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A New Vasculitis Activity Score for Predicting Death in Myeloperoxidase-Antineutrophil Cytoplasmic Antibody-Associated Vasculitis Patients

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Key Words
Myeloperoxidase-antineutrophil cytoplasmic antibody · Birmingham Vasculitis Activity Score · Japanese Vasculitis Activity Score · Odds ratio · Receiver operating characteristic · Mortality rate

Abstract
Background/Aims: Myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA)-positive microscopic polyangiitis patients with renal involvement have been shown to have a progressive clinical course. In this study, we compared the clinical utility of the Japanese Vasculitis Activity Score (JVAS) with the Birmingham Vasculitis Activity Score (BVAS) for predicting death in patients with MPO-ANCA-associated renal involvement. ***Methods:*** Sixty-nine patients with MPO-ANCA-associated vasculitis with renal involvement (22 males and 47 females, age 69.8 ± 8.7 years) were enrolled in this study. We retrospectively investigated which score was better for predicting the poor prognosis of patients. ***Results:*** The mortality rate of the patients within 2 years after disease onset was 33% (23/69). JVAS was not correlated with BVAS. Univariate logistic regression analysis for death showed that the odds ratio (OR) of JVAS was statistically significant (OR 1.76, 95% confidence interval, CI, 1.29–2.41, $p < 0.001$), while that of BVAS was not (OR 1.07, 95% CI 0.98–1.16, $p = 0.14$). Moreover, a multivariate model showed that JVAS was an independent determinant of death (OR 1.59, 95% CI 1.12–2.25, $p = 0.009$). The area under the receiver operating characteristic curve for JVAS was 0.778, which was significantly larger ($p = 0.02$) than that for BVAS (0.586). The estimated optimal cut-off point of JVAS for the prediction of death was 5. At this point, the sensitivity was 82.6% and the specificity was 60.9%. ***Conclusion:*** We demonstrated that compared with BVAS, JVAS was a simpler and more reliable measure for predicting death in patients with MPO-ANCA-associated vasculitis with renal involvement.

Introduction

Antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV) is characterized by necrotizing inflammation of small vessels, which comprise three different diseases entities: Churg-Strauss syndrome, mi-

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Table 1. Scoring of JVAS

Parameter score	Serum creatinine mg/dl	Age years	Pulmonary lesion	Serum CRP mg/dl
0	<3.0	<60	–	<2.6
1	3.0–6.0	60–69		2.6–10
2	≥6.0	≥70	+	≥10.0
3	Dialysis therapy			

CRP = C-reactive protein.

croscopic polyangiitis, and Wegener's granulomatosis [1, 2]. ANCA specific for myeloperoxidase (MPO-ANCA) or proteinase 3 (PR3-ANCA) is implicated in the pathogenesis of AAV [3]. In vitro, ANCA can activate primed neutrophils to release inflammatory mediators and, in conjunction with the alternative pathway of the complement system, damage and lyse endothelial cells [4, 5]. In vivo, transfer of splenocytes from MPO-deficient mice immunized with mouse MPO into wild-type mice resulted in intrinsic pauci-immune renal vasculitis in these animals [5]. In addition, Wegener's granulomatosis is closely associated with PR3-ANCA, while MPO-ANCA is clinically involved in necrotizing small vessel vasculitis such as microscopic polyangiitis and Churg-Strauss syndrome [6, 7].

Although the estimated annual incidence of AAV in Japan [8] is similar to that in Europe [9, 10] and the USA [11], there are some regional differences in ANCA subsets and renal histology; in Japan, MPO-ANCA-positive microscopic polyangiitis is more common than PR3-ANCA-associated glomerulonephritis. Glomerulonephritis in relation to microscopic polyangiitis has more characteristics of chronic injury than that in PR3-ANCA-associated Wegener's granulomatosis [12]. Further, MPO-ANCA-positive microscopic polyangiitis patients with renal involvement have been shown to have a progressive clinical course, which can often lead to renal death [13, 14].

There are a couple of scores that could evaluate disease activity of AAV [13, 15, 16]. Among them, the Birmingham Vasculitis Activity Score (BVAS) [15] is one of the most commonly used and standard assessments for disease activity in AAV. Indeed, several clinical reports have shown that BVAS is useful for evaluating disease activity and therapeutic response or relapse in patients with AAV [15–17]. Further, a higher BVAS value was reported to be one of the independent poor prognostic factors of patient survival in AAV [18]. However, as far as we know, there are no studies examining the clinical utility of the BVAS value for predicting prognosis of MPO-ANCA-positive microscopic polyangiitis patients with renal involvement. Further, it is difficult to assess disease activity and prognosis by BVAS because its weighted score is based on clinical symptoms and signs in 9 separate organ systems. As MPO-ANCA-positive microscopic polyangiitis is more common in rapidly progressive glomerulonephritis in Japan than in Europe [8], and the Japanese Vasculitis Activity Score (JVAS), proposed by the Research Committee of Intractable Vasculitis Syndrome of the Ministry of Health, Labor and Welfare of Japan, could evaluate disease activity with a sum score of 4 clinical parameters, including age, serum creatinine and C-reactive protein (CRP) levels, and pulmonary lesion [19] (table 1), and is simpler than BVAS, we compared the utility of BVAS with JVAS for predicting prognosis of MPO-ANCA-associated microscopic vasculitis with renal involvement in Japan.

