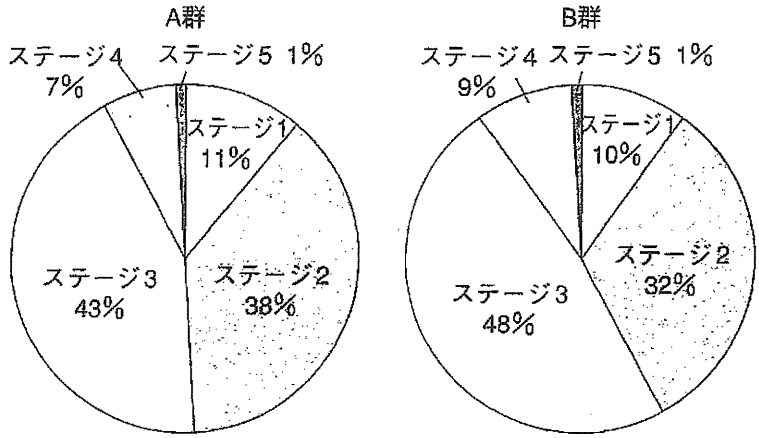

図 6　参加患者 CKD ステージ別割合

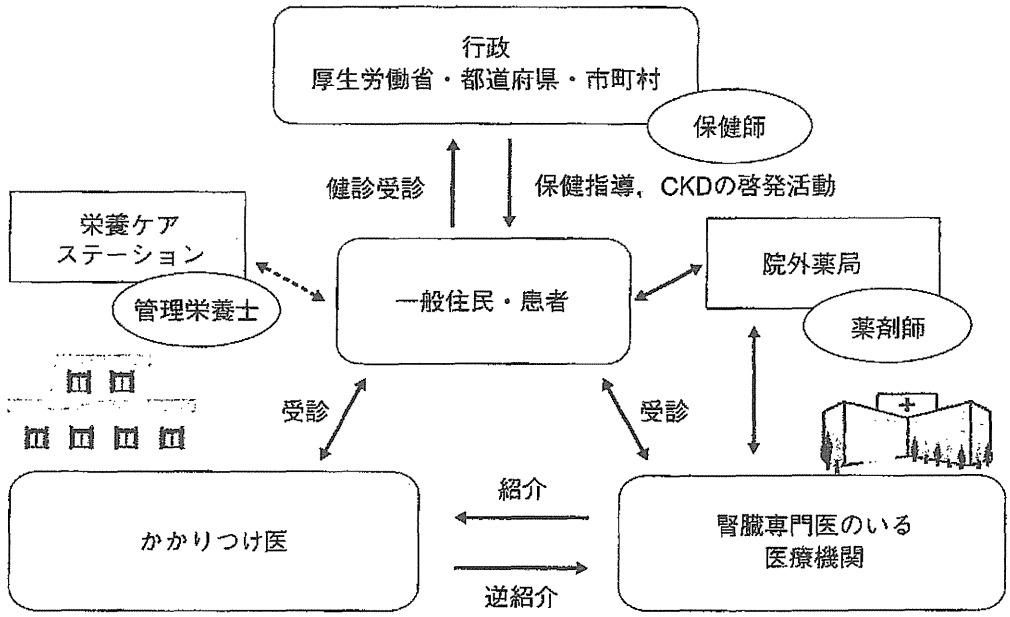

図 7　CKD 医療連携システム

師会の全医師への CKD 診療についての啓発が今後必要と考えられる。本研究では，参加地区医師会にて定期的に CKD 講演会を実施し，医師会所属全医師を対象に CKD 診療の啓発を行う試みが行われている。実際に，岡山大学より本研究参加を依頼している 4 医師会(岡山市医師会，倉敷医師会，美作医会，府中地区医師会)においても，各地区医師会所属の先生方を対象として，CKD 地域医療連携，CKD の検査についての CKD 講演会を実施した。

一般市民への啓発活動

CKD 地域医療連携システムの構築，CKD 対策の推進を行ううえで，一般市民への CKD 概念の普及・啓発が必要と考えられる。そのような背景から，2009 年 3 月 12 日の世界腎臓デーに合わせて日本全国で「世界腎臓デー 2009 腎臓チェックキット配布キャンペーン “あなたの腎臓，だいじょうぶ？”(主催：日本慢性腎臓病対策協議会：J-CKDI)」が開催された。東京，名古屋，岡山，近江八幡，高知，三重，山口の

全国7都市で一般市民への検尿キット配布キャンペーンを実施し，検尿の重要性，CKDについての啓発活動を行った。

岡山会場でも2008年に引き続いて，2009年3月12日早朝，岡山駅にて岡山市長，腎臓専門医，コメディカル，学生，患者などが一般市民へ検尿キット1,500個，CKD啓発パンフレットなどを配布した。新聞・TVによる取材も多く，一般市民へのCKDの啓発活動を効果的に行うことができた。

岡山市におけるCKD地域医療連携

CKD診療における地域医療連携の取り組みについては，これまでに全国各地で試みられているが，なかでも浜松市における取り組みがよく知られている。浜松地区では，約10年前より聖隷浜松病院腎臓内科 磯崎泰介医師らを中心として，腎臓専門医と浜松市医師会との病診連携による総合的腎疾患診療システムの構築が実施されている[3]。磯崎らによると，約10年間で，かかりつけ医から腎臓専門医への新規年間紹介患者数は2.6倍に増加し，腎臓専門医からかかりつけ医への逆紹介も3.0倍に増加した[3]。浜松市でのCKD地域医療連携への取り組みを参考に，2007年7月に岡山市にて，当科を中心に岡山市内のかかりつけ医と岡山市内の6腎臓専門医施設との医療連携ネットワーク(OCKD-NET：Okayama CKD Network)を設立した。

その際に実施した，岡山市内のかかりつけ医への医療連携に関するアンケート調査では(回答数111名)，「病院への紹介」に関して，よく紹介する58%，たまに紹介する42%であったが，「病院からの逆紹介」については，よくある10%，たまにある51%，ほとんどない39%と，腎臓専門医からの逆紹介の比率は低頻度にとどまっている現状がうかがわれた。「専門医と医療連携しにくい理由」(複数回答)としては，専門施設が不明である，専門医と面識がないが44%であり，腎臓専門医施設リストならびに腎臓専門医のプロフィールのかかりつけ医への周知・広報が必要と考えられた。また，「医療連携において腎臓専門医に期待する役割」(複数回答)としては，薬物療法などの治療方針決定77%，生活および食事指導と教育入院59%，透析導入45%であった。

一方，腎臓専門医へのアンケート調査において，「かかりつけ医と医療連携を行いにくい原因」(複数回答)としては，かかりつけ医をよく知らない35%，紹介時の情報提供が不十分24%などであり，かかりつけ医のプロフィールの腎臓専門医への周知が必要と考えられた。また，「かかりつけ医に期待する役割」(複数回答)としては，common disease(感冒など)への対応23%，病状変化時の迅速な再紹介23%，定期的な検査19%，定期的な投薬・注射19%であった。

上記調査結果を基に，OCKD-NETでは腎臓専門医のプロフィールおよびMAPを作成し，参加かかりつけ医に配布し，さらに腎臓専門医が閲覧可能な，かかりつけ医のプロフィールおよびMAPを作成している。さらに，年2回のセミナーを実施し，その際には医療連携の現状紹介を実際の症例提示も交えて，かかりつけ医および腎臓専門医からの双方向性の形式で行っている。また現在，OCKD-NET独自のCKD診療クリニカルパスならびにOCKD-NET手帳を作成している。

おわりに

FROM-J研究は2012年3月までの予定であるが，本研究より得られるアウトカムを基に，より腎臓病重症化予防，透析導入患者増加の抑制につながる効果的なCKD地域医療連携や診療支援システムの構築・確立(図7)が期待される。さらに，今後はFROM-J参加医師会のみならず，全国の都道府県単位でキーパーソンなどを中心として，地区医師会の協力を得て地域連携パスの作成などにより地域医療連携を推進し，CKDへの取り組みを進める必要がある。

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Hypertension Research (2013), 1–7

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ORIGINAL ARTICLE

Significance of estimated salt excretion as a possible predictor of the efficacy of concomitant angiotensin receptor blocker (ARB) and low-dose thiazide in patients with ARB resistance

