NaCl vs. placebo, $P = 0.004$; habitual diet group [HDS vs. LDS] by supplementation [NaCl vs. placebo], $P = 0.02$; telmisartan + HCT vs. telmisartan alone, $P = 0.01$; Table 3, Fig. 1).

NaCl supplementation in HDS and LDS groups

There was no significant difference in the mean AER response (log treatment – log baseline) to telmisartan with or without

Table 3—Analysis of treatment effects on AER response according to habitual sodium intake, NaCl versus placebo supplementation, and telmisartan versus telmisartan plus HCT

Overall analysis of AER response to interventions	Telmisartan + placebo	Telmisartan + NaCl	Telmisartan + HCT + placebo	Telmisartan + HCT + NaCl
HDS Mean (log [AER] treatment – log [AER] baseline)	–0.233	–0.221	–0.507	–0.431
HDS median AER (treatment/baseline) ratio	0.792	0.802	0.602	0.650
HDS corresponding percentage decrease	20.8%	19.8%	39.8%	35.0%
LDS mean (log [AER] treatment – log [AER] baseline)	–0.365	–0.075	–0.726	–0.126
LDS median AER (treatment/baseline) ratio	0.694	0.928	0.484	0.882
LDS corresponding percentage decrease	30.6%	7.2%	51.6%	11.8%
Effect of habitual diet group on AER response to short-term NaCl supplementation	Placebo	NaCl	Difference (placebo – NaCl, 95% CI)	
HDS mean (log [AER] treatment – log [AER] baseline)	–0.37	–0.33	–0.04 (–0.28 to 0.19)	
HDS median AER (treatment/baseline)	0.691	0.719		
HDS corresponding percentage decrease	30.9%	28.1%		
LDD mean (log [AER] treatment – log [AER] baseline)	–0.55	–0.10	–0.45 (–0.68 to –0.21)	
LDS median AER (treatment/baseline)	0.577	0.905		
LDS corresponding percentage decrease	42.3%	9.5%		
AER response to telmisartan vs. telmisartan + HCT	Telmisartan	Telmisartan + HCT	Difference (HCT – no HCT, 95% CI)	
Mean (log [AER] treatment – log [AER] baseline)	–0.22	–0.45	–0.22 (–0.40 to –0.04)	
Median AER (treatment/baseline)	0.800	0.640		
Corresponding percentage decrease	20.0%	36.0%		

Telmisartan + HCT vs. telmisartan alone, $P = 0.01$; NaCl vs. placebo supplementation, $P = 0.004$; habitual diet group (HDS vs. LDS) by supplementation (NaCl vs. placebo), $P = 0.02$. Telmisartan, 40 mg/day telmisartan; NaCl, salt supplementation 100 mmol NaCl/day; HCT, 12.5 mg/day hydrochlorothiazide.