Patients and Methods

From 1995 to 2009, 69 patients (22 males and 47 females, age 69.8 ± 8.7 years) were diagnosed as new-onset MPO-ANCA-associated microscopic vasculitis with renal involvement in our hospitals and then followed up. All patients were found to be positive for MPO-ANCA, negative for PR3-ANCA or anti-glomerular basement membrane antibody. Fifty-five patients (79.7%) were classified as microscopic polyangiitis and 14 patients (20.3%) as renal limited vasculitis, according to the definition of the Chapel Hill Consensus Conference [20, 21] and/or the criteria of the European Systemic Vasculitis Study Group [22].

Medical records at the time of admission were obtained. The following values were evaluated: hemoglobin, serum creatinine, blood urea nitrogen (BUN), CRP, JVAS, BVAS, proteinuria, and hematuria. Almost all patients (97%) received standard immunosuppressive treatments (intravenous injection of methylprednisolone, oral corticosteroid or immunosuppressants). All patients provided written informed consent to undergo renal biopsy and to participate in the study, and were followed up until death or 2 years after the first admission. The current study received approval from the Ethical Committee of Kurume University Hospital.

Statistical Analysis

Data are appropriately shown as mean ± standard deviation (SD) or median (minimum–maximum). Differences between characteristics of survivors and non-survivors were tested by using χ^2 test, Fisher's exact test, Student's t test or Welch's t test. The association between JVAS and BVAS was assessed by Spearman rank correlation coefficient. The odds ratio (OR) of these two parameters for death was estimated by logistic regression analysis. The outcome event was all-cause mortality within 2 years after the initial diagnosis of MPO-ANCA-associated vasculitis with renal in-

volvement. To evaluate the clinical utility of JVAS and BVAS values for predicting the death in our patients, we calculated the sensitivity and specificity of these scores in receiver operating characteristic (ROC) analysis. A two-sided value of $p < 0.05$ was considered to be statistically significant. All statistical analyses were performed using the SAS version 9.2 (SAS Institute, Cary, N.C., USA).

Results

Demographic and Clinical Data

The clinical characteristics of the patients are shown in table 2. Serum creatinine, CRP, JVAS and BVAS were: 2.9 (0.47–15.7) mg/dl, 6.9 (0.09–27.4) mg/dl, 5.0 ± 2.1, and 17 (12–36), respectively. Systemic symptoms such as malaise, myalgia, arthralgia/arthritis, high fever and weight loss were observed in the majority of patients (89.1%), and 1.7% of the patients had pulmonary involvement, 74.5% nervous symptoms, 36.4% eyes and ear nose tract symptoms, 21.8% abdominal symptoms, 18.2% skin lesions, and 9.1% cardiovascular symptoms.

Correlates of Mortality with Clinical Variables

Almost all patients received immunosuppressive therapy for AAV such as intravenous injection of methylprednisolone and oral administration of corticosteroid and cyclophosphamide. As shown in table 3, among our patients there were no significant differences in immunosuppressive treatments between survivors and non-survivors. Of the 69 patients enrolled, 23 (33.3%) died within 2 years after the initial diagnosis of MPO-ANCA-associated vasculitis with renal involvement. The number of deaths within 3, 3–6, 6–12, and 12–24 months after the initial diagnosis were 13, 2, 5 and 3, respectively. Ten patients died from active vasculitis, 7 from severe interstitial pneumonia or pulmonary hemorrhage, and 3 from enteritis. Ten patients died from infection. One died from stroke, and 2 patients from unknown causes. Twenty patients underwent hemodialysis (HD), of which 12 patients died and 4 needed maintenance HD, while 4 did not require HD therapy during the follow-up periods.

As shown in figure 1, the mortality rate increased with age, and age was a significant risk factor of death [OR per 5-year increment 1.50, 95% confidence interval (CI) 1.07–2.13, p = 0.018]. Fifty percent of the patients older than 76 years died within 2 years after the initial diagnosis.