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The purpose of this study was to assess the factors affecting the efficacy of combination therapy with losartan and thiazide, with a focus on the significance of salt excretion, via a multicenter observational study. Adult patients with essential hypertension showing therapy resistance to angiotensin receptor blocker (ARB) as a monotherapy or in combination with Ca channel blockers (CCB) were enrolled, and their previously administered ARBs were replaced with the combination tablet containing losartan (50 mg per day) and hydrochlorothiazide (12.5 mg per day). Blood pressure and biochemical parameters were monitored for a year. The baseline blood pressure (153.4 ± 14.8/86.4 ± 11.3 mm Hg) was significantly lowered at the 3rd month (137.3 ± 17.4/78.2 ± 11.1 mm Hg, $n = 93$) and was maintained at this lower level until the 12th month (135.3 ± 14.0/76.4 ± 11.1 mm Hg, $n = 74$). The baseline value of estimated salt excretion (eSE), calculated using Tanaka's formula, differed significantly between the high and low treatment response groups, which were defined by the average change in mean blood pressure (MBP-C, −11.3 mm Hg; eSE = 10.8 ± 2.9 g per day in high responders *vs.* 9.2 ± 2.3 g per day in low responders, $P = 0.004$). Univariate and multivariate analyses showed a significant correlation between eSE and MBP-C ($R = -0.288$, $P = 0.007$) and indicated the clinical effectiveness of eSE as a possible predictor for MBP-C ($P = 0.021$). In addition, the urine Na-to-Cr ratio (NCR) demonstrated significant correlations with eSE ($R = 0.848$, $P < 0.001$) and MBP-C ($R = -0.344$, $P < 0.001$). These results suggest that eSE or NCR could, to a certain extent, predict the efficacy of combination therapy with losartan and low-dose thiazide in patients demonstrating ARB resistance. Combination therapy with losartan and thiazide might thus be suitable for patients with a large amount of salt excretion.
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Keywords: angiotensin receptor blocker; salt excretion; salt sensitivity; thiazide

INTRODUCTION

It has been well established that salt intake is highly related to blood pressure. In general, changes in the body's salt balance should affect the maintenance of blood pressure,[1] and salt load always induces an increase in blood pressure, even in normal subjects.[2] The central role of salt balance or intake on the blood pressure is supported by the observation that a majority of the genetic abnormalities that cause hypertension are closely related to the functional abnormalities involved in the excretion of salt from the kidneys.[3] The role of impaired salt balance in blood pressure elevation is particularly important for Japanese people because the Japanese diet includes large amounts of salt. The recent annual report from the National Institute of Health and Nutrition of Japan showed that the average salt intake in Japanese men and women is 12.0 and 10.3 g per day, respectively, which are near the highest levels among the developed countries.[4] Excess salt intake results in salt accumulation in the body, leading to an increase in the extracellular fluid (ECF) volume and resultant intravascular volume overload.[5] Salt intake or accumulation also generates vascular resistance through cellular atrophy and increased nitric oxide production in the vascular smooth muscle.[6,7] Furthermore, a high salt intake induces pressure natriuresis to accelerate renal salt excretion.[8] All of those factors and mechanisms lead to an elevation of blood pressure. Excessive salt intake is also involved in the activation of the renin–angiotensin system in the blood vessels, brain and kidney,[9] the development of obesity[10] and insulin resistance,[11,12] and the activation of TGF-β[13] or NFκB.[14,15]

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All of those factors also contribute to the elevation of blood pressure. In addition, excess salt intake is known to directly induce blood pressure elevation by increasing the salt concentration in the hypothalamus, which leads to the angiotensin-related activation of the sympathetic nervous system.[16,17] Thiazide, a diuretic agent that mainly demonstrates salt elimination, could decrease the elevated blood pressure by reducing ECF volume and triggering the additional mechanisms indicated above. Indeed, recent large-scale clinical trials have shown that thiazide is clinically effective for the treatment of hypertension.[18]

Angiotensin receptor blockers (ARBs) are now recommended as first-line antihypertensive agents in a variety of guidelines for hypertension therapy in various countries, including in the latest Japanese guidelines (JSH-2009), because ARBs have superior effects on blood pressure and various organ-protective benefits.[19–21] However, ARB monotherapy sometimes fails to achieve a sufficient decrease in blood pressure. Some patients who show resistance to ARB monotherapy might exhibit over-consumption or over-accumulation of salt, which would overcome or cancel the effect of ARBs. Such a pathological setting might be particularly prominent among patients with enhanced salt sensitivity. It is known that resistance to ARB monotherapy is frequently observed in patients with obesity, metabolic syndrome, chronic kidney disease (CKD) or diabetes, and in patients with a high salt intake, all of whom are likely to show enhanced salt sensitivity.[19,20] Consequently, the coadministration of thiazide to patients who exhibit resistance to ARB monotherapy is a suitable strategy to consider. Indeed, ARB and thiazide combination therapy is recommended in a variety of guidelines for hypertension therapy.[19,20] The clinical effectiveness of ARB and thiazide combination therapy would be expected to indicate a correlation between this therapeutic modality and the amount of salt in the body or the amount of salt intake. However, this issue has not been sufficiently analyzed at the clinical level. The present study was designed to study the factors that contribute to decreasing blood pressure by focusing on the correlation between treatment response and salt excretion (or intake) in cases resistant to either ARB monotherapy or combination therapy with an ARB and a Ca channel blocker (CCB) in a multicenter cohort study in Saitama Prefecture in Japan (Saitama Anti-hypertension Losartan-hydrochlorothiazide Trial: the SALT study group). It is hoped that the results will expand our treatment options for patients with ARB-resistant hypertension.

METHODS

Study subjects

This study was conducted at 16 centers participating in the SALT study group (Appendix). The study was performed in accordance with the principles of the Declaration of Helsinki, and the investigational protocol was approved by the Ethics Committee for Human Studies at the Saitama Medical University. Patients who visited one of the participating centers between May 2008 and April 2010, were diagnosed with essential hypertension, and were prescribed an ARB with or without concomitant CCBs for >1 month were considered for screening. Among those patients, adult cases who did not achieve the target blood pressure for anti-hypertension therapy described in the 2004 Japanese Society of Hypertension Guidelines for the Management of Hypertension (≤130/85 mm Hg for young and middle-aged adults and ≤140/90 mm Hg for adults older than 75 years)[22] were considered potential candidates for entry into the trial. All of the enrolled patients provided their informed consent. Patients were excluded from the study if they were taking any type of diuretic or thiazolidinedione and if they exhibited renal insufficiency (serum creatinine >2.00 mg dl^{-1} or estimated glomerular filtration rate (eGFR) <30 ml min^{-1}), heart failure (New York Heart Association functional class III or IV for dyspnea at exertion) or severe liver dysfunction.

Study protocol

After screening, 104 patients were enrolled in the study. Their blood and first morning urine were sampled for baseline biochemical laboratory data, and their ARB regimens were switched to a regimen of concomitant losartan (50 mg per day) and hydrochlorothiazide (HCTZ, 12.5 mg per day) by use of combination tablet. After the medication switch, the enrolled patients were followed up monthly at the individual centers for a 12-month period. The follow-up visits included blood pressure measurement and medical interviews to confirm the absence of adverse effects from the medications. At the 3rd- and 12th-month visits, each patient again provided blood and urine samples for the same measurements that were taken at baseline. During the first 3 months of follow-up, 11 cases were excluded from this study because the patients were not compliant with the medication regimen (4 cases) or because of loss to follow-up due to a move or other causes (7 cases). Consequently, 93 participants (38–95 years old) finished the initial 3-month observation. The baseline characteristics of the 93 participants who were eligible for analysis are provided in Table 1, along with the number and average doses of previously prescribed ARBs. During the next 9 months of follow-up, another 19 patients were excluded from the study because they discontinued the medications (9 cases), were lost to follow-up (9 cases) or withdrew consent (1 case); thus the final group consisted of the 74 participants who were successfully followed up for 12 months. Estimated salt excretion (eSE, g per day) was converted from the value of estimated 24-h Na excretion (24HUNaV), which was determined using the following equation, proposed by Tanaka *et al*:[23]

predicted value of 24-h urine Cr (PRCr, mg per day)
$= -2.04 \times \text{age} + 14.89 \times \text{body weight (kg)} + 16.14 \times \text{height (cm)} - 2244.45$
$24\text{HUNaV (mEq per day)} = (21.98 \times (\text{uNa/uCr}) \times \text{PRCr})^{0.392}$
$\text{eSE (g per day)} = (58.5 \times 24\text{HUNaV})/1000$

Statistical analysis

All biochemical parameters except brain natriuretic peptide (BNP) and the urine albumin-to-creatinine ratio (ACR) are expressed as the means ± s.d. As the BNP and ACR values did not show normal (parametric) distribution, they were expressed as median, first and third quartile values. The significance of the difference for continuous variables with parametric distribution was

Table 1 Baseline characteristics and drug usage in patients over a 3-month observation period

n		93
Age (years)		67.7 ± 12.6
Male (*n*)		55 (59.1%)
BMI (kg m^{-2})		24.6 ± 3.6
Obesity (*n* (%))		32 (34.4%)
Diabetes (*n* (%))		20 (21.5%)
Chronic kidney disease (*n* (%))		21 (22.6%)
Dyslipidemia (*n* (%))		41 (44.1%)
Cerebrovascular diseases (*n* (%))		15 (16.1%)
Acute coronary syndrome (*n* (%))		4 (4.3%)
Pre-prescribed ARB	n *(%)*	*Average doses (mg per day)*
Olmesartan	25 (26.9)	20.0
Losartan	22 (23.7)	50.0
Valsartan	18 (19.4)	92.5
Telmisartan	14 (15.1)	38.7
Candesartan	11 (11.8)	7.6
Irbesartan	3 (3.2)	100.0
Total	93 (100)	—

Abbreviations: ARB, angiotensin receptor blocker; BMI, body mass index.

determined with a paired *t*-test if the analysis of variance (ANOVA) demonstrated equal distribution, and it was determined with Welch's *t*-test if the ANOVA demonstrated non-equal distribution. Analysis of the mean values of unpaired variables with parametric distribution was made using a *t*-test followed by ANOVA. The significance of paired and unpaired variables with non-parametric distribution was evaluated using Wilcoxon's signed-rank test and Mann–Whitney's *U*-test, respectively. For all of the statistical analyses, we used a microcomputer-assisted program with SPSS (Version 10.0) for Windows Xp (SPSS, Chicago, IL, USA), and *P*-values <0.05 were considered significant.

