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Short-term dietary salt supplementation blunts telmisartan induced increases in plasma renin activity in hypertensive subjects with type 2 diabetes mellitus

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Abstract

Background: Current guidelines recommend low dietary salt intake in people with diabetes to reduce blood pressure. However, in people with diabetes, low salt intake has been associated with increased mortality.

Aims: We examined the effect of the angiotensin II receptor blocker (ARB), telmisartan, with and without dietary sodium chloride (NaCl) supplementation, on blood pressure (mean arterial pressure, MAP), plasma renin activity (PRA), serum aldosterone level and estimated glomerular filtration rate (eGFR) in hypertensive patients with type 2 diabetes.

Method: In a randomised, double blind, controlled study (RCT), twenty-eight patients with type 2 diabetes, treated with telmisartan (40mg daily) were randomised to receive two weeks of placebo or NaCl capsules (100mmol/24h). Following a six-week washout period, the protocol was repeated in reverse order (NaCl or placebo). 24 hour urinary sodium excretion (24hUNa), ambulatory blood pressure monitoring and blood tests were performed before and after each study phase.

Results: Telmisartan associated increase in PRA was blunted by approximately 50% during salt supplementation compared with placebo, mean PRA: 0.48 ug/l/hr during salt vs 0.23ug/l/hr during placebo ($p<0.001$). There was also a trend towards blunting of ARB induced increases of serum aldosterone. As previously demonstrated in this cohort, salt supplementation significantly reduced the MAP lowering effects of telmisartan ($p<0.05$) in association with a marginal increase in eGFR ($p=0.05$).

Conclusion: This study demonstrates that salt supplementation blunts the telmisartan induced increase in PRA in patients with type 2 diabetes.

Introduction

Cardiovascular and renal disease are well recognized complications of diabetes that contribute significantly to the burden of disease[1]. Hypertension is a leading modifiable risk factor[2,3]. In order to optimise blood pressure control in patients with chronic disease, current Australian guidelines recommend reducing dietary salt (sodium/NaCl/Na) intake to <75mmol/24h[4].

Despite the blood pressure lowering effects of reduced dietary salt intake[5], in patients with diabetes, a paradoxical association between low salt intake and increased overall mortality has been demonstrated[6-8]. In patients with type 2 diabetes, an inverse association between all cause mortality and 24 hour urinary sodium excretion (24hUNa) has been observed, such that subjects with the lowest 24hUNa had the highest cumulative hazard ratio for all cause mortality[6].

In the general population, increasing dietary salt intake by 125-150mmol/24h has been associated with decreases in plasma renin activity (PRA), aldosterone, noradrenaline and adrenaline[9]. In patients with hypertension and coronary artery disease, raised PRA is an independent predictor of cardiovascular mortality[10]. Raised serum aldosterone is similarly associated with increased cardiovascular mortality in patients with heart failure[11]. In patients with diabetes, we have observed a relationship between high serum aldosterone and low 24hUNa[12]. This raises the possibility that increased renin angiotensin aldosterone system (RAAS) activity may contribute to the adverse outcomes observed in patients with low 24hUNa.

In hypertensive patients with diabetes, our group has previously demonstrated that dietary salt supplementation blunts both the blood pressure response to telmisartan[5] and the albuminuric excretion rate[13] in those with habitual low salt diet. How salt supplementation negates the effects of telmisartan is not clear. However, it could involve an effect on RAAS activity. The present analysis was therefore carried out in order to evaluate the effect of short-term dietary sodium chloride (NaCl) supplementation on plasma renin activity (PRA), serum aldosterone and

estimated glomerular filtration rate (eGFR) in patients with type 2 diabetes during angiotensin II receptor blocker (ARB, telmisartan, 40mg) use.

Methods

In a randomised, double blind, cross-over, placebo controlled study, patients with type 2 diabetes, treated with 40mg of telmisartan, were randomised to receive two weeks of placebo or NaCl capsules (100mmol/24h). All 28 patients were recruited from diabetes clinics at Austin Health, a tertiary referral centre. As part of routine care, patients attending these clinics have 24hUNa and albumin excretion rate (AER) measured. Inclusion criteria were type 2 diabetes, hypertension (blood pressure >140/90mmHg or taking antihypertensive treatment) and AER between 10-200 μg/min (as determined by the median value of three 24h urine samples collected consecutively over 12 months).