We next examined the correlation of JVAS with BVAS in our patients. As shown in figure 2, JVAS was not correlated with BVAS (p = 0.26, p = 0.02). The OR of JVAS for death (1.76, 95% CI 1.29–2.41) was statistically significant ($p < 0.001$), while that of BVAS was not (1.07, 95% CI 0.98–1.16, p = 0.14; table 4). Bivariate logistic regression analysis revealed that JVAS (OR 1.74, 95% CI 1.26–2.40, $p < 0.001$), but not BVAS (OR 1.05, 95% CI 0.95–1.16, p = 0.37) was significantly associated with death. Further, in age- and BVAS-adjusted multivariate logistic regression analysis, JVAS was found to be an independent determinant of death in our AAV subjects (OR 1.59, 95% CI 1.12–2.25, p = 0.009). The area under the curve (AUC) of ROC for JVAS was 0.78 (95% CI 0.66–0.89), which was significantly larger (p = 0.02) than that for BVAS (0.59, 95% CI 0.44–0.73; fig. 3). The estimated optimal cutoff point of JVAS for the prediction of death was 5. At this point, the sensitivity was 82.6% and the specificity was 60.9%. Using this cutoff point, patients were categorized into high- and low-risk groups. Multivariate logistic re-

Table 2. Clinical characteristics of the patients

Number (% of female)	69 (68%)
Age, years	69.8 ± 8.7
Hemoglobin, g/dl	9.0 ± 1.6
Creatinine, mg/dl	2.9 (0.47–15.7)
Serum urea nitrogen, mg/dl	36.8 (9.0–140.0)
C-reactive protein, mg/dl	6.9 (0.09–27.4)
JVAS	5.0 ± 2.1
BVAS	17 (12–36)
Proteinuria, g/day	0.85 (0.0–9.0)
Hematuria, %	100

Results are appropriately given as the mean ± SD or the median (range, minimum–maximum).

Table 3. Treatment substances between survivor and non-survivors

	Survivors	Non-survivors	p value
Age, years	67.91 ± 8.34	73.39 ± 8.55	0.015
Males/females, n	14/32	8/15	0.72
Methylprednisolone intravenous injection for 3 days, mg/kg/day	14.49 ± 5.78	14.27 ± 5.90	0.90
Corticosteroid (oral administration), mg/kg/day	0.79 ± 0.20	0.81 ± 0.27	0.72
Cyclophosphamide (oral administration), mg/kg/day	0.96 ± 0.20	0.98 ± 0.49	0.87

Table 4. OR of mortality in MPO-ANCA-associated vasculitis patients with renal involvement

	Crude model		Bivariate model[1]		Multivariate model[2]	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
JVAS	1.76 (1.29–2.41)	<0.001	1.74 (1.26–2.40)	<0.001	1.59 (1.12–2.25)	0.009
BVAS	1.07 (0.98–1.16)	0.14	1.05 (0.95–1.16)	0.37		

[1] Bivariate model includes JVAS and BVAS simultaneously.
[2] Multivariate model includes JVAS, BVAS and age.

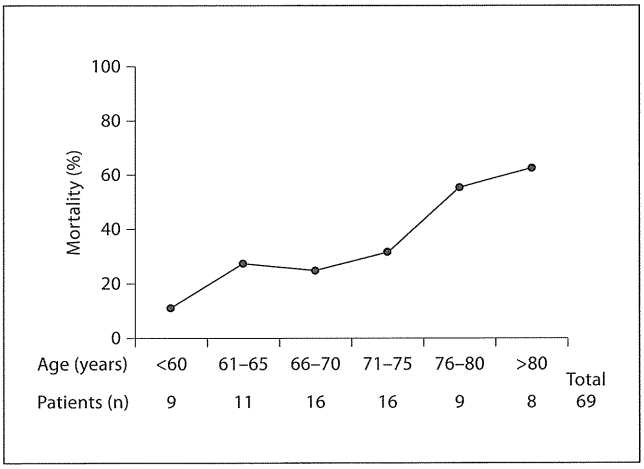
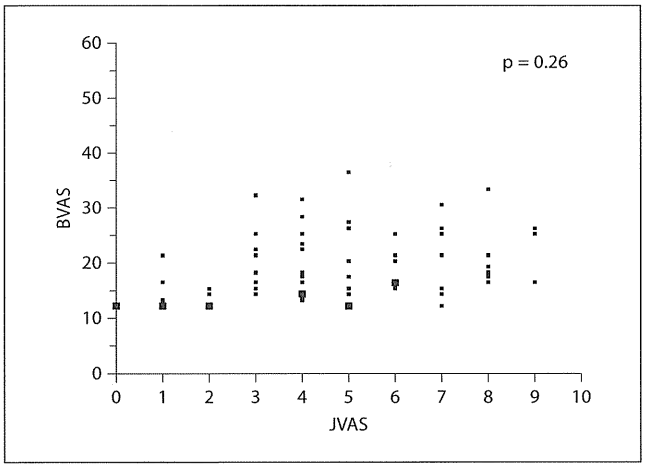


Fig. 1. ■■■.