RESULTS

Figure 1 shows the changes in the average systolic blood pressure (SBP) and diastolic blood pressure (DBP) values in the patients who completed the 12-month observation (Figure 1a), and the average changes in blood pressure from the baseline values are also depicted (Figure 1b). In the 3rd month, both SBP and DBP showed a significant decrease from baseline ($153.4 \pm 14.8/86.4 \pm 11.3$ mm Hg at baseline, $137.3 \pm 17.4/78.2 \pm 11.1$ mm Hg in the 3rd month). However, the blood pressures did not change further over the subsequent 9 months ($135.3 \pm 14.0/76.4 \pm 11.1$ mm Hg in the 12th month), indicating that the significant decrease in blood pressures achieved by the losartan and thiazide combination therapy occurred within the initial 3 months. The blood pressure changes in the 3rd month were -16.1 ± 13.6 mm Hg for SBP and -7.9 ± 12.1 mm Hg for DBP, as shown in Figure 1b.

Table 1 shows the baseline characteristics of the enrolled patients who completed the first 3 months of observation (93 cases). The criteria for obesity, diabetes and dyslipidemia were as follows: obesity, body mass index (BMI) $\geqslant 25.0$; diabetes, the use of anti-hyperglycemic medications or fasting blood glucose >125 mg dl^{-1}; dyslipidemia, the use of lipid-lowering medications or total cholesterol $\geqslant 220$ mg dl^{-1} and/or high-density lipoprotein-cholesterol $\leqslant 40$ mg dl^{-1} and/or triglyceride $\geqslant 150$ mg dl^{-1}. The ARBs that the subjects were taking upon enrollment in this study are also listed in Table 1, along with their average doses. Thirty-five patients were concomitantly taking a CCB upon their enrollment in this study; the CCBs used included amlodipine (20 cases, 5.6 mg per day in average), long-acting nifedipine (6 cases, 23.3 mg per day), azelnidipine (5 cases, 12.8 mg per day), benidipine (2 cases, 6.0 mg per day), cilnidipine (1 case, 10.0 mg per day) and nicardipine (1 case, 5.0 mg).

The time-differential changes in the biochemical parameters of the blood and urine tests are summarized in Table 2. The majority of parameters, including serum K, serum uric acid, blood sugar and hemoglobin A1c, did not show significant differences during the observation period. The eGFR based on a Japanese population[24] showed a significant decrease at the 3rd month, although there was no significant difference in eGFR between the 3rd and 12th months. The BNP level and ACR also showed significant decreases in the 3rd month compared with their baseline values, and the ACR showed a further significant decrease in the 12th month compared with its value in the 3rd month.

Mean blood pressure (MBP, shown by $((SBP + DBP) \times 2)/3$) decreased from 109.6 ± 10.7 mm Hg at baseline to 98.2 ± 11.1 mm Hg in the 3rd month, and the average MBP-change was -11.3 ± 11.7 mm Hg. Based on this value, the enrolled patients were divided into two groups, a high treatment response group (MBP-change $\leqslant -11$ mm Hg) and a low treatment response group (MBP-change > -11 mm Hg), to assess possible contributory factors to the reduction in blood pressure, as shown in Table 3. With the exception of DBP and eSE, none of the parameters were significantly different between the two groups. The eSE value in the low-response group was significantly lower than that in the high-response group, indicating that eSE and baseline DBP might be the only parameters that show a significant difference related to the blood pressure-change induced by combination therapy. Subsequently, the correlation between eSE and the change in MBP was assessed using univariate analysis. The results showed that aside from DBP and MBP, eSE was the only parameter to show a significant correlation with MBP change, as Table 4 shows. The baseline eSE also demonstrated a significant correlation with SBP and DBP change in the 3rd month, as demonstrated in Figures 2a and b. To confirm the significance of eSE as a predictive factor for the efficacy of this combination therapy, multivariate analysis was also applied. Parameters that showed a high probability in the univariate analysis or were presumed to be clinically important were examined for their significance as predictor variables. The analysis showed that eSE was the only factor that significantly predicted a change in MBP, with the exception of baseline DBP (Table 4). Additionally, the difference in parameters between the groups with high and low salt excretion was also studied using the enrolled patients' mean eSE value (9.95 ± 2.70 g per day). In the high eSE group, the MBP-change (-14.2 ± 10.6 *vs.* -8.4 ± 11.3 mm Hg, $P=0.013$) and ACR

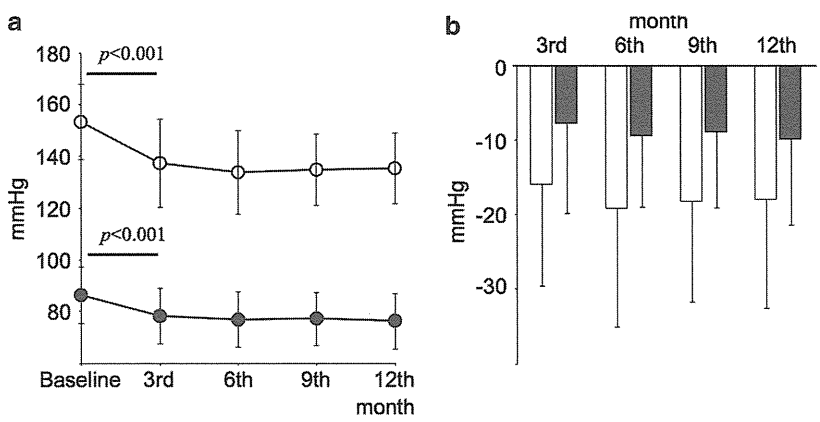

Figure 1 Changes in blood pressure over a 12-month observation period. (**a**) Changes in the average SBP (open circle) and DBP (closed circle), and (**b**) changes in SBP (open bar) and DBP (closed bar) from the baseline values in patients who underwent 12 months of observation ($n=74$) are depicted. The results are expressed as the means ± s.d. DBP, diastolic blood pressure; SBP, systolic blood pressure.

Table 2 Changes in biochemical parameters

	0 M (n = *93*)	*3 M* (n = *93*)	*12 M* (n = *74*)
Blood test			
Albumin ($g\,dl^{-1}$)	4.33 ± 0.39	4.28 ± 0.31	4.25 ± 0.40
eGFR ($ml\,min^{-1}$)	78.8 ± 19.8	71.8 ± 19.3**	71.3 ± 0.20.2**
Urea nitrogen ($mg\,dl^{-1}$)	15.5 ± 4.3	17.1 ± 5.0**	16.3 ± 4.3
Uric acid ($mg\,dl^{-1}$)	5.73 ± 1.70	5.63 ± 1.62	5.89 ± 1.73
Na ($mEq\,l^{-1}$)	141.2 ± 1.6	140.1 ± 2.1	140.6 ± 2.4
K ($mEq\,l^{-1}$)	4.27 ± 0.57	4.27 ± 0.60	4.16 ± 0.59
Cl ($mEq\,l^{-1}$)	103.7 ± 2.7	101.9 ± 3.1	102.0 ± 2.5
BNP ($pg\,ml^{-1}$)	22.9 (10.9, 37.7)	16.0 (6.7, 33.6)**	14.4 (5.4, 41.0)**
FBS ($mg\,dl^{-1}$)	119.4 ± 51.8	110.7 ± 33.0	117.6 ± 39.0
A1c (%)	5.4 ± 1.1	5.5 ± 1.0	5.6 ± 1.1
Urine test			
Creatinine ($g\,l^{-1}$)	0.84 ± 0.54	0.80 ± 0.22	0.91 ± 0.59
Na (mEq per g of Cr)	120.8 ± 51.9	130.8 ± 66.5	121.1 ± 57.0
K ($mEq\,l^{-1}$)	35.9 ± 26.9	40.9 ± 30.4	34.4 ± 23.4
ACR (μg per mg of Cr)	11.2 (5.8, 46.3)	8.7 (4.6, 16.5)**	4.6 (2.8, 14.9)**,##

Abbreviations: ACR, albumin-to-creatinine ratio; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; FBS, fasting blood sugar; M, months.
Note: Values of BNP and ACR are expressed as the median (1st quartile, 3rd quartile).
*$P<0.05$ *vs.* 0 M, **$P<0.01$ *vs.* 0 M.
#$P<0.05$ *vs.* 3 M, ##$P<0.01$ *vs.* 3 M.