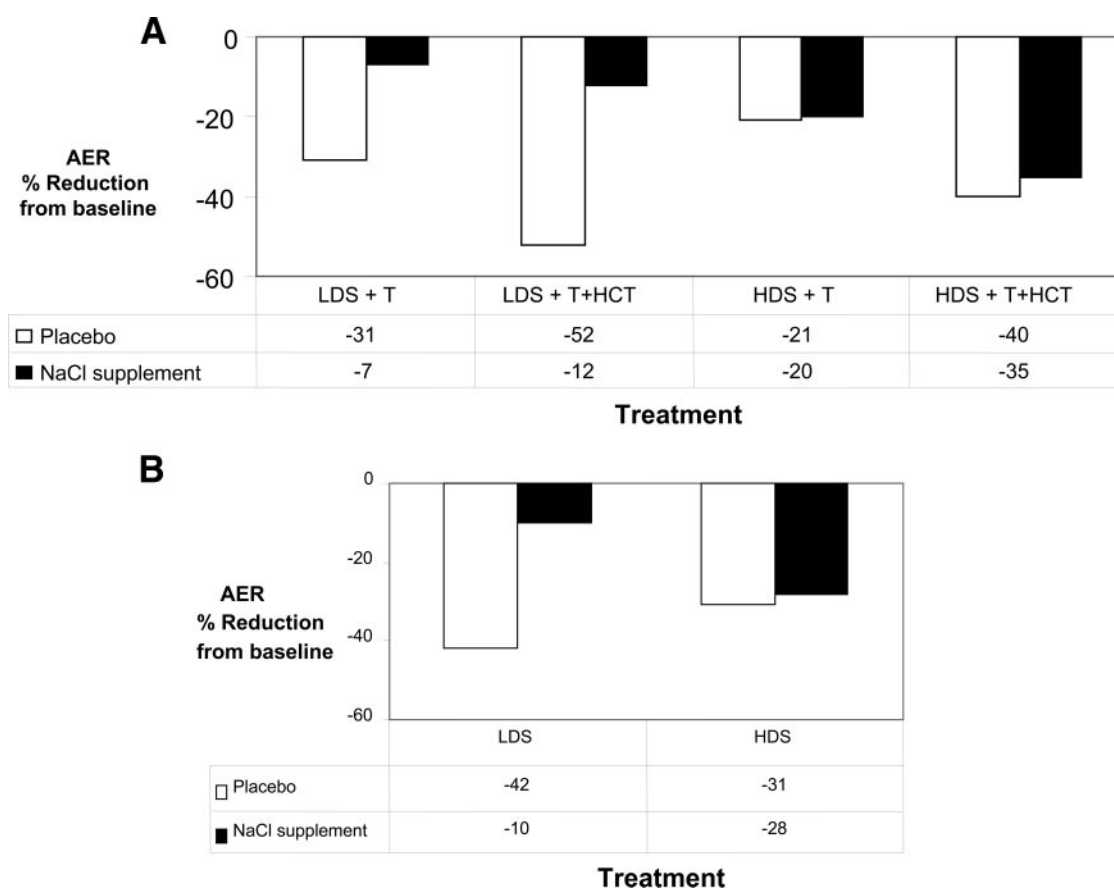


Figure 1—Effects of salt (NaCl) supplementation on the AER response to telmisartan (T) $\pm$ hydrochlorothiazide (HCT) in the habitual high dietary salt (HDS) and low dietary salt (LDS) groups. A: Effects of various treatments on AER. B: Combined analysis of telmisartan $\pm$ HCT data. A three-way ANOVA model was used to analyze results by examining the intragroup (NaCl vs. placebo and telmisartan vs. telmisartan plus hydrochlorothiazide) and the intergroup (HDS vs. LDS) variables. Telmisartan plus HCT vs. telmisartan alone, $P = 0.01$; NaCl vs. placebo supplementation, $P = 0.004$; habitual diet group (HDS vs. LDS) by supplementation (NaCl vs. placebo), $P = 0.02$.

HCT in patients in HDS or LDS groups in the absence of NaCl supplementation. However, a significant decrease in the AER response was seen with administration of NaCl compared with placebo capsules ($P = 0.004$). This was mainly accounted for by a statistically significant two-way interaction of NaCl supplementation and habitual diet group ($P = 0.02$, Table 3, Fig. 1).

In the LDS group, the AER response to telmisartan with or without HCT, expressed as the percentage decrease from baseline, was reduced from 42.3% with placebo to 9.5% with NaCl supplementation, representing a relative reduction of 77.5% of the effects of telmisartan $\pm$ HCT ($P = 0.02$, Fig. 1B). In contrast, in the HDS group, the percentage reduction in AER from baseline was similar during placebo and NaCl supplementation (30.9 vs. 28.1%, respectively), representing a non-significant relative reduction of 9.1% of the effects of telmisartan with or without HCT ($P = 0.7$, Fig. 1B).

Telmisartan versus telmisartan plus HCT

Dual therapy with telmisartan and HCT demonstrated an increase in the AER response when compared with telmisartan alone. The percentage reduction in AER from baseline in subjects treated with telmisartan alone was 20.0 vs. 36.0% with telmisartan plus HCT, representing a relative reduction of 44% ($P = 0.01$, Table 3). The percentage reduction in AER in the LDS group treated with telmisartan without HCT was of similar magnitude to the reduction in AER in HDS plus telmisartan plus HCT ($P = 0.39$).

CONCLUSIONS— The main finding of the current study was that, in patients with habitual low dietary salt intake, NaCl supplementation resulted in an $\sim 75\%$ reduction in the AER response to telmisartan with or without HCT, whereas NaCl supplementation did not affect the AER response in the habitual high dietary salt intake group. Moreover,

the combination of telmisartan and HCT increased the AER response by $\sim 45\%$ compared with telmisartan alone in both the HDS and LDS groups. The changes in AER seen in this study were independent of changes in blood pressure.

The results of this study are consistent with previous findings that have found a relationship between dietary salt intake and AER, independent of changes in blood pressure. In a cross-sectional study from France of 839 normotensive subjects without diabetes, the relationship between urinary sodium excretion and AER was independent of sex, age, BMI, and systolic blood pressure (9). Another large cross-sectional community study of 7,850 subjects from the Netherlands showed a positive relationship between dietary sodium intake and AER that was independent of other cardiovascular risk factors including blood pressure (8). Changes in dietary sodium intake may have intra-renal effects independent of blood pressure. A recent study demon-

strated that alpha adducin 1 and ACE genotypes may jointly influence urine albumin levels in uncomplicated essential hypertensive men independently of blood pressure and other coexisting factors (10). α -Adducin gene exerts complex biological effects on sodium and volume homeostasis by interacting with the epithelial sodium channel, the sodium-potassium-chloride transporter, and sodium-potassium adenosine triphosphatase (10). Moreover, dietary sodium intake may play an even more important role in the pathogenesis of increased albuminuria in subjects with diabetes compared with those without diabetes because there is an increase in exchangeable sodium in the setting of diabetes (11,12).