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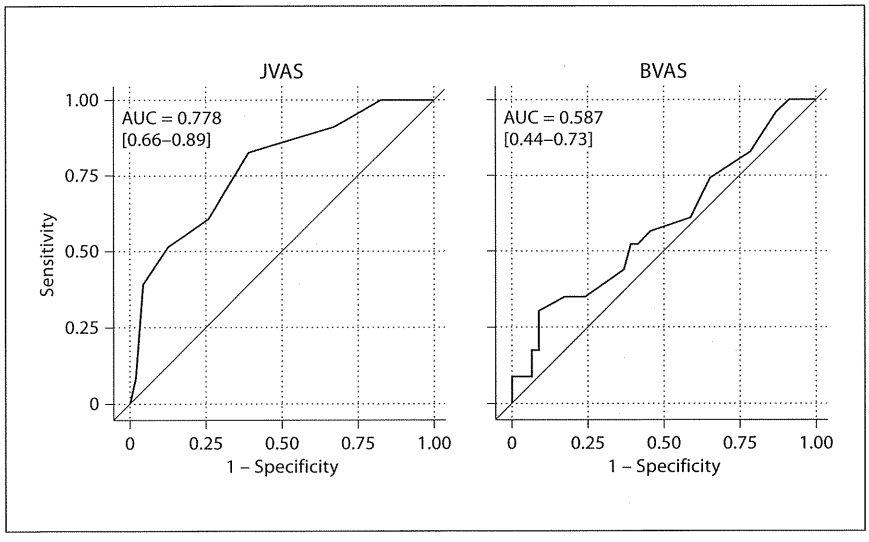

Fig. 3. ■■■.

gression analysis showed that OR for death of the high-risk group was 6.2 (95% CI 1.7–21.6, p = 0.005) after adjustment for age.

Discussion

In this study, we demonstrated for the first time that, although age was significantly associated with death in patients with MPO-ANCA-associated vasculitis with renal involvement, JVAS was an independent predictor for poor prognosis within 2 years of initial diagnosis in these subjects. BVAS is a more precise measurement of the dissemination of vasculitis than JVAS, but its clinical use has potential limitations because (1) to evaluate the 68-item lists in 9 separate organ systems is complex in a clinical setting, and (2) weights of 1–3 were determined empirically [23]. Therefore, the present results suggest that compared with BVAS, assessment by JVAS [19] may be more feasible for evaluating disease severity and death in MPO-ANCA-associated microscopic vasculitis with renal involvement in Japan.

The mortality rate was reported to be significantly associated with the BVAS value in systemic vasculitis patients, including polyarteritis nodosa, microscopic polyangiitis and Churg-Strauss syndrome [16]. Further, in the multivariate Cox regression, the BVAS value on admission was one of the significant predictors of mortality in AAV [18]. However, BVAS was not associated with death in our subjects. The differences in subject population (systemic vasculitis vs. MPO-ANCA-associated vasculitis with renal involvement) and ethnicity could account for the discrepant results. Itabashi et al. [17] reported that age but not BVAS value at the onset of the disease was associated with death in Japanese subjects with AAV, thus supporting our speculation. In addition, renal injury is more severe in MPO-ANCA-positive microscopic polyangiitis patients [12]. Microscopic polyangiitis patients are also reported to have a tendency toward increased mortality compared with other types of AAV [16, 18]. Therefore, BVAS may not be a suitable tool for predicting the mortality in the severe form of AAV with rapidly progressive glomerulonephritis. Harper and Savage [24] previously reported that the 5-year survival rate of ANCA-positive glomerulonephritis patients was 60–80%, and age and renal dysfunction were associated with poor prognosis; their results are consistent with our present findings. Intensive therapy with steroids and cyclophosphamide resulted in complete remission rates of greater than 90% [24], but it is unlikely that immunosuppressive drugs could confound the present results because among our patients there were no significant differences in immunosuppressive treatments between the survivors and non-survivors.