Table 3 Comparative analysis of baseline parameters between high and low responders

	High responders (MBP-change ⩾ −11 mm Hg, n = *46)*	*Low responders (MBP-change < −11 mm Hg,* n = *47)*
Age (years)	66.1 ± 14.2	69.2 ± 10.6
BMI ($kg\,m^{-2}$)	24.6 ± 3.2	24.5 ± 4.0
SBP (mm Hg)	157.6 ± 14.7	152.3 ± 14.8
DBP (mm Hg)	93.0 ± 11.6	80.9 ± 9.4**
Incidence of diabetes (*n*)	11 (22.0%)	9 (20.9%)
eGFR ($ml\,min^{-1}$)	85.4 ± 26.6	77.9 ± 28.0
Uric acid ($mg\,dl^{-1}$)	5.6 ± 1.6	5.6 ± 1.8
Na ($mEq\,l^{-1}$)	140.9 ± 1.8	141.3 ± 1.6
K ($mEq\,l^{-1}$)	4.22 ± 0.45	4.29 ± 0.61
BNP ($pg\,ml^{-1}$)	23.6 (10.3, 50.3)	22.9 (10.9, 34.96)
A1c (%)	5.34 ± 0.77	5.51 ± 1.24
ACR (μg per mg of Cr)	17.1 (6.0, 53.3)	10.0 (5.6, 26.8)
eSE (g per day)	10.8 ± 2.9	9.2 ± 2.3*

Abbreviations: ACR, albumin-to-creatinine ratio; BMI, body mass index; BNP, brain natriuretic peptide; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; eSE, estimated salt excretion; MBP, mean blood pressure; SBP, systolic blood pressure.
High responders were defined as those with a decline in mean blood pressure of >11 mm Hg over the first 3 months. Values of BNP and ACR indicate median value in addition with 1st and 3rd quartile values in the parenthesis as distribution of those values do not show normal distribution.
*$P<0.05$, **$P<0.01$.

Table 4 Univariate and multivariate analyses the decline of mean blood pressure over a 3-month observation

	Univariate analysis		*Multivariate analysis*		
Parameters (at 0 M)	*Correlation coefficient* (R)	P-*value*	*Partial regression coefficient*	*s.e.*	P-*value*
Age (years)	0.050	n.s.			
BMI ($kg\,m^{-2}$)	0.008	n.s.	0.050	0.336	n.s.
Baseline SBP (mm Hg)	−0.179	n.s.			
Baseline DBP (mm Hg)	−0.565	<0.001	−0.570	0.087	<0.001
Baseline MBP (mm Hg)	−0.511	<0.001			
eGFR ($ml\,min^{-1}$)	−0.067	n.s.	−0.026	0.045	n.s.
Uric acid ($mg\,dl^{-1}$)	0.154	n.s.			
Na ($mEq\,l^{-1}$)	0.009	n.s.			
K ($mEq\,l^{-1}$)	0.149	n.s.			
BNP ($pg\,ml^{-1}$)	−0.064	n.s.	−0.139	2.712	n.s.
A1c	0.001	n.s.			
ACR (μg per mg of Cr)	−0.150	n.s.	−0.061	1.595	n.s.
eSE (g per day)	−-0.287	0.007	−0.224	0.412	0.021

Abbreviations: ACR, albumin-to-creatinine ratio; BMI, body mass index; BNP, brain natriuretic peptide; DBP, diastolic blood pressure; eSE, estimated salt excretion; MBP, mean blood pressure; n.s., not significant; SBP, systolic blood pressure.
Coefficient of determination in this model = 0.42.

(17.7, 7.6, 61.4 *vs.* 7.5, 4.9, 16.9 μg per mgCr, indicating median, 1st and 3rd quartile values, $P = 0.012$) were significantly higher than in the low eSE group. The efficacy of the urine Na-to-creatinine ratio (NCR) as a substitutional parameter for eSE was also assessed because eSE calculation using Tanaka's formula is still fairly complex for use in clinical settings. The univariate analysis showed a significantly high correlation between eSE and NCR, as shown in Figure 2c. As expected from the correlation between NCR and eSE, significant correlation between NCR and MBP change in the 3rd month was also demonstrated by the univariate analysis, suggesting that the NCR was also useful as a predicting parameter of the efficacy of the losartan/thiazide combination therapy.

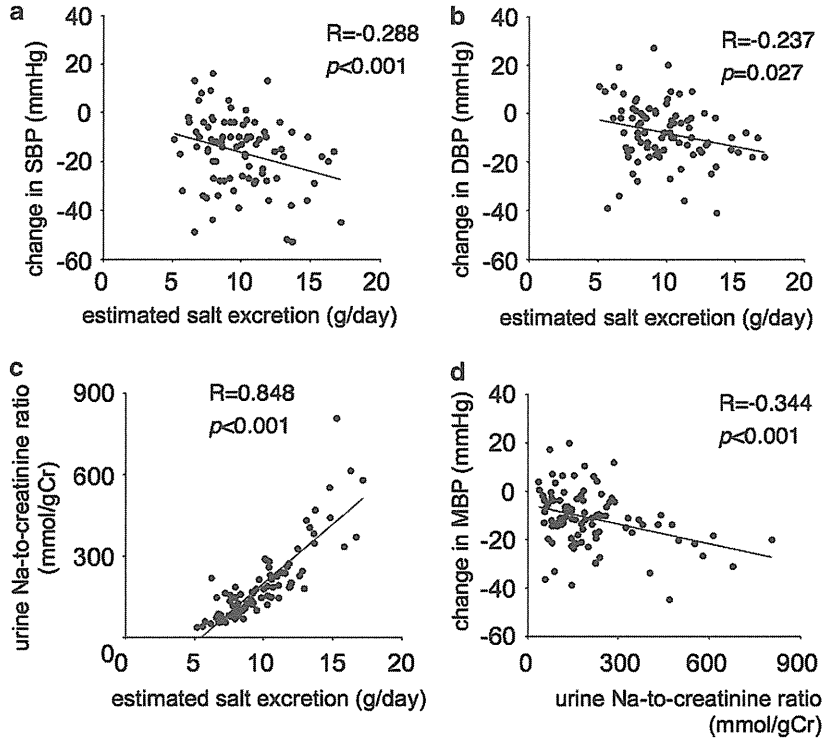

Figure 2 The correlation between estimated salt excretion and changes in systolic or diastolic blood pressure and the correlation between urine Na-to-Cr ratio and estimated salt excretion or changes in mean blood pressure in the 3rd month. The individual correlations between changes in blood pressure during the initial 3 months and baseline eSE were plotted ($n=93$). The relationships between (**a**) baseline eSE and SBP changes and (**b**) baseline eSE and DBP changes were plotted. Correlations between (**c**) baseline NCR and baseline eSE and (**d**) baseline NCR and MBP changes were also plotted. *R* indicates the regression coefficient. Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; eSE, estimated salt excretion; NCR, urine Na-to-creatinine ratio.

DISCUSSION

The present study showed that combination therapy with losartan and low-dose hydrochlorothiazide successfully lowered blood pressures in patients whose hypertension was resistant to ARB monotherapy or ARB and CCB combination therapy. As the types and doses of preadministered ARBs varied among the individual patients enrolled in this study, it could be considered that the clinical advantages obtained with the combination therapy did not result from the addition of thiazide alone, but from the concomitant use of losartan and thiazide. The present study also revealed that the clinical efficacy of combination therapy with losartan and thiazide was more prominent in patients with high levels of salt excretion, suggesting that the presumed salt intake and the efficacy of the combination therapy are highly correlated. Simultaneously, the correlation between eSE and MBP changes might indicate that more than a few patients with ARB monotherapy- or ARB and CCB combination-resistant hypertension demonstrated thiazide-responsive, salt-sensitive features.

The clinical effectiveness of thiazide has been examined for many years. The Joint National Council (JNC)-7 guideline positions thiazide at the center of antihypertensive therapy.[20] Similarly, the latest Japanese guideline for hypertension therapy, JSH-2009, recommend that a low dose of thiazide be adopted as a concomitant agent.[19] Multiple clinical studies have elucidated the potential effects of combination therapy with an ARB and thiazide.[25–27] Successful reduction of the proteinuria that remains after ARB monotherapy or ARB-CCB combination therapy has also been reported in a clinical study of patients treated with losartan plus thiazide.[28] The present study clearly shows that hypertensive patients who showed ARB monotherapy-resistant hypertension demonstrated a significant further decrease in blood pressure and a significant reduction in ACR by switching to losartan and thiazide combination therapy, in agreement with previous studies. The combination therapy is considered to be especially beneficial for preventing thiazide-associated hyperuricemia and ARB-associated hyperkalemia because those adverse effects should be canceled by the losartan-associated acceleration of uric acid excretion and the thiazide-associated acceleration of potassium excretion, respectively.[29] Indeed, there was no significant change in the serum concentration of potassium and uric acid throughout the entire observation period in this study.