Patients were excluded from participation if AER >200 μg/min, serum creatinine >200μM, serum potassium >5.0mM, HbA_{1C} >10.0% and in cases of major systemic illness. Informed consent was obtained from all patients prior to study participation. Ethics approval was obtained from the Austin Health Human Research Ethics Committee and the study was allocated registration number ACTRN012606000128594 through the Australian Clinical Trials Registry.

As part of the original study, patients were categorised into high and low habitual dietary salt intake groups on the basis of 24hUNa[5,13]. Effects of salt supplementation during combined telmisartan and hydrochlorothiazide (HCT) use also formed part of the original study. For the purposes of this analysis, there was no categorisation into high and low salt intake at baseline and dietary salt intake was analysed as a continuum due to the small sample size (n=28). As the effect of salt supplementation on blood pressure was similar during telmisartan and placebo and telmisartan and HCT supplementation[5], patients treated with telmisartan alone were analysed in the present study.

Study Protocol

The study was carried out in four phases, as described in detail previously[5,13]. Briefly, all patients underwent a six-week washout period prior to the commencement of the study. During the washout phase, alternative antihypertensive medications that have no effect on the RAAS were administered to patients requiring treatment to maintain BP <160/95mmHg. Austin Health pharmacy oversaw the randomization process. Using computer programs, patients were randomised into two groups in a double-blinded manner (Group A and Group B). Following the washout period, all patients received 40mg telmisartan for four weeks. During the final two weeks, patients in Group A received additional placebo capsules while patients in Group B received NaCl capsules. This was followed by another six-week washout, after which all subjects recommenced telmisartan 40mg. NaCl and placebo capsules were then administered in reverse order, thereby allowing patients to act as their own controls.

NaCl and placebo capsules were produced by a local registered compounding pharmacy (Thompsons Pharmacy, Bulleen, Victoria, AUSTRALIA). Patients were administered a total of 100mmol NaCl every 24h. Placebo capsules contained lactose.

Twenty-four hour ambulatory blood pressure (ABP) measurements were recorded using oscillometric methods with a portable measuring system. 24-hour urine collection was performed at baseline and following each supplement phase. Urinary sodium excretion for each participant was corrected for by adjusting average creatinine excretion for all the urine samples.

Overnight fasting blood samples were collected at baseline and following each supplement phase. As the upright position is associated with increased PRA[14], all blood samples were collected in the morning, after participants had been in the seated position for at least 5 minutes. eGFR was determined using the MDRD formula (eGFR = 32788 x serum creatinine $^{-1.154}$(μmol/L) x Age$^{-0.203}$ x [1.212 *if black*] x [0.742 *if female*][15].

Statistical Analysis

Changes in PRA, serum aldosterone, blood pressure and eGFR from baseline during each supplementation phase were analysed using the paired t-test. Statistical analysis was performed using IBM SPSS Statistics (Version 21.0, IBM Co-operation). Skewed variables (PRA and serum aldosterone) underwent logarithmic transformation prior to analysis.

Results

Participants

Thirty-two patients were recruited for the study. Three patients were unable to complete the study and one patient was unable to tolerate NaCl capsules due to nausea. Twenty eight patients completed the study[5,13].

Baseline characteristics

Mean age was 62 years and sixty-eight percent of patients were male. Mean BMI and HbA1c were 32.5kg/m^2 and 7.3%, respectively. At baseline, mean MAP was 99±6 mmHg and eGFR was 71±14 ml/min/1.73m^2. No significant differences in baseline $\log_{10}$(PRA) (p=0.89), $\log_{10}$(serum aldosterone) (p=0.49) or eGFR (p=0.83) were demonstrated following each six-week washout period, indicating adequate telmisartan washout and no order effect of the interventions on RAAS activity. Sixty-one percent of patients had eGFR ranging from 60-89 ml/min/1.73m^2 and eighteen percent had eGFR ≤ 59ml/min/1.73m^2. At baseline, mean 24hUNa was 195 ± 106 mmol/24hr.

PRA and Serum Aldosterone

Salt supplementation led to a halving of the ARB associated increase in PRA, Figure 1A. The mean difference in $\Delta\log_{10}$(PRA) during telmisartan and placebo compared with telmisartan and salt was 0.23 ug/l/hr (95% CI: 0.08 – 0.38, p<0.001).