Components of items evaluated by JAVS and BVAS differ [15, 19]. JVAS is composed of items such as age and CRP, whereas BVAS includes symptoms and signs of extrapulmonary-renal organ vasculitis. The present study showed that JVAS, but not CRP is associated with death and is independent of age. These observations suggest the clinical utility of assessment using JVAS, especially in the evaluation of both age and CRP for predicting mortality in MPO-ANCA-positive glomerulonephritis patients. Further, symptoms and signs of extrapulmonary-renal organ vasculitis may not necessarily reflect fetal organ damage. To evaluate them could not increase the sensitivity and specificity of BVAS for the prediction of death in MPO-ANCA-associated vasculitis patients with renal involvement. Little et al. [25] reported that the greatest threat to patients with AAV in the first year of therapy is from adverse events rather than active vasculitis. At disease onset before therapy, JVAS was able to predict poor prognosis in our subjects; therefore, it may be a useful tool to determine which patients should be intensively treated with immunosuppressants. In other words, patients with MPO-ANCA-associated renal involvement whose JVAS value is ≥ 5 points may have to be treated more intensively.

The potential limitations of our study were that it was retrospective and had a small sample size. Further, we could not totally exclude the possibility that immunosuppressive treatments could affect the relationship between the JVAS value at disease onset and poor prognosis in our subjects. In addition, whether JVAS could be a good predictor of poor prognosis for other ethnic patients remains unclear. Further large-scale prospective studies will be required to address this issue.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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Review

Role of advanced glycation end products (AGEs) and oxidative stress in vascular complications in diabetes ☆

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ABSTRACT

Background: A non-enzymatic reaction between reducing sugars and amino groups of proteins, lipids and nucleic acids contributes to the aging of macromolecules, whose process has been known to progress at an accelerated rate under hyperglycemic and/or oxidative stress conditions. Over a course of days to weeks, early glycation products undergo further reactions such as rearrangements and dehydration to become irreversibly cross-linked, fluorescent protein derivatives termed advanced glycation end products (AGEs).
Scope of review: In this paper, we review the role of AGE–oxidative stress axis and its therapeutic interventions in vascular complications in diabetes.
Major conclusions: AGEs elicit oxidative stress generation and subsequently cause inflammatory and thrombogenic reactions in various types of cells via interaction with a receptor for AGEs (RAGE), thereby being involved in vascular complications in diabetes. In addition, mitochondrial superoxide generation has been shown to play an important role in the formation and accumulation of AGEs under diabetic conditions. Further, we have recently found that a pathophysiological crosstalk between AGE–RAGE axis and renin–angiotensin system (RAS) could contribute to the progression of vascular damage in diabetes.
General significance: These observations suggest that inhibition of AGE–RAGE–oxidative stress axis or blockade of its interaction with RAS is a novel therapeutic strategy for preventing vascular complications in diabetes.

1. Introduction

Diabetic retinopathy and nephropathy are the leading causes of acquired blindness and end-stage renal disease (ESRD), respectively, which could account for disabilities in patients with diabetes [1,2]. Also, in Japan, about 14,000 people per year become ESRD due to diabetes, and its number is still increasing. Further, cardiovascular disease (CVD) accounts for about 30–40% of death in diabetic patients in Japan, and average life span in diabetic patients is about 9–13-years shorter, compared with non-diabetic subjects. Two landmark clinical studies, Diabetes Control and Complication Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) [3,4] have shown that intensive blood glucose or blood pressure (BP) control significantly reduces the risk for the development and progression of vascular complications in diabetes. However, strict control of blood glucose is often difficult to maintain and may increase the risk of hypoglycemia. Moreover, current therapeutic options for the treatment of hypertension are far from satisfactory in diabetes. Therefore, to develop novel therapeutic strategies that specifically target vascular complications in diabetes is actually desired.

Various hyperglycemia-elicited metabolic and hemodynamic derangements such as increased formation of advanced glycation end products (AGEs), enhanced production of reactive oxygen species (ROS), stimulation of protein kinase C (PKC), and the activation of the renin–angiotensin system (RAS) have been proposed to contribute to vascular complications in diabetes [1,2]. However, which molecular pathway is the most dominant one remains to be clarified. Meanwhile, a recent follow-up study after DCCT, called DCCT-Epidemiology of Diabetes Interventions and Complications (DCCT-EDIC) Research, has provided us with a clue to the solution of this problem. In this trial, all patients had received intensive therapy. Therefore, the differences of blood glucose control between original intensive therapy group and conventional one were abolished a couple of years after the end of DCCT trial. However, those who had been on original intensive therapy still maintained their advantage in terms of reduced risk of the development and progression of diabetic nephropathy and retinopathy during the EDIC periods, despite hyperglycemia [5,6]. Intensive therapy during the DCCT resulted in decreased progression of intima-media thickness and subsequently reduced the risk of nonfatal myocardial infarction, stroke, or death from cardiovascular disease by 57% 11 years after the end of the trials [7,8]. Further, a recent follow-up study of UKPDS, called UKPDS80, also has shown that benefits of an intensive therapy in patients with type 2 diabetes are sustained after the cessation of the trial [9]. In this