It seems reasonable to consider that the efficacy of thiazide would be at least somewhat correlated with the amount of salt accumulation in the body or the amount of salt intake, although such a correlation has not been directly demonstrated yet. Uzu *et al.*[30] demonstrated that the antihypertensive effect of thiazide was more obvious in patients with nocturnal blood pressure elevation who showed a large amount of salt excretion compared with cases without nocturnal blood pressure elevation who showed a smaller amount of salt excretion. Although this study did not show a direct correlation between salt excretion and the effectiveness of thiazide, the relationship was indirectly indicated based on clinical observation. In the present study, the advantage of eSE as a parameter to predict

the efficacy of losartan and thiazide combination therapy was shown via stratified, univariate and multivariate analyses, although a rough relationship between thiazide effectiveness and salt excretion or intake has been previously discussed only for stratified groups, such as those with high or low salt intake.[30,31]

Multiple formulas have been proposed for estimating salt excretion. However, we considered that it would be difficult to apply these formulas to this study, because some of them require the measurement of lean body mass[32] or the use of the second urine after awaking as a urine sample.[33] Tanaka *et al.*[23] have reported that sodium excretion for 24 h could be estimated by the use of urine sodium and Cr concentration and the estimated Cr excretion for 24 h, which would be calculated based on the age, body weight and height of individual cases. The Japanese Society of Hypertension recommends using Tanaka's formula.[34] In the present study, estimated sodium excretion was converted to estimated salt excretion, which was considered a reasonable accurate estimate of the salt intake. Indeed, Tanaka *et al.*[23] demonstrated that the estimated salt excretion was highly representative of the salt intake. Therefore, the present study suggests that the effectiveness of combined losartan and thiazide for therapy-resistant hypertension would be significantly affected by salt intake and that the estimation and assessment of salt excretion would be helpful for establishing a strategy for therapy-resistant hypertension.

While salt load causes elevation of blood pressure even in normal subjects,[35] there are individuals who show an especially pronounced blood pressure elevation in response to salt intake, that is, salt-sensitive hypertensives.[2] It is generally believed that the major clinical features of salt-sensitive hypertension are female sex, obesity, insulin resistance and high incidence of diabetes, renal damage (such as microalbuminuria) and dyslipidemia.[2] The National Health and Nutrition Survey of Japan reported that the prevalence of obesity and the average BMI in Japan were 30.4% and 23.1 in males and 20.2% and 22.3 in females,[4] whereas those of the patients enrolled in this study were 32.7% and 24.5 in males and 42.1% and 24.6 in females, indicating that the study subjects had an obesity prevalence that was higher than that of the Japanese population. Similarly, the enrolled patients also showed a higher prevalence of other parameters, such as dyslipidemia, diabetes and CKD.[4] These clinical features of the patients in this study match the clinical profile of salt-sensitive hypertension, which might have contributed to the appearance of a correlation between eSE and MBP change in this study. It is presumed that patients with salt-sensitive hypertension basically suffer from an impairment of renal salt excretion,[36,37] suggesting that their salt intake exceeds their salt excretion. Consequently, a realistic salt intake would be assumed to be more likely than the estimated amount. In any case, patients with salt-sensitive hypertension whose blood pressure is predominantly determined by the salt load or accumulation would be considered resistant to ARB monotherapy, but should respond to the combination of an ARB plus thiazide. Alternately, it might also be suggested that many of the patients with resistance to ARB monotherapy or ARB plus CCB combination therapy might have a higher incidence of salt-sensitive hypertension.

Despite the clinical advantages, daily salt excretion or intake assessments are not realistically straightforward because eSE calculation remains complex in the clinical setting. The present study also showed that NCR might be a more reliable parameter than eSE for estimating daily salt excretion, at least in the patients enrolled in this study. In general, the 95% reliable range for the average population is determined by the following equation:

mean $\pm$ (square root of D) $\times k$, where D indicates the number of samples divided by the variance of population, and k indicates the reliability coefficient (1.96 for 95% reliability).

Consequently, the 95% reliable range of eSE in the high-responder group would be from 14.5 to 8.4 g per day. An analysis of the correlation between eSE and NCR resulted in the following equation:

NCR = 43.8 $\times$ eSE $-$238.9 (mmol per g of Cr).

Therefore, the 95% reliable range of eSE in the high-responder group would correspond to 396–134 per g of Cr of NCR. Indeed, one study reported that an NCR of 134 mmol per g of Cr might correspond to the salt excretion of Japanese people with average salt intakes, although the study results were based on second urine samples after awaking.[34] Therefore, the study's clinical analysis of NCR suggests that $\sim$130 mmol per g of Cr or more would be a rough standard for cases that might be expected to show a prominent response to combination therapy with losartan and thiazide.

In conclusion, eSE or NCR could be used to assess the efficacy of losartan and low-dose thiazide combination therapy in patients who demonstrate resistance to ARB monotherapy. Combination therapy with losartan and thiazide might be well suited to patients who show ARB resistance and high levels of salt excretion.

Limitations

There were some limitations to this study. First, this study was an observational study in the same population rather than a comparative study. Additionally, the number of enrolled cases was $<$100, and a gender bias existed. These issues raise the possibility that the results obtained in this study are not generally applicable to other populations. However, even in a limited population, the finding of a correlation between estimated salt excretion or intake and efficacy of anti-hypertension therapy using losartan plus thiazide is of clinical importance.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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APPENDIX

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Original Paper

Release From Glomerular Overload by the Addition of Low-dose Thiazide in Patients With Angiotensin Receptor Blocker-Resistant Hypertension

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Key Words
Glomerular filtration rate • Renoprotective effect • Losartan • Thiazide • Albuminuria

Abstract
Background/Aims: This multicenter, prospective, observational study assessed the renoprotective effects of losartan/thiazide combination therapy in terms of lowering the estimated glomerular filtration rate (eGFR). ***Methods:*** Adult patients with angiotensin receptor blocker (ARB)-resistant essential hypertension (n = 104) were enrolled and switched to combination therapy with losartan (50 mg/day) and hydrochlorothiazide (12.5 mg/day). ***Results:*** eGFR values declined significantly during the first 3 months, and changes in eGFR were assessed according to tertiles of the eGFR decrease ratio at 3 months. Only the high eGFR decrease (1st tertile) group showed significantly greater decreases in baseline eGFR and albumin-to-creatinine ratio (ACR) during the first 3 months. Additionally, the assessment according to tertiles of the baseline eGFR showed a significant decrease in eGFR and ACR during the first 3 months in the high baseline eGFR (1st tertile) group, but not in the moderate (2nd tertile) and low baseline eGFR (3rd tertile) groups. ***Conclusion:*** The present results revealed that losartan/thiazide combination therapy attenuated glomerular overload, indicating that this therapy may provide glomerular protection in patients with an elevated GFR without causing prolonged damage to renal function.

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Introduction

Angiotensin receptor blockers (ARBs) are used commonly for anti-hypertension therapy and have been recommended as a first-line therapeutic strategy in several hypertension guidelines [1-3]. The principal advantage of ARBs are that they exert various protective effects in organs in addition to lowering blood pressure [4-8]. Thiazide diuretic agents are used as second-line drugs for hypertensive patients with ARB resistance and they are also recommended for concomitant use with ARBs in several guidelines [1, 2]. Indeed, a large-scale clinical study has reported clinical advantages of an ARB and thiazide combination therapy [9].

We recently conducted a multicenter, prospective, observational study in the Saitama Prefecture of Japan (the Saitama Anti-hypertension Losartan-hydrochlorothiazide Trial: SALT study), wherein we studied the clinical effectiveness of losartan/thiazide combination therapy in patients with hypertension that was resistant to either ARB monotherapy or concomitant ARB + calcium channel blocker (CCB) therapy [10]. The results showed that estimated salt excretion (eSE) at baseline was significantly correlated with the magnitude of blood pressure decrease, and that eSE could predict the efficacy of the combination therapy [10]. The study also demonstrated a significant decrease in the estimated glomerular filtration rate (eGFR) during the first 3 months after the switch to ARB/thiazide combination therapy [10].

It is generally considered that a decrease in the GFR or an increase in serum creatinine (Cr) levels indicates a deterioration in renal function. However, in certain cases, a decreased GFR may indicate attenuation of a pressure overload in the glomerulus. A sub-analysis of the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study revealed that an acute decrease in the GFR during the initial period after the switch to losartan predicted a slower decrease in long-term renal function, indicating that the initial decrease in GFR provided a long-term renoprotective effect [11]. In addition, a decrease in the GFR at the onset of losartan/thiazide combination therapy generally predicts a subsequent slower decline in renal function, presumably because it reflects a decrease in glomerular pressure [12]. These results strongly suggest that a decline in the GFR does not necessarily indicate a deterioration in renal function. However, the significance of the GFR decrease caused by combined ARB/thiazide therapy has not been studied sufficiently, particularly its relationship with the associated anti-proteinuric effect.

In this study, we performed a sub-analysis of the SALT study to evaluate the clinical significance of the decline in eGFR. This involved assessing the relationships among the decline in eGFR, the baseline values of eGFR, decrease in blood pressure, and changes in albuminuria. The results showed that a significant decline in the eGFR occurred only in patients with high baseline eGFR values. These patients also showed a significant decrease in albuminuria. The results indicated that the renoprotective effect of losartan/thiazide combination therapy was attributable to amelioration of the hyperfiltration state of glomerular hemodynamics. Our findings thus contribute to knowledge about therapeutic strategies for the clinical management of ARB-resistant hypertension and the renoprotection associated with these strategies.