Salt supplementation had a smaller effect on serum aldosterone compared with PRA. Salt supplementation led to a 28% reduction in the ARB induced increase in serum aldosterone levels (p=0.05), Figure 1B. Mean difference in $\Delta\log_{10}$(serum aldosterone) between salt and placebo supplementation was 0.05 pmol/L (95% CI: -0.04 – 1.1pmol/L, p=0.05).

Blood pressure

As described previously[5], salt supplementation reduced the telmisartan induced decrease in mean arterial blood pressure (MAP) by approximately 50%. The mean change in MAP was 4 mmHg (95% CI: 0.5 - 6 mmHg, p<0.05), Figure 1C.

eGFR

Angiotensin II receptor blockade with telmisartan and placebo did not lead to any significant changes in eGFR. However, telmisartan and salt supplementation led to a 4% increase in eGFR over the two-week period. The mean change in eGFR after four weeks of telmisartan therapy was 0.5 ml/min/1.73m^2 with placebo compared with 3.0ml/min/1.73m^2 during salt supplementation (p = 0.05), Figure 1D.

Discussion

The key finding of the current study is that short-term salt supplementation is associated with a small, but significant reduction in the ARB associated increase of PRA and a similar trend towards blunting of ARB associated increase of serum aldosterone in hypertensive patients with type 2 diabetes. A reduction in the ARB induced decrease in MAP of 4mmHg was also demonstrated. However, short-term salt supplementation was not associated with a reduction in eGFR.

The association between dietary salt supplementation and PRA and serum aldosterone suppression is consistent with our understanding of the interplay between salt intake and RAAS activity. Several neurohormonal mechanisms regulate the balance between salt intake, renal

plasma flow and measured glomerular filtration rate (GFR). The RAAS in particular plays a crucial role in maintaining cardiovascular health in the salt depleted state[16]. Reduced dietary salt intake attenuates renal plasma flow, which stimulates renin, angiotensin II and aldosterone release[16]. Several studies have reported an exponential relationship between salt intake, PRA and serum aldosterone[17,18], where such increases are most pronounced when 24hUNa is less than 120mmol/24h[17,19]. In healthy subjects, angiotensin converting enzyme inhibitor (ACE-i) use is associated with five-fold and two-fold increases in PRA and serum aldosterone respectively[20]. In contrast, Sim et al[21] observed no difference in ACE-i or angiotensin II receptor blocker (ARB) use across increasing PRA quartiles in 7887 hypertensive patients. Rather, increased diuretic use and consequent volume depletion were associated with increasing PRA levels.

Acting in conjunction with the RAAS, neural control of sodium appetite is a further mechanism that maintains sodium homeostasis[22,23]. A meta-analysis of 69,000 healthy subjects found mean 24hUNa to be 159 mmol/24h, with a 95% confidence interval ranging from 114 to 210 mmol/24h[22]. Such tight sodium regulation is hypothesised to arise from a physiological need to maintain a minimum level of salt intake. Increased RAAS activity in the setting of salt depletion prevents adverse consequences such as hypotension, reduced GFR and hyperkalemia secondary to increased aldosterone secretion[24]. Furthermore, despite the blood pressure lowering effects of reduced dietary salt intake, lower 24hUNa has been shown to be paradoxically associated with increased cardiovascular and overall mortality risk within the general population and in patients with diabetes[6,25].

Increased RAAS activity in the setting of low dietary salt intake, therefore, provides a possible mechanism for the observation of increased overall mortality in patients with diabetes and low 24hUNa. A recent Cochrane review concluded that reduced dietary salt intake lead to significant increases in PRA and serum aldosterone in the general population. Conversely, increases in daily dietary salt intake in the order of 125-150mmol/24h is associated with significant reductions in PRA, serum aldosterone, adrenaline and noradrenaline[9]. In patients with established

cardiovascular disease sodium depletion secondary to dietary salt restriction and diuretic use can induce PRA increases[24], enhancing pre-existing sodium depletion[24]. Furthermore, increased cardiovascular mortality in patients with elevated PRA could not be attributed to blood pressure increases, as systolic blood pressure was found to decrease as PRA rose[24]. Sealey et al suggested that careful liberalisation of salt intake sufficient to reduce reactive hyperreninaemia without inducing unacceptable increases in blood pressure may benefit such patients[24]. We also recognise that salt supplementation increases blood pressure. In this study, 100mmol of NaCl blunted the ARB induced decrease in MAP by 4mmHg. This is of relevance to patients who are have not reached the renewed American Diabetes Association recommendations of 140/80mmHg[26].