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study, despite an early loss of glycemic differences between original intensive therapy group and conventional one, a continued reduction in microvascular risk and emergent risk reductions for myocardial infarction and death from any cause were observed during 10 years of post-trial follow-up [9]. These findings demonstrate that so-called 'metabolic memory' could cause chronic abnormalities and exert carry-over effects in diabetic vessels that are not easily reversed, even by subsequent, relatively good control of blood glucose. In other words, these observations suggest a long-term beneficial influence of early metabolic control, that is, legacy effect on the risk of vascular complications and death in both type 1 and type 2 diabetic patients. Among the various biochemical pathways implicated in vascular complications in diabetes, biochemical nature of AGEs and their mode of action are most compatible with the concept of 'metabolic memory' [10–12].

The concept of AGEs was first built up by a French chemist, L.C. Maillard a century ago [10–12]. He reported that brown-fluorescent products were generated when amino acids were heated with reducing sugars. Since then, food chemists have long studied this process as a source of flavor, color, and texture changes in cooked or stored foods. But, in 1980s, it was realized that this process could also occur *in vivo* [10–12].

Reducing sugars such as glucose can react non-enzymatically with amino groups of proteins to form Amadori products [12–14]. Over the course of days to weeks, these Amadori products undergo further rearrangement reactions to form irreversibly cross-linked senescent macroprotein derivatives called AGEs. The formation and accumulation of AGEs have been known to progress at an accelerated rate under diabetes. AGEs are hardly degraded and remain for a long time in diabetic tissues even if glycemic control is improved. There is accumulating evidence that AGEs elicit oxidative stress generation in various types of cells through the interaction with a receptor for AGEs (RAGE) and subsequently evoke inflammatory and thrombogenic reactions, thereby playing an important role in the development and progression of vascular complications in diabetes [14–18]. Further, AGEs are reported to up-regulate RAGE expression in various cell types and induce sustained activation of transcriptional factor nuclear factor-κB (NF-κB) [17]. Therefore, it is conceivable that the AGE–RAGE-induced oxidative stress generation further potentiates the formation and accumulation of AGEs and subsequent RAGE overexpression in diabetes. These positive feedback loops between AGEs and RAGE-downstream pathways could make a vicious cycle, thus providing a mechanistic basis for understanding why there could exist the phenomenon of 'metabolic memory' in vascular complications in diabetes. In addition, we have recently found that a pathophysiological crosstalk between AGE–RAGE axis and RAS could contribute to the progression of vascular damage in diabetes as well [19]. Taken together, these observations suggest that inhibition of AGE–RAGE–oxidative stress axis or blockade of its interaction with RAS is a novel therapeutic strategy for preventing vascular complications in diabetes. In this paper, we review the pathophysiological role of AGE–oxidative stress axis and its therapeutic interventions in vascular complications in diabetes.

2. Role of AGEs, RAS and pigment epithelium-derived factor (PEDF) in diabetic retinopathy

2.1. Pericyte loss and dysfunction

Pericytes are elongated cells of the mesodermal origin, wrapping around and along endothelial cells (ECs) of small vessels [20]. The earliest histopathological hallmark of diabetic retinopathy is loss of pericytes [20]. In parallel with loss of pericytes, several characteristic changes including thickening of the basement membrane, hyperpermeability, and microaneurysm formation are observed [20]. Since pericytes have played an important role in the maintenance of microvascular homeostasis, loss of pericytes could predispose the vessels to angiogenesis, thrombogenesis and EC injury, thus leading to full-blown clinical expression of diabetic retinopathy [1].

Retinal pericytes accumulate AGEs during diabetes [21], which would be expected to have a detrimental influence on pericyte survival and function in diabetes. Indeed, AGE–RAGE-mediated ROS generation has been shown to induce apoptotic cell death of retinal pericytes by increasing the activity of caspase-3, a key enzyme in the execution of apoptosis [22,23]. Further, we have found that beraprost sodium, a prostacyclin analog or forskolin, an activator of adenylate cyclase protects against the AGE-induced pericyte apoptosis by suppressing ROS generation and subsequent RAGE overexpression [24]. Since cyclic AMP elevating agents were known to block ROS generation in neutrophils by inhibiting reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity [25], NADPH oxidase might be a source of ROS production elicited by AGEs and be a target of beraprost sodium.

Pericyte dysfunction has also been considered one of the characteristic features of the early phase of diabetic retinopathy [1]. AGEs act on pericytes to stimulate vascular endothelial growth factor (VEGF) expression [23]. VEGF is a specific mitogen to ECs, also known as vascular permeability factor, and is thought to be a pivotal factor in the pathogenesis of proliferative diabetic retinopathy [26]. Furthermore, retinal VEGF level was found to be associated with the breakdown of the blood–retinal barrier, thus being involved in vascular hyperpermeability in background retinopathy [27,28]. These observations suggest that AGEs might be involved in diabetic retinopathy by inducing VEGF overexpression in pericytes as well.