Materials and Methods

Study subjects

The SALT study was a multicenter, prospective, observational study. The main outcomes and complete study design, organization, clinical measures, exclusion criteria, and baseline characteristics have been published [10]. The study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee for Human Studies at Saitama Medical University. We included patients aged 38–85 years with essential hypertension who were administered an ARB with or without the concomitant administration of a CCB over a 1-month period (May 2008 to April 2010). Patients

who did not meet the target blood pressure levels described in the 2004 Japanese Society of Hypertension Guidelines for the Management of Hypertension (≤130/85 mmHg for young and middle-aged adults, ≤ 140/90 mmHg for adults aged > 75 years) [13] after this antihypertension therapy and who provided informed consent were enrolled in the SALT study. As described [10], patients were excluded from the study if they had been administered any type of diuretic or thiazolidinedione agent or if they exhibited advanced renal insufficiency (serum Cr > 2.00 mg/dL or eGFR < 30 mL/min), heart failure (New York Heart Association functional class III or IV for dyspnea at exertion), or severe liver dysfunction.

Study protocol and clinical profile of the participants

A total of 104 patients who underwent SALT study screening were included in the present study. After blood and urine sampling to obtain baseline laboratory data, the ARB treatment in these patients was switched to the daily administration of a tablet of a compound drug (Preminent®) that contains losartan (50 mg) and hydrochlorothiazide (12.5 mg). The first morning urine was collected for biochemical analysis. The enrolled patients visited individual centers for the measurement of blood pressure and medical interviews until the 12th month. At the 3rd- and 12th-month visits, each patient provided blood and urine samples using methods similar to those used for the baseline sample collection. As described [10], 93 and 74 participants completed the 3-month and 12-month observations, respectively. At the baseline, the patients' mean age was 67.7 ± 12.6 years and their mean body mass index (BMI) was 24.6 ± 3.6 kg/m^2 [10]. The ratio of males was 59.1% (55 cases). The prevalence of obesity was 34.4% (n = 32), diabetes 21.5% (n = 20), and dyslipidemia 44.1% (n = 41). The criteria for diagnosing obesity, diabetes, and dyslipidemia were as follows: obesity, body mass index (BMI) ≥ 25.0 kg/m^2; diabetes, use of antihyperglycemic medication or fasting blood glucose levels > 125 mg/dL; dyslipidemia, use of lipid-lowering medication or total cholesterol levels ≥ 220 mg/dL and/or high-density lipoprotein cholesterol levels ≤ 40 mg/dL and/ or triglyceride levels ≥ 150 mg/dL. The ARBs being taken by the patients at enrollment and their mean doses were as follows: olmesartan (n = 25, 26.9%, 20.0 mg/day), losartan (n = 22, 23.7%, 50.0 mg/day), valsartan (n = 18, 19.4%, 92.5 mg/day), telmisartan (n = 14, 15.1%, 38.7 mg/day), candesartan (n = 11, 11.8%, 7.6 mg/day), and irbesartan (n = 3, 3.2%, 100.0 mg/day). Thirty-five patients were receiving concomitant CCB therapy at enrollment in the study, including amlodipine (n = 20; mean dose, 5.6 mg/day), long-acting nifedipine (n = 6, 23.3 mg/day), azelnidipine (n = 5, 12.8 mg/day), benidipine (n = 2, 6.0 mg/day), cilnidipine (n = 1, 10.0 mg/day), and nicardipine (n = 1, 5.0 mg). eSE (g/day) was calculated and assessed as described previously [14]. Briefly, the value was calculated from estimated 24-h Na excretion (24HUNaV) using the following equations proposed by Tanaka et al. [14]:

predicted value of 24-h urine Cr (PRCr, mg/day) =
−2.04 × age + 14.89 × body weight (kg) + 16.14 × height (cm) − 2244.45
24HUNaV (mEq/day) = [21.98 × (uNa/uCr) × PRCr]$^{0.392}$
eSE (g/day) = (58.5 × 24HUNaV)/1000

Statistical analysis

All biochemical parameters except brain natriuretic peptide (BNP) and urine albumin-to-Cr ratio (ACR) are expressed as means ± standard deviations. BNP and ACR values did not have a parametric distribution; therefore, they are expressed as median and 1st- and 3rd-quartile values. We determined the significance of differences in continuous variables with a parametric distribution by paired t-tests if an analysis of variance (ANOVA) demonstrated equal distribution and by Welch's t-test if the ANOVA demonstrated a nonequal distribution. The mean values of unpaired variables with a parametric distribution were analyzed using the two-tailed t-tests for two groups comparison and two-tailed multiple t-test with a Bonferroni correction for multiple group comparisons followed by ANOVA. The significance of paired and unpaired variables with a nonparametric distribution was evaluated using Wilcoxon's signed-rank test and the Mann-Whitney U-test, respectively. All statistical analyses were undertaken using a microcomputer-assisted program with SPSS (ver 20.0) for Windows Xp (SPSS Inc., Chicago, IL, USA). A p-value of < 0.05 was considered significant.

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Table 1. Changes in biochemical parameters

	0 months (n = 93)	3 months (n = 93)	12 months (n = 74)
Blood pressure			
SBP (mmHg)	154.9 ± 14.9	137.4 ± 16.9**	135.2 ± 14.1**
DBP (mmHg)	86.9 ± 12.1	78.6 ± 11.2**	76.2 ± 11.0**
Blood test			
Albumin (g dl^{-1})	4.33 ± 0.39	4.28 ± 0.31	4.25 ± 0.40
Cr (mg dl^{-1})	0.71 ± 0.21	0.80 ± 0.21**	0.80 ± 0.22**
eGFR (ml min^{-1})	78.8 ± 19.8	71.8 ± 19.3**	71.3 ± 0.20.2**
Uric acid (mg dl^{-1})	5.73 ± 1.70	5.63 ± 1.62	5.89 ± 1.73
Na (mEq l^{-1})	141.2 ± 1.6	140.1 ± 2.1	140.6 ± 2.4
K (mEq l^{-1})	4.27 ± 0.57	4.27 ± 0.60	4.16 ± 0.59
Cl (mEq l^{-1})	103.7 ± 2.7	101.9 ± 3.1	102.0 ± 2.5
TC (mg dl^{-1})	202.7 ± 37.7	200.4 ± 35.5	187.8 ± 37.1
TG (mg dl^{-1})	152.7 ± 96.4	159.4 ± 109.5	143.0 ± 76.7
BNP (pg ml^{-1})	22.9 (10.9, 37.7)	16.0 (6.7, 33.6)**	14.4 (5.4, 41.0)**
FBS (mg dl^{-1})	119.4 ± 51.8	110.7 ± 33.0	117.6 ± 39.0
A1c (%)	5.4 ± 1.1	5.5 ± 1.0	5.6 ± 1.1
Urine test			
Creatinine (g l^{-1})	0.84 ± 0.54	0.80 ± 0.22	0.91 ± 0.59
Na (mEq gCr^{-1})	120.8 ± 51.9	130.8 ± 66.5	121.1 ± 57.0
K (mEq l^{-1})	35.9 ± 26.9	40.9 ± 30.4	34.4 ± 23.4
ACR (μg $mgCr^{-1}$)	11.2 (5.8, 46.3)	8.7 (4.6, 16.5)**	4.6 (2.8, 14.9)** ##

The BNP and ACR results are expressed as median values (in parentheses) because these variables did not have a parametric distribution. Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; FBS, fasting blood sugar; ACR, albumin-to-creatinine ratio.
* $p < 0.05$ vs. 0 months, ** $p < 0.01$ vs. 0 months, # $p < 0.05$ vs. 3 months, ## $p < 0.01$ vs. 3 months

Results

Physiological and biochemical parameters

The time-related changes in biochemical parameters as measured in the patients' blood and urine samples are listed in Table 1. Both systolic and diastolic blood pressure decreased significantly within the first 3 months, although no significant change was observed over the next 9 months. The majority of biochemical parameters, including serum potassium levels, uric acid levels, and glucose tolerance, showed no significant change during the 1-year observation period. Significant changes in serum Cr levels and eGFR were observed in the first 3 months but not in the next 9 months. BNP levels also showed a significant decrease in the first 3 months. Urine analysis showed that ACR decreased significantly in the first 3 months as well as over the following 9 months.

Stratified analysis of baseline parameters by eGFR decrease ratio at 3 months and the time-differential changes in blood pressure, eGFR and ACR in each group

To elucidate the clinical profile of the patients who showed a decrease in eGFR, we first calculated the decrease ratio of eGFR at 3 months to assess the effects of the losartan/thiazide combination therapy on the changes in eGFR values and the residual albuminuria. The patients were stratified according to tertiles of the eGFR decrease ratio at 3 months. As shown in Table 2, the baseline values of BMI, blood pressure, BNP, ACR, and eSE were not different between the three groups. The baseline eGFR in the high eGFR decrease group (1st tertile) was significantly greater than that in the moderate and low eGFR decrease (2nd and 3rd tertiles) groups. As shown in Fig. 1, the residual albuminuria decreased significantly in the high eGFR decrease group but not in the other two groups. In all three groups, blood pressure showed equal and significant decreases in the first 3 months, with no change over the next 9 months.