To our knowledge, comparisons of the AER and blood pressure responses to RAAS blockade and thiazide diuretic in the setting of habitual high versus low sodium intake and the addition of NaCl have not been performed in humans with or without diabetes. Only a limited number of clinical studies have examined the relationship between dietary sodium intake, AER, RAAS blockade, and diuretics. Studies in subjects with (5) and without (3,6) diabetes have shown that the anti-proteinuric effects of RAAS blockade are dependent on dietary sodium intake. A low-salt diet increases renal blood flow in both experimental diabetes (13) and in type 1 diabetes (14). Furthermore, subjects with type 2 diabetes and hypertension have reduced renal plasma flow when dietary salt intake is high (15). The effect of dietary salt on the diabetic kidney presents a paradox that cannot be explained by primary vascular effects of the neurohormonal or pressure natriuresis systems (16).

We observed an $\sim 75\%$ reduction in the AER response to telmisartan with or without HCT in the LDS group with NaCl supplementation, whereas there was no difference in the AER response in the HDS group with the same NaCl supplementation. Given that the sodium-RAAS relationship is logarithmic and that the RAAS is most likely totally suppressed in the setting of HDS, the addition of NaCl to HDS does not equate to NaCl addition to the LDS group. In the HDS group, the mean baseline urinary sodium excretion was ~ 270 mmol/24 h, whereas in LDS, it was ~ 120 mmol/24 h, implying that the RAAS is fully suppressed during habitual high salt intake. When related to habitual salt intake, NaCl supplementation resulting in an increase in urinary sodium ex-

cretion of $\sim 60\%$ mmol represents an increment in urinary sodium excretion of $\sim 50\%$ in the LDS group compared with an increment of $\sim 25\%$ in the HDS group. Hence, the AER response to telmisartan with or without HCT under long-term low-salt intake can still be blunted by NaCl supplementation, whereas the AER response under long-term high salt intake is not altered by additional NaCl.

The addition of HCT to telmisartan increased the AER response by $\sim 45\%$ in this study. In a previous study in nondiabetic subjects with overt proteinuria, the addition of HCT to RAAS blockade led to a further 56% reduction in proteinuria (7). However, hydrochlorothiazide monotherapy does not appear to influence proteinuria in nondiabetic (17) and diabetic subjects (18,19). In our study, the combination of a thiazide diuretic with RAAS blockade led to a reduction in AER in the setting of both high and low sodium intake. In the present study, telmisartan alone in the habitual low dietary salt group produced a similar AER response compared with the high dietary salt group treated with telmisartan plus HCT. This raises the possibility that potentiating the anti-albuminuric effects of RAAS inhibition can possibly be achieved by maintaining a low habitual salt intake in a similar fashion to adding a thiazide diuretic to subjects with habitual high salt intake. If patients can maintain a habitual low salt intake, this might negate the need for the addition of a thiazide diuretic to RAAS blockade and hence avoid some of the potential metabolic effects of thiazide therapy. However, in clinical practice, many patients will require the addition of at least one other antihypertensive agent to RAAS blockade to achieve blood pressure targets and reduce AER. These agents are likely to include a thiazide diuretic and/or a calcium channel blocker.

In conclusion, the AER response to telmisartan with or without HCT during habitual low salt intake can still be blunted by NaCl supplementation, whereas the AER response during habitual high salt intake is not altered by additional NaCl. In industrialized countries, dietary sodium consumption is generally above the recommended targets of 100 mmol/24 h (20,21). Albuminuria has been considered a risk marker for progressive loss of renal function in type 2 diabetes with nephropathy, as well as a target for therapy (22). Based on the results of the RENAAL study, it has been suggested that reduction of residual albu-

minuria to the lowest achievable level should be viewed as a goal for future renoprotective treatments (22). New public health policies, such as the World Action on Salt and Health program (23), may facilitate long-term maintenance of a low dietary salt intake, and this may help to maximize the anti-albuminuric effects of angiotensin receptor blockade with or without thiazide diuretic therapy. However, it is not yet known whether changes in AER associated with variations in dietary salt intake will be reflected in hard renal or cardiovascular end points. In addition, it remains to be shown whether variations in dietary intake of potassium, calcium, and magnesium may influence the response of albuminuria and/or blood pressure to variations in dietary salt intake.

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