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Aliskiren Reduces Morning Blood Pressure in Hypertensive Patients with Diabetic Nephropathy

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Abstract

Diabetic nephropathy (DN) is a leading disease that requires renal replacement therapy. The progression of renal dysfunction in DN is faster than the other renal diseases. While antihypertensive therapy reduces albuminuria, a good indicator for the progression, hypertension in DN is treatment resistant. Among patients with DN who took angiotensin receptor blockers (ARBs), 27 patients who exhibited poor control of albuminuria were enrolled into the study. Angiotensin receptor blocker was exchanged to aliskiren (150–300 mg/d) and clinical parameters were followed for 6 months. Exchange to aliskiren decreased albuminuria (1.57 $\pm$ 0.68 to 0.89 $\pm$ 0.45 g/gCr, $P < .01$) without changes in estimated glomerular filtration rate and office blood pressure (BP). Body weight and hemoglobin A1c were not altered. Aliskiren also reduced plasma renin activity (2.0 $\pm$ 0.9 to 1.2 $\pm$ 0.6 ng/mL/h, $P < .01$). While evening BP was unchanged, morning systolic BP (139 $\pm$ 8 to 132 $\pm$ 7 mm Hg, $P < .01$) and diastolic BP (81 $\pm$ 7 to 76 $\pm$ 6 mm Hg, $P < .05$) were decreased significantly after 6 months. Our results indicated that aliskiren decreased BP, especially morning BP in hypertensive patients with DN. The present data suggest that aliskiren exerts renoprotective actions including reduction in albumin excretion for patients with DN.

Keywords: diabetes, home blood pressure, glomerular hypertension, pulse wave analysis, renin–angiotensin system

INTRODUCTION

Increasing prevalence of diabetes and its complication is a socioeconomical problem all over the world (1). Diabetic retinopathy and diabetic nephropathy (DN) are leading causes of blindness and renal replacement therapy in adults. Diabetic nephropathy is a major cause of morbidity and mortality in patients with type 2 diabetes. The development and progression of DN is associated with poor glycemic control, hypertension, impaired salt sensitivity, and the activation of renin–angiotensin system (RAS). Improvement of these abnormalities should be the therapeutic target for DN. Indeed, numerous clinical trials have reported that strict control of blood glucose, lowering blood pressure (BP), or RAS inhibition is effective in delaying the progression of DN (2,3). Furthermore, the implementation of an aggressive multifactorial management plan as early as possible after the development of DN is important in preventing the progression of the disease, inducing the remission/regression of early DN (4).

The study on patients with DN demonstrated that the addition of aliskiren, a direct renin inhibitor, reduced albuminuria without significant changes in estimated glomerular filtration rate (eGFR) and office BP (5). However, Ito et al. (6) reported that aliskiren reduced both office BP and albuminuria with increases in eGFR in patients with advanced DN. The both studies are surprising, because the former reported renoprotective action of aliskiren that was not associated with BP control, and the latter depicted that RAS inhibition increased eGFR in patients with chronic kidney disease (CKD). To the best of our knowledge, statins constitute only the class of pharmacological agents that may increase eGFR (7).

In this study, we examined the effects of the exchange from an angiotensin receptor blocker (ARB) to aliskiren in hypertensive patients with DN who had exhibited poor control of albuminuria. Our data indicated that aliskiren decreased albuminuria and morning BP without changes in eGFR. The present results suggest that aliskiren exerts strong renoprotection for patients with DN.

METHODS

Prospective studies were performed to characterize renal effects of a direct renin inhibitor, aliskiren, on DN. Hypertensive patients with DN who regularly visited

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our office at Saitama Medical University were enrolled for the study after informed consent was obtained. The study was approved by the Institutional Ethics Committee. Hypertension was defined as systolic blood pressure (SBP) more than 140 mm Hg, diastolic blood pressure (DBP) exceeding 90 mm Hg, and/or administration of antihypertensive drugs. Diabetes is diagnosed by medical history or biochemical data, and DN was diagnosed by persistent abnormality in urine analysis (albuminuria). Serum creatinine and age were used to estimate eGFR with modification of diet in renal disease study equation revised for Japanese (8). As patients persistently excreted albumin above 30 mg/gCr despite treatment with an ARB, they were considered to have poor control of albuminuria according to the guidelines from Japanese Society of Hypertension (http://www.jpnsh.org/data/CKD-kouketsuatsu.pdf [accessed April 18, 2012]), and were considered candidates for the exchange from an ARB to aliskiren. Initially, the dosage of aliskiren was started at 150 mg/day once in the morning, and increased up to 300 mg/day once in the morning when brachial BP was over 130/80 mm Hg. The usage of the other antihypertensive drugs was permitted (Table 1), and the doses of all other drugs remained unchanged during the study.

The following patients were excluded: patients with nephrotic syndrome; patients with severe renal failure including those on dialysis or renal transplantation; patients treated with corticosteroid or immunosuppressant; patients with myocardial infarction or stroke including transient ischemic attack within 6 months; patients with unstable angina pectoris; patients with valvular heart diseases or persistent arrhythmia; patients with aortic aneurysm or aortic replacement with artificial vessels; patients with heart failure or left ventricular ejection fraction of 40% or less; or patients being treated for a disorder based on the opinion of the physician. Patients were educated to take 6 g salt and 0.7 g/kg protein daily (http://www.jpnsh.org/data/CKD-kouketsuatsu.pdf) (9,10).

Table 1. Patients' backgrounds at study entry

Age (y/o)	60 ± 10
Sex (male/female)	15/12
Body weight (kg)	64 ± 11
Height (cm)	160 ± 11
Body mass index (kg/m^2)	25 ± 3
Hemoglobin A1c (%)	6.8 ± 1.1
Duration of diabetes (y)	11 ± 7

ARB used previously	Number of patients	Dose (mg)
Losartan	8	81 ± 26
Candesartan	5	8 ± 3
Irbesartan	4	88 ± 25
Olmesartan	4	23 ± 13
Valsartan	3	93 ± 61
Telmisartan	3	47 ± 31

The other antihypertensives	Number of patients
Calcium antagonists	21
β-Blockers	6
α-Blockers	7
Diuretics	14
Miscellaneous	2

Abbreviation: ARB – angiotensin receptor blocker.

Blood pressure was measured between 9 and 11 am using a mercury sphygmomanometer; the first and the fifth Korotkoff sounds were used to identify SBP and DBP values, respectively. Two measurements were performed on the patient in the sitting position for 5 and 10 minutes, respectively, and the average of the two values on a day was taken as the clinical BP for the purpose of efficacy analysis. Radial artery pulse waveform was also recorded by an automated tonometric system, HEM-9000AI (Omron Healthcare, Kyoto, Japan) with patients in a sitting position (11). The waveform was calibrated automatically using built-in oscillometric brachial sphygmomanometry. The peak and bottom of the radial pressure wave were adjusted to brachial SBP and DBP, respectively. The HEM-9000AI algorithm automatically performed online detection of the second peak (late systolic inflection) based on the second maxima of the fourth derivative of the radial pressure waveform to determine the late or second SBP (SBP2), an index of central BP. SBP2 is well correlated with aortic SBP measured simultaneously by direct catheter method (12). Augmentation index (AI) was calculated by dividing SBP2 – DBP by SBP – DBP. Two measurements were taken 5 minutes apart, and their average was used for analysis. Single personnel performed all waveform measurements to circumvent interobserver errors. After an overnight fast, blood and urine samples were taken before the exchange and 6 months later (13).

After being shown how to measure their own BP, patients were instructed to record their BP at home in the sitting position (14). Blood pressure was measured twice a day; once in the morning before breakfast after voiding within 1 hour of awakening, and once in the evening within 1 hour before going to bed. Each blood pressure was measured after 3–5 minutes rest in the sitting position almost every day. Home blood pressure was measured using semi-automatic devices, which operate on the cuff-oscillometric principle. All devices were calibrated with sphygmomanometer at the time of instruction, and the devices showing BP difference less than 5 mm Hg were applied for the study. Weekly averaged blood pressure was used to assess the divergence of BP by medication.

Data were expressed as means ± SD. Analysis of variance, Student t test, Fisher's exact test and simple regression analysis were used. $P < .05$ was considered as statistically significant.

RESULTS

Patients' backgrounds are detailed in Table 1. The patients who had taken an ARB once in the morning were enrolled from April to October in the year 2010.

We did not restrict the patients regarding ARB usage, and the patients treated with various ARBs were enrolled. At the end of the study, the doses of aliskiren were averaged to 239 ± 75 mg/day. Body weight (to 64 ± 12 kg) and hemoglobin A1c (to 6.7% ± 1.1%) were not altered by this exchange from an ARB to aliskiren.

As shown in Figure 1, the exchange from an ARB to aliskiren altered neither office BP (133 ± 8/78 ± 7 to 132 ± 8/77 ± 6 mm Hg) nor pulse rate (78 ± 8 to 77 ± 8 bpm). However, aliskiren decreased plasma renin activity (2.0 ± 0.9 to 1.2 ± 0.6 ng/mL/h, $n = 27$, $P < .01$) significantly (Figure 2). Figure 3 summarized the effects of exchanging from an ARB to aliskiren on central hemodynamics. The exchange failed to induce changes in SBP2 (118 ± 9 to 117 ± 8 mm Hg). Augmentation index was not significantly varied by the exchange of RAS inhibitors (73 ± 9 to 73 ± 8).

However, albumin excretion (1.57 ± 0.68 to 0.89 ± 0.45 g/gCr, $P < .01$) was decreased by the exchange from an ARB to aliskiren (Figure 4) without changes in eGFR (35 ± 20 to 35 ± 19 mL/min/1.73 cm^2). Because albumin excretion may not follow normal distribution, it was converted to natural logarithm and analyzed again. Statistical significance was also attained using this method (0.34 ± 0.50 to −0.24 ± 0.53 ln[g/gCr], $P < .01$). Moreover, the incidence of hyperkalemia (serum potassium over 5.5 mEq/L or prescribed potassium exchange resin) was not increased by the exchange (by Fisher's exact test). At the start of the study, 5 out of 27 patients exhibited hyperkalemia. At the end of the study, 6 patients exhibited hyperkalemia. Indeed, plasma aldosterone concentration (193 ± 97 to 186 ± 98 pg/mL) was not reduced by the exchange from an ARB to aliskiren (Figure 2).

The exchange of RAS inhibitors resulted in improvement in home BP (Figure 5). Morning systolic (139 ± 8 to 132 ± 7 mm Hg, $P < .01$) and diastolic blood pressures (81 ± 7 to 76 ± 6 mm Hg, $P < .05$) were reduced by the exchange from an ARB to aliskiren. However, significant changes were not seen in evening BP (129 ± 8/75 ± 7 to 128 ± 7/73 ± 7 mm Hg). To facilitate the comparison, changes in albumin excretion by exchanging from an ARB to aliskiren were plotted against variations in morning SBP

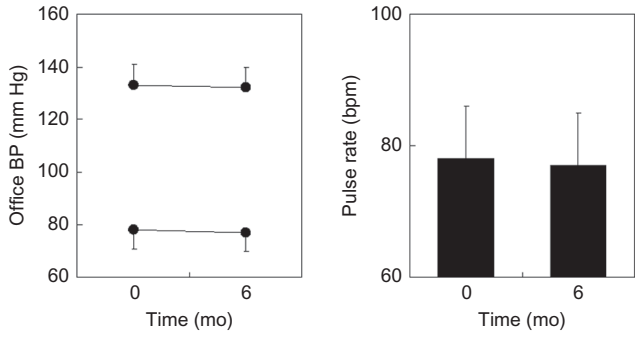

Figure 1. The effects of the exchange from an ARB to aliskiren on office BP and pulse rate. Abbreviations: ARB – angiotensin receptor blocker; BP – blood pressure.

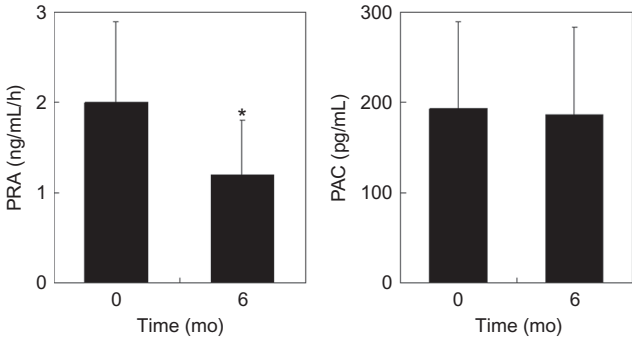

Figure 2. The influences of the exchange from an ARB to aliskiren on PRA and PAC. *Significant difference from basal value. Abbreviations: ARB – angiotensin receptor blocker; PAC – plasma aldosterone concentration; PRA – plasma renin activity.

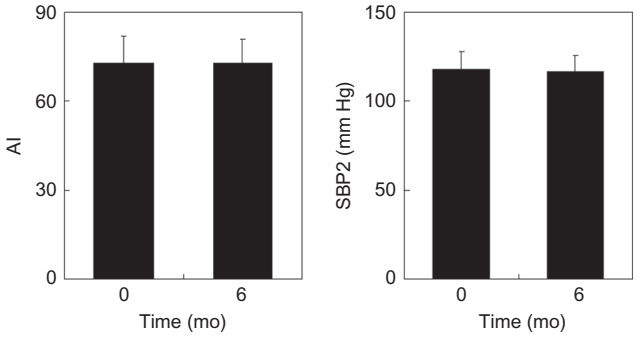

Figure 3. The impacts of the exchange from an ARB to aliskiren on AI and central blood pressure (SBP2). Abbreviations: AI – augmentation index; ARB – angiotensin receptor blocker.

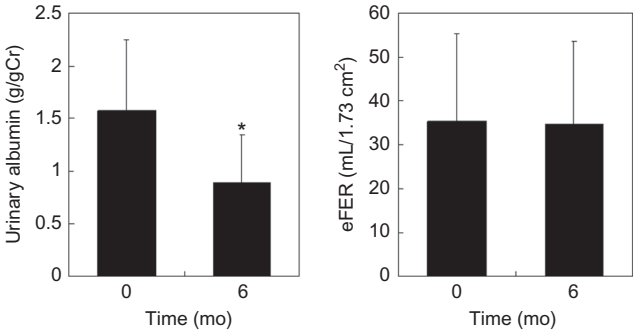

Figure 4. The effects of the exchange from an ARB to aliskiren on urinary albumin excretion and eGFR. *Significant difference from basal value. Abbreviations: ARB – angiotensin receptor blocker; eGFR – estimated glomerular filtration rate.

(Figure 6). Simple regression analysis revealed a significant positive correlation (slope = 0.121 g/gCr/mm Hg, $R^2 = 0.38$, $P < .01$). Reductions in albuminuria were the greater as aliskiren obtained the larger morning BP drops.

DISCUSSION

The characteristics of DN constitute afferent arteriolar dilation leading to glomerular hypertension and hyperfiltration (15). Investigators reported various mechanisms

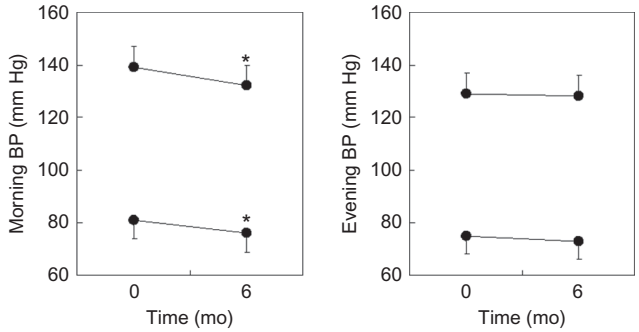

Figure 5. The influence of the exchange from an ARB to aliskiren on morning BP and evening BP, respectively. *Significant difference from basal value. Abbreviations: ARB – angiotensin receptor blocker; BP – blood pressure.

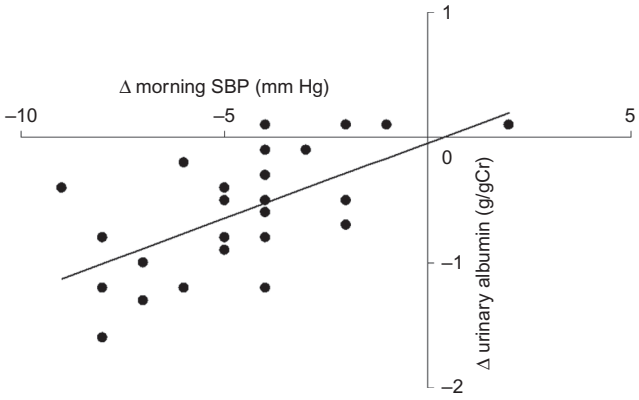

Figure 6. Relationship between changes in morning BP and changes in urinary albumin. The line indicates simple regression line. Abbreviation: BP – blood pressure.

for afferent arteriolar dilation, including decreased activity of calcium channels, increased open probability of potassium channels, and decreased tubuloglomerular feedback signaling (16,17). It is well known that angiotensin directly elicits preferential efferent arteriolar constriction (18). However, angiotensin is also a positive modulator of tubuloglomerular feedback, providing strong constrictor tone for afferent arterioles. Thus, an incomplete RAS inhibition may not improve glomerular hypertension, but rather worsen it.

Diabetes not only causes microangiopathy but also macroangiopathy (19). Pathology of arteriosclerosis in diabetes involves atherosclerosis and medial calcification. Both of them increase arterial stiffness, and elevate reflection pressure and then central arterial pressure (20). The Anglo-Scandinavian cardiac outcomes trial studies showed that combination treatment with amlodipine and converting enzyme inhibitor showed better cardiovascular prognosis than that with β-blocker and diuretics, and that the former therapy decreased central BP or AI more than the latter though brachial BPs were similar between groups (21,22). We have demonstrated that decreasing central BP or AI reduced proteinuria in CKD patients (11). However, the present data indicated that aliskiren did not preferentially decrease central BP or AI more than brachial BP in DN patients, compared to ARBs. Thus, our results suggest that aliskiren and ARB share similar influences on central hemodynamics when brachial BP was indistinguishably controlled.

Aliskiren has a very long half-life exceeding 40 hours, possessing long-acting antihypertensive effects (23). Indeed, Palatini et al. (24) described that the magnitude of worsening BP control by a missed dose of aliskiren was less than that of irbesartan. Our data constitute new demonstrations that aliskiren reduced morning BP in patients with DN, compared to ARBs. We enrolled DN patients who had taken various ARBs. It was reported that irbesartan had longer half-life than the other ARBs in humans (25). However, in this study, the degree of reductions in morning BP by the exchange was similar when that was compared among original ARBs. The differing doses of ARBs may account for the discrepancy. The present results suggest that aliskiren induces long-lasting RAS inhibition in DN, being useful in getting fair BP control over 24 hours.

Various possible mechanisms may account for the present observation that aliskiren decreased albuminuria without changes in eGFR (Figure 7). Although RAS inhibitors improve insulin resistance (26), glycemic control was maintained throughout this study. It is unlikely that metabolic improvement by exchanging to aliskiren contributed to decreasing albuminuria in this study. Persistent inhibition of RAS with aliskiren could recover nephrin expression. Angiotensin induces podocyte injury to reduce nephrin, allowing albumin leak from glomeruli (27). Decreases in systemic BP or efferent arteriolar resistance by aliskiren should reduce glomerular capillary pressure, reducing albuminuria. Angiotensin elevates BP and induces preferential efferent arteriolar constriction (18). Aliskiren would ameliorate mesangial injury, thereby maintaining eGFR by increasing ultrafiltration coefficient. Angiotensin contracts mesangial cells, decreasing glomerular surface area (28). Volume expansion leads to an increase in glomerular filtration rate dependent on an increment of glomerular (renal) blood flow in rats (29). Similar mechanism might be important in maintaining eGFR in DN patients, as exchanging to aliskiren could increase renal blood flow. Aliskiren may delay the progression of tubular damage in DN. Angiotensin promotes tubulointerstitial alterations, facilitating renal fibrosis (30).

Blood pressure usually showed daily alterations even in normotensive people; high in the morning, getting lower in the afternoon, and lowest during sleep (31). We have previously demonstrated that morning SBP predicts the progression of renal dysfunction in DN patients (14). Consistent with the above, the present observations indicated that aliskiren reduced albuminuria, and further provided the evidence that reductions in morning SBP by aliskiren were associated with those of albuminuria. Albuminuria predicts renal and cardiovascular prognosis (32). Collectively, although final conclusions should be waited for ongoing larger scale studies

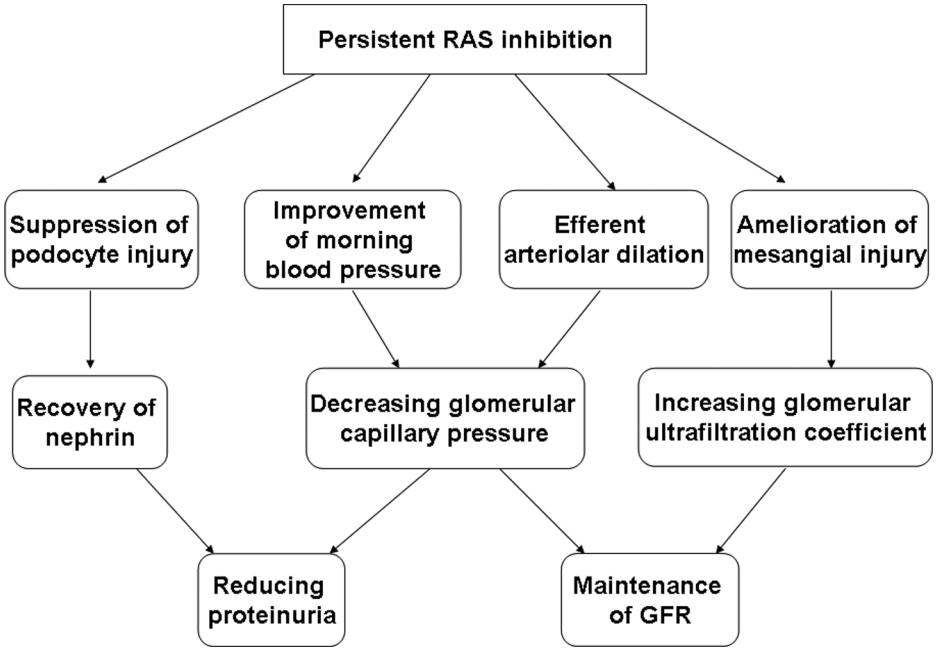

Figure 7. Possible glomerular mechanisms that allow aliskiren to decrease albuminuria without changes in glomerular filtration rate. Abbreviation: GFR – glomerular filtration rate.

with longer observation period including Alpen Glow (aliskiren prevents the eGFR in Japanese hypertensive patients with CKD), the present results suggest that aliskiren exerts strong renal and cardiovascular protection for patients with DN.

This study has limitations. First, the study has only one arm, lacking in randomized time control. Blood pressure shows seasonal variations. Please note that patient enrollment was not performed in winter. Second, the observation period was relatively short. To assess the effects of aliskiren on eGFR, the study with longer period would be required. Third, great cautions should be required to extend present results to advanced DN, since strong RAS inhibition may induce acute renal failure in patients with intravascular volume contraction such as nephrotic DN (http://www.jpnsh.org/data/CKD-kouketsuatsu.pdf). Fourth, plasma aldosterone was not decreased by aliskiren despite reduction of renin activity in this study. In addition to RAS, serum potassium regulates aldosterone levels.

In summary, aliskiren decreased morning BP in hypertensive patients with DN, exerting renoprotective actions including reduction in albumin excretion.

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