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Table 2. Baseline values of parameters in the groups with a high, moderate, and low eGFR decrease ratio

parameters	high eGFR decrease (1st tertitle)	moderate eGFR decrease (2nd tertitle)	low eGFR decrease (3rd tertitle)
n	31	31	31
eGFR-reduction rate	0.74 ± 0.09**##	0.91 ± 0.05	1.09 ± 0.14
baseline BMI (kg m^{-2})	24.6 ± 3.9	24.7 ± 4.1	24.9 ± 3.3
baseline SBP (mmHg)	157.5 ± 15.3	154.2 ± 13.2	149.8 ± 16.3
baseline DBP (mmHg)	87.7 ± 15.1	85.0 ± 9.7	88.3 ± 9.7
baseline eGFR (ml min^{-1})	89.6 ± 31.3**#	71.0 ± 14.5	74.0 ± 14.6
baseline BNP (pg ml^{-1})	25.3 (17.4, 42.4)	27.0 (15.8, 51.0)	21.5 (7.6, 35.0)
baseline ACR (μg $mgCr^{-1}$)	14.2 (5.8, 47.3)	10.1 (6.1, 55.3)	8.6 (4.8, 17.8)
baseline eSE (g day^{-1})	10.08 ± 2.65	10.02 ± 2.86	9.51 ± 2.27

The first and second tertile values of eGFR decrease were 0.85 and 0.99, respectively. The values of BNP and ACR represent the median values (in parentheses) because these variables did not have a parametric distribution. Abbreviations: eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; ACR, albumin-to-creatinine ratio; eSE, estimated salt excretion.
** $p < 0.01$ vs. the moderate eGFR decrease group, # $p < 0.05$ vs. the low eGFR decrease group, ## $p < 0.01$ vs. the low eGFR decrease group

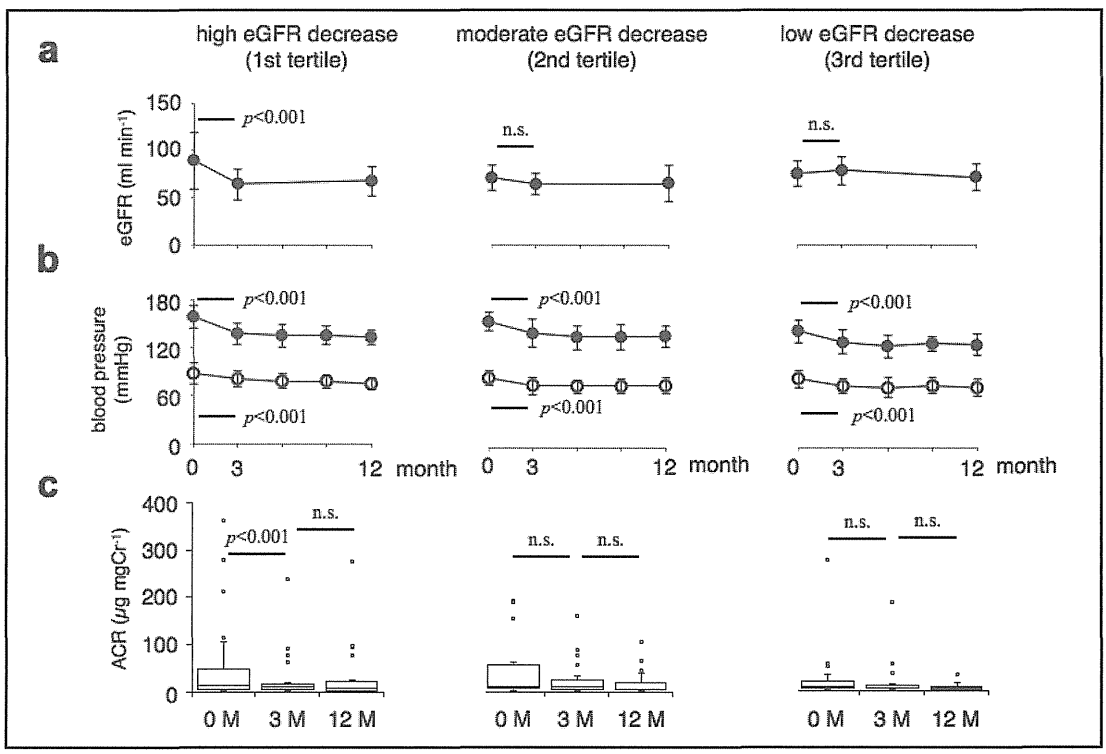

Fig. 1. Tertile analysis of estimated glomerular filtration (eGFR) decrease ratio at the 3rd month. Time-related changes in eGFR at 0, 3, and 12 months (a) and systolic (closed circles) and diastolic (open circles) blood pressure at 0, 3, 6, 9 and 12 months (b) are expressed as mean ± SEM in the 1st, 2nd, and 3rd tertiles of eGFR decrease. The urine albumin-to-creatinine ratio at 0, 3, and 12 months (c) are depicted in the box plot, where the box represents the interquartile range (Q1-Q3).

Stratified analysis of baseline parameters by baseline eGFR and the time-differential changes in blood pressure, eGFR and ACR in each group

Because the decreases in eGFR and albuminuria were related to the significant decrease in high baseline eGFR values, we next divided the patients into three tertiles of baseline eGFR values. As shown in Table 3, there was no significant difference in the baseline value of all other parameters, including albuminuria and eSE. The changes in eGFR, blood pressure, and

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Table 3. Baseline values of parameters in the groups with high, moderate, and low baseline eGFR values

parameters	high baseline eGFR (1st tertile)	moderate baseline eGFR (2nd tertile)	low baseline eGFR (3rd tertile)
n	31	31	31
baseline eGFR (ml min^{-1})	102.2 ± 25.7**##	76.1 ± 5.2	59.3 ± 8.1
baseline BMI (kg m^{-2})	24.6 ± 3.9	24.1 ± 3.7	25.1 ± 3.5
baseline SBP (mmHg)	158.4 ± 16.0	152.0 ± 14.7	151.5 ± 11.8
baseline DBP (mmHg)	90.6 ± 13.8	84.8 ± 11.0	85.8 ± 11.7
baseline BNP (pg ml^{-1})	14.6 (7.8, 29.6)	22.2 (9.6, 47.5)	23.8 (18.8, 36.6)
baseline ACR (μg mgCr^{-1})	12.8 (5.8, 33.6)	10.1 (5.9, 18.9)	7.7 (4.8, 40.6)
baseline eSE (g day^{-1})	9.58 ± 2.85	9.28 ± 2.34	10.53 ± 2.79
age	63.1±12.8	68.7±13.4	70.2±11.6
BMI	24.6±3.9	24.1±3.7	25.1±3.5
incidence of diabetes	20.7%	16.1%	16.7%

The first and second tertile values of baseline eGFR were 85.3 and 68.9 mL/min, respectively. Values of BNP and ACR represent the median values (in parentheses) because these variables did not have a parametric distribution.
Abbreviations: eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; ACR, albumin-to-creatinine ratio; eSE, estimated salt excretion
** $p < 0.01$ vs. The moderate baseline eGFR group, ## $p < 0.01$ vs. the low baseline eGFR group

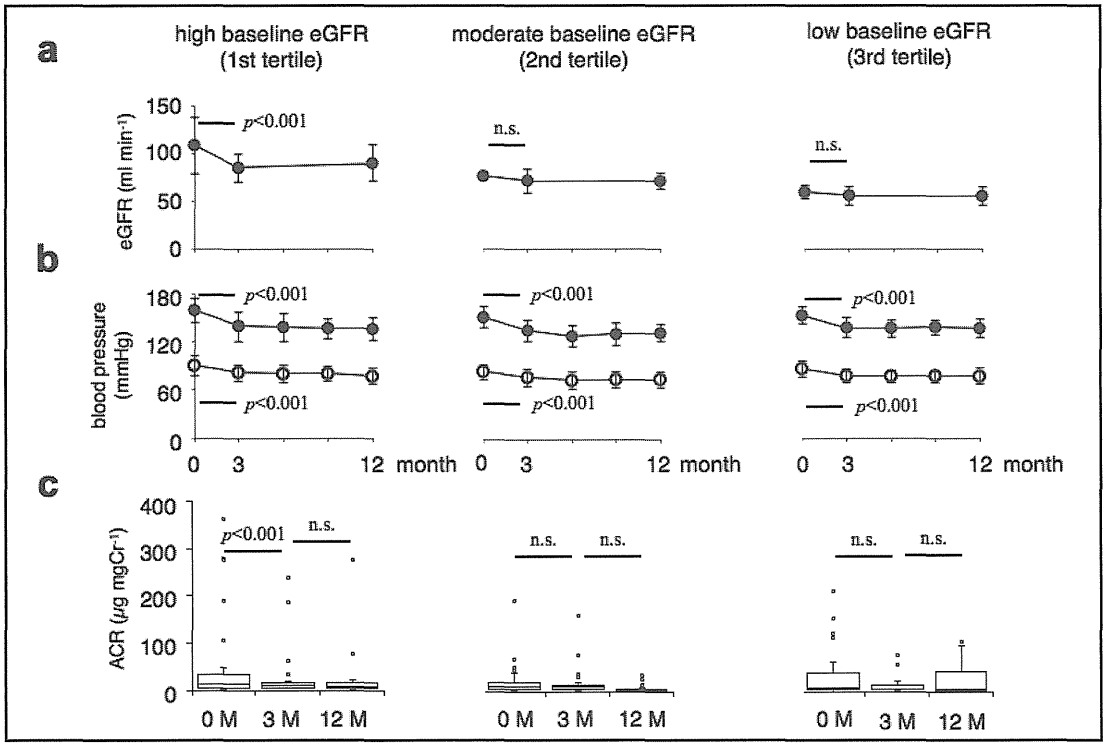

Fig. 2. Tertile analysis of baseline eGFR. Time-related changes in eGFR at 0, 3, and 12 months (a) and systolic (closed circles) and diastolic (open circles) blood pressure at 0, 3, 6, 9, and 12 months (b) are expressed as mean ± SEM in the 1st, 2nd, and 3rd tertiles of baseline eGFR. The urine albumin-to-creatinine ratio at 0, 3, and 12 months (c) are depicted in the box plot, where the box represents the interquartile range (Q1-Q3).

ACR during the observation period are shown in Fig. 2. Patients in the high baseline eGFR group (1st tertile) exhibited a significant decrease in eGFR during the first 3 months, with no change over the next 9 months. In contrast, patients in the moderate baseline eGFR (2nd tertile and 3rd tertile) groups exhibited no significant change in eGFR during the observation period. Both systolic and diastolic blood pressure decreased equally during the first 3 months in all three groups and remained at this level for the next 9 months, indicating that

the decrease in eGFR observed in the high baseline eGFR group was independent of the decrease in blood pressure. In contrast, the albuminuria that persisted after ARB monotherapy or ARB + CCB combination therapy decreased during the first 3 months only in the high baseline eGFR group.

As demonstrated in Fig. 3, the univariate analysis of the correlation between the baseline eGFR values and the eGFR decrease at the 3rd month showed an inverse correlation between these variables (correlation coefficient = 0.484, $p < 0.01$), indicating that patients with a high baseline eGFR achieved a greater decrease in eGFR by the 3rd month.

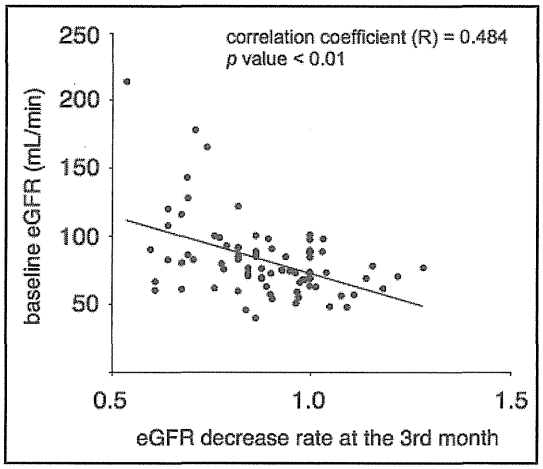

Fig. 3. Correlation between the baseline eGFR and the eGFR decrease ratio at the 3rd month. Individual baseline eGFR values and eGFR decrease ratios at the 3rd month are plotted by a trend line ($n = 93$).

Discussion

This study of patients with ARB- or ARB/CCB-resistant hypertension showed that a significant decrease in the eGFR was achieved by switching to losartan/thiazide combination therapy. We observed that the decrease in the eGFR did not occur in all patients, although it occurred independently of changes in systemic blood pressure in the patients with a high baseline eGFR accompanied by a considerable decrease in the eGFR during the first 3 months. This decrease in eGFR was also associated with a significant decrease in albuminuria, which had persisted even after treatment with either ARB monotherapy or ARB/CCB combination therapy.

The finding of a significant decrease in the eGFR during the first 3 months of losartan/thiazide treatment was in agreement with the results obtained in a previous clinical study [15]. It would be expected that the total body fluid volume would decrease after the addition of thiazide because of the increased elimination of salt. Ito et al. reported that switching to losartan/thiazide combination therapy ameliorated chronic heart failure associated with a decrease in BNP and an increase in Cr levels [16]. These results are compatible with those of the current study. A decrease in body fluid volume and the associated decrease in GFR may be common outcomes after switching to ARB/thiazide treatment.

However, the present study revealed that the decline in ACR was not directly influenced by the decline in body fluid volume and systemic blood pressure. Our stratified analysis of median values of ACR decline during the initial 3 months (3.1 μg/mgCr) showed that the baseline BNP values were not statitically different between the high and low ACR decline groups (17.5 [6.1, 35.9] pg/mL versus 14.9 [8.5, 28.3] pg/mL) although baseline eGFR values were significantly different between the two groups (84.8 ± 29.8 versus 73.9 ± 16.4 mL/min, data not shown in the Result). This observation might indicate that the ACR decline was not directly influenced by the decrease in body fluid volume. The decrease in eGFR values did not occur in all patients in the present study. Our stratified analysis of baseline eGFR values showed a significant decrease only in the patients with the highest baseline values, and the univariate analysis demonstrated an inverse correlation between baseline eGFR values and the eGFR decrease rate at the 3rd month. These results indicate that the switch to losartan/thiazide combination therapy did not cause an equal decrease in eGFR in all patients with ARB-resistant hypertension; this decrease was observed only in the patients with high baseline values or a considerable initial decrease in the eGFR. These patients

would be considered to have glomerular hyperfiltration (GHF), a hemodynamic state that results in podocyte damage [17] and is considered to act as a trigger for a further sequential cascade that leads to glomerular sclerosis [18]. The pathological significance of GHF is that a decrease in high baseline eGFR values does not necessarily indicate the development of renal impairment; rather, it indicates correction of the hyperfiltration state in the glomerulus. The blood pressure-independent decrease in albuminuria, which had persisted even after ARB treatment, in association with the significant decrease in eGFR provides evidence that the decrease in eGFR in patients with high baseline eGFR values appears to be a renoprotective effect.

It has been reported that losartan/thiazide combination therapy may further decrease albuminuria that persists after ARB treatment [19]. In addition, concomitant use of telmisartan and thiazide has been shown to result in a significantly greater decrease in albuminuria compared with telmisartan alone [20]. It is generally accepted that the additive effects of combination therapy with an ARB and thiazide on a further decrease in proteinuria are independent of the decrease in blood pressure. Matsui et al. reported that the concomitant use of olmesartan and thiazide resulted in a more obvious antiproteinuric effect compared to the combination of olmesartan and the CCB azelnidipine, whereas the decline in systemic blood pressure was more evident with the latter combination [21]. The findings of the present study are in agreement with these earlier findings in that the significant decrease in albuminuria was not related to the decrease in blood pressure; rather, it was related to the decrease in the eGFR.

A large-scale clinical study targeting patients without diabetes showed that thiazide treatment alone did not have an antiproteinuric effect [22], indicating that the antiproteinuric effect of ARB/thiazide combination therapy was not caused by thiazide alone but was a consequence of the concomitant use of the ARB. Imanishi et al. reported that the severity of albuminuria did not correlate with systemic blood pressure but showed a significant correlation with glomerular pressure, indicating that an elevated GFR may be involved, at least in part, in the development of albuminuria [23]. It is therefore reasonable to suspect that losartan/thiazide combination therapy provides glomerular protection in patients with an elevated GFR, ultimately leading to further glomerular sclerosis. Zhou et al. [24] demonstrated the superior effects of losartan/thiazide combination therapy on whole kidney and glomerular hemodynamics in spontaneous hypertensive rats (SHRs) treated with NG-nitro-L-arginine methyl ester (L-NAME). These rats are used as an experimental model for hypertensive glomerulopathy. The Zhou study revealed a significant and additive decrease in renal vascular resistance (RVR) and glomerular capillary pressure (P_G) following a concomitant administration of losartan and a thiazide [24]. These results strongly suggest that the combination therapy affected whole kidney and glomerular hemodynamics to an extent that was sufficient to normalize the pressure load in the glomerulus, leading to improved GHF and a decrease in glomerular injury [24]. The clinical advantage of this combination therapy providing glomerular protection by decreasing the GFR has not been demonstrated clearly, although a series of large-scale clinical trials showed that the blood pressure-lowering effect of combination therapy was potentially greater than that of ARB monotherapy [25-28].

Conclusion

The present study of patients with ARB-resistant hypertension and elevated GFR showed that combination ARB/thiazide therapy may normalize glomerular hemodynamics, resulting in a protective effect in the glomerulus. The results of the study may contribute to decision-making in terms of therapeutic strategies for patients with ARB-resistant hypertension.

Conflict of Interests

The authors have no conflict of interest to disclose.

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