We report that salt supplementation reduced telmisartan induced increases in PRA ($p<0.001$) with a similar trend for increases in serum aldosterone levels ($p=0.05$). A cross-sectional study conducted by our group in patients with diabetes, reported that low 24hUNa was associated with high serum aldosterone levels ($p<0.001$), both in the presence and absence of RAAS modifying agents[12]. However, the significance of changes in circulating PRA in response to salt loading is difficult to quantify. For instance, ARB use has been reported to overestimate effective PRA activity by up to 90%[27]. What is more, achieving absolute reductions in PRA should be approached with caution. The ALTITUDE trial in subjects treated with ARB or ACE-i, demonstrated a trend to increased cardiovascular mortality in subjects randomised to treatment with the direct renin inhibitor, aliskrenin, compared with placebo and ARB or ACE-i [28].

The relationship between dietary salt intake and progression to end-stage kidney disease is poorly understood. In a post-hoc analysis of 500 non-diabetic patients taking ACE-i, initial increases in the risk of developing end stage renal disease associated with increased dietary salt intake were lost after adjusting for albuminuria[29]. Altered renal haemodynamics are a prominent feature of diabetes. Glomerular filtration rate and renal plasma flow may increase during the early stages of diabetes and gradually decline as disease progresses[30]. In one of the earliest studies in normoalbuminuric patients with type 1 diabetes, Miller et al demonstrated that dietary

salt restriction was associated with a trend towards increased GFR (p=0.05) and increased renal plasma flow (p=0.005)[18]. However, following adjustment for confounding factors, no association was observed between longitudinal dietary salt intake and risk of development of chronic kidney disease after 5.5 years of follow-up in high risk patients with diabetes in the ONTARGET study[31].

We report a trend towards increased eGFR as a result of short-term dietary salt supplementation (mean increase: 3ml/min/1.73m^2, p=0.05), however, there was no associated increase in eGFR following telmisartan and placebo supplementation. This finding differs from expected reductions in eGFR following ARB and salt administration and cannot be assumed to have a direct relationship with the long-term eGFR trajectory. However, salt supplementation was associated with a 4% increase in eGFR compared with telmisartan and placebo. Several studies have demonstrated increased renal plasma flow without changes to measured GFR in diabetic patients treated with ACE-i and ARB[32,33]. The lack of effective renal plasma flow measurements following salt supplementation is a limitation of the current study.

Study strengths include the use of a randomised, double blinded, placebo controlled design and 24hUNa to determine daily dietary salt intake. As 90% of dietary salt is renally excreted, 24hUNa remains the most accurate estimate of dietary salt intake[34]. A further strength of the study was the correction of 24hUNa by adjusting for average creatinine excretion over six samples collected during the study duration from each patient for accuracy and completeness. A major limitation of the current study was the small number of study participants, emphasising the need for care when making generalisations of study findings.

This study demonstrates a blunting of ARB associated increases in RAAS activity following salt supplementation with evidence of a trend towards small increases in eGFR in the short-term. It is difficult to determine whether these short-term effects will persist. However, increased RAAS activity in the setting of low dietary salt intake, if carried into the long-term, may provide some explanation for findings of increased overall and cardiovascular mortality associated with

reduced dietary salt intake in diabetic patients. In keeping with recent recommendations from the Institute of Medicine, which no longer support reducing dietary salt intake to ≤65mmol/24hr[35] and in observational studies examining salt intake over time in people with diabetes[36], our findings emphasise the need to strike a balance in salt intake that mitigates both the risks posed by excessive increases in BP with those of increased RAAS activity. At present, we cannot exclude the possibility that salt appetite and cardiovascular risk are linked to a common unidentified aetiological factor, which may be specific to patients with diabetes. These findings call for further research into the effects of long-term low salt intake on the renin angiotensin aldosterone system, endothelial function and sympathetic nervous system activity in people with diabetes.