The local RAS is activated under diabetes [29]. Angiotensin II (Ang II) stimulated intracellular ROS generation, decreased DNA synthesis and simultaneously up-regulated VEGF mRNA levels in cultured retinal pericytes, all of which are blocked by the treatment with telmisartan, an Ang II type 1 receptor blocker (ARB) or an antioxidant, *N*-acetylcysteine (NAC) [30,31]. Further, Ang II has been shown to potentiate the deleterious effects of AGEs on pericytes by inducing RAGE expression [32]. *In vivo*, AGE injection stimulated RAGE expression in the eye of spontaneously hypertensive rats, which was blocked by telmisartan. *In vitro*, Ang II-type 1 receptor-mediated ROS generation elicited RAGE gene expression in retinal pericytes through NF-κB activation [32]. In addition, Ang II augmented the AGE-induced pericyte apoptosis [32]. These findings suggest the pathophysiological crosstalk between the AGE–RAGE–oxidative stress axis and the RAS in pericyte loss and dysfunction.

Pigment epithelium-derived factor (PEDF) is a glycoprotein that belongs to the superfamily of serine protease inhibitors with complex neurotrophic, neuroprotective, anti-angiogenic, anti-oxidative and anti-inflammatory properties, any of which could potentially be exploited as a therapeutic option for the treatment of vascular complications in diabetes [33–37]. PEDF inhibited the AGE-induced ROS generation and subsequently prevented apoptotic cell death of pericytes by restoring bcl-2 gene expression [23]. Further, we have found that anti-PEDF antibodies inhibit the growth-stimulating effects of co-cultured ECs on pericytes [38,39]. These observations suggest that PEDF could be an EC-derived mitogen or survival factor for retinal pericytes. In addition, since Ang II-type 1 receptor interaction decreased PEDF mRNA levels in ECs, suppression of EC-derived PEDF production by Ang II may also be involved in progression of diabetic retinopathy. Taken together, these findings suggest that blockade of the pathophysiological crosstalk between the AGE–RAGE system and the RAS or substitution of PEDF proteins might be a promising therapeutic strategy for preventing pericyte loss and dysfunction at early phase of diabetic retinopathy (Fig. 1).

In animal studies, treatment of diabetic rats for 26 weeks with aminoguanidine, an inhibitor of AGE formation, prevented a 2.6-fold accumulation of AGEs at branching sites of pre-capillary arterioles and thereby prevented abnormal EC proliferation and significantly

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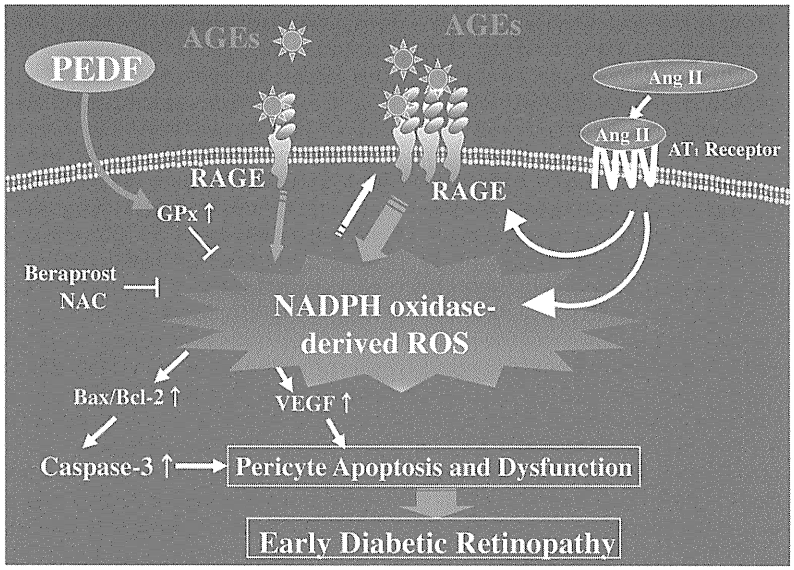

Fig. 1. Role of AGE–RAGE axis and RAS in early diabetic nephropathy. Ang II, Angiotensin II; GPx, glutathione peroxidase; AT1 receptor, Ang II type 1 receptor; NAC, *N*-acetylcysteine.

diminished pericyte dropout [40]. The derivative of vitamin B_6, pyridoxamine, a specific post-Amadori inhibitor, has also been shown to prevent retinal capillary dropout in experimental diabetic retinopathy [41]. Moreover, an anti-oxidant, α-lipoic acid administration decreased retinal 8-hydrooxy-2′deoxyguanosine (8-OHdG) and nitrotyrosine levels and subsequently inhibited retinal capillary cell apoptosis in streptozotocin-induced diabetic rats [42]. These observations further suggest the active participation of the AGE–RAGE-mediated ROS generation in pericyte loss in diabetic retinopathy.