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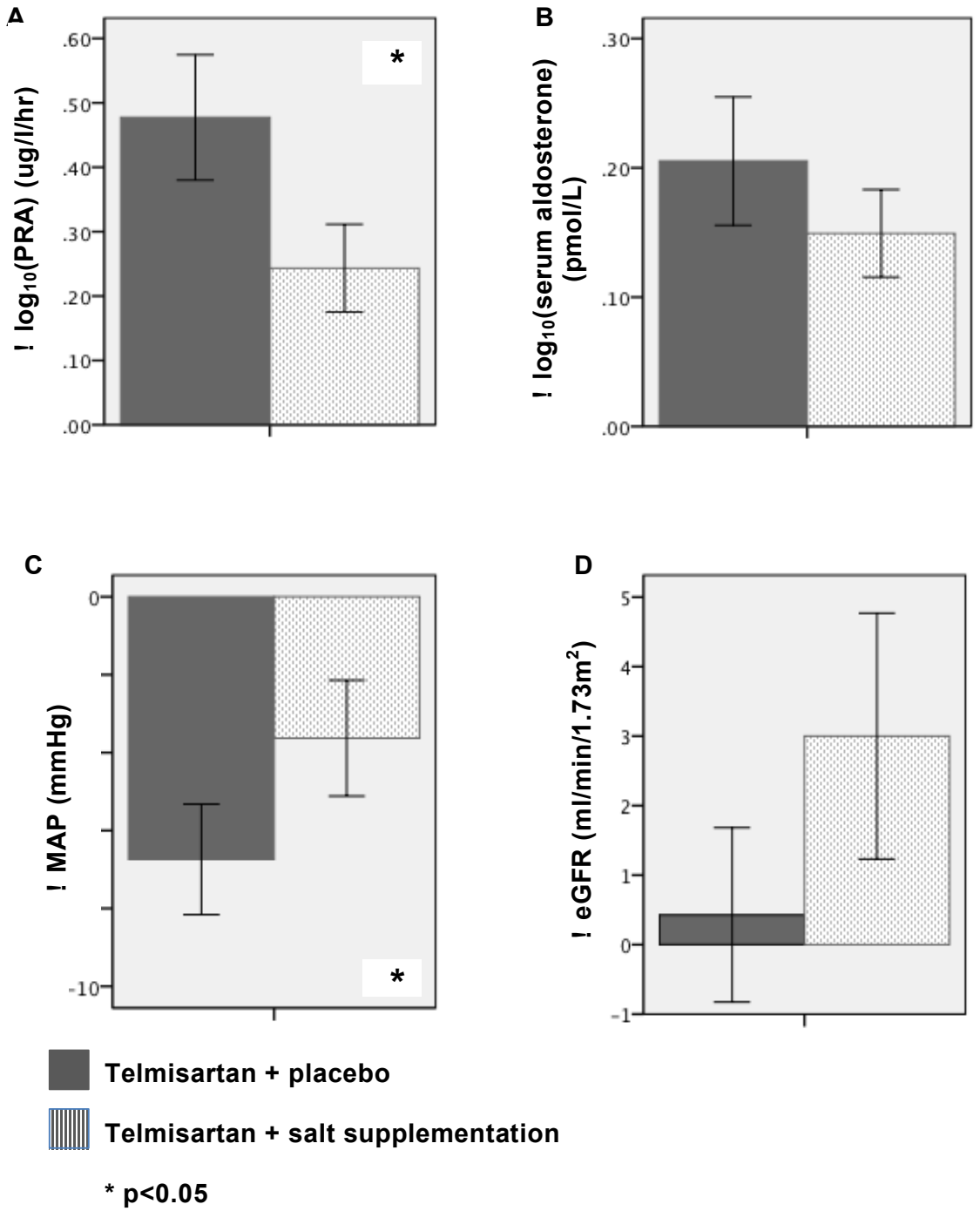
Figure 1: Change in (a) $\log_{10}$(PRA) *p<0.001,* (b) $\log_{10}$(serum aldosterone) *p=0.05,* (c) mean arterial pressure (MAP) *p<0.05*, (d) estimated glomerular filtration rate (eGFR) *p=0.05* from baseline during telmisartan and placebo (solid grey) versus telmisartan + salt supplementation (white and grey). * denotes p<0.05 (Values are mean ± SEM unless otherwise indicated). Results analysed using paired t-test



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