2.2. Hyperpermeability, inflammation, thrombosis and angiogenesis

Vascular permeability in the retina plays a key role in a wide array of sight-threatening eye diseases such as diabetic retinopathy, and VEGF has been known as a major etiologic factor that increases retinal vascular permeability [28,43,44]. Using a model system for non-proliferative diabetic retinopathy, Liu et al. found that PEDF effectively abated VEGF-induced vascular permeability [43]. PEDF may inhibit the VEGF-induced vascular hyperpermeability via suppression of NADPH oxidase-driven ROS generation [45,46]. Further, we have found that PEDF inhibits AGE-signaling to vascular hyperpermeability in rats [28]. Intravenous administration of AGEs to normal rats not only increased retinal vascular permeability by stimulating VEGF expression, but also decreased retinal PEDF levels [28]. Simultaneous treatments with PEDF inhibited the AGE-elicited VEGF-mediated permeability by down-regulating mRNA levels of p22phox and gp91phox, membrane components of NADPH oxidase and subsequently decreasing retinal levels of an oxidative stress marker, 8-OHdG. PEDF also inhibited the AGE-induced vascular hyperpermeability in ECs by suppressing VEGF expression, which was evaluated by transendothelial electrical resistance. In addition, PEDF decreased ROS generation in AGE-exposed ECs by suppressing NADPH oxidase activity via down-regulation of mRNA levels of p22phox and gp91phox. This led to blockade of the AGE-elicited Ras activation and NF-κB-dependent VEGF gene induction in ECs. These results indicate that the central mechanism for PEDF inhibition of the AGE-signaling to vascular permeability is by suppression of NADPH oxidase-mediated ROS generation and subsequent VEGF expression. Since vitreous level of PEDF was significantly lower in patients with diabetic macular edema (DME) than in non-diabetic patients and diabetic patients without retinopathy, and its level was significantly lower in patients with hyperfluorescent DME than in those with minimally fluorescent DME [47], PEDF may play a protective role against vascular hyperpermeability in diabetic retinopathy.

AGEs are implicated in the process of vascular inflammation as well [48]. AGEs have been shown to increase leukocyte adhesion to cultured retinal microvascular ECs by inducing intracellular cell adhesion molecule-1 (ICAM-1) expression [49]. This phenomenon is also apparent in non-diabetic mice infused with preformed AGEs, which results in significant leukostasis and blood–retinal barrier dysfunction in these mice. Since retinal VEGF has been found to induce ICAM-1 expression, thus leading to leukostasis and breakdown of blood–retinal barrier *in vivo* [50], the AGE-elicited pro-inflammatory reactions could be partly mediated by VEGF induction. Moreover, we have recently found that AGEs increase monocyte chemoattractant protein-1 (MCP-1) and ICAM-1 expression in microvascular ECs through intracellular ROS generation, thereby inducing T-cell adhesion to ECs [51,52]. Since MCP-1 levels in the vitreous fluids are correlated with the severity of proliferative diabetic retinopathy [53], AGEs would be one of the key pro-inflammatory factors for the progression of diabetic retinopathy. In addition, AGEs not only decrease endothelial nitric oxide synthase (NOS) mRNA levels in ECs, but also reduce NO (nitric oxide) bioavailability by inactivating NO to form peroxynitrite via ROS generation [54]. Reduced synthesis and/or bioavailability of NO may accelerate vascular injury in diabetic retinopathy because NO exerts anti-inflammatory and anti-thrombogenic properties *in vivo* [54].

PEDF inhibits the AGE-induced ICAM-1 and MCP-1 induction as well as NO suppression in ECs by blocking the NADPH oxidase-mediated ROS generation [28,52,54–56]. *In vivo*, administration of PEDF or pyridoxal phosphate, an AGE inhibitor decreased retinal levels of 8-OHdG, an oxidative stress marker and subsequently suppressed ICAM-1 expression and retinal leukostasis in diabetic rats [55]. Further, intravenous administration of AGEs to normal rats increased ICAM-1 gene expression and retinal leukostasis, which were blocked by PEDF [55]. PEDF inhibited diabetes- or AGE-induced RAGE overexpression by blocking ROS-mediated NF-κB activation as well [56]. Intravitreal injection of PEDF was also found to reduce vascular hyperpermeability in rat models of diabetes, which was associated with decreased levels of retinal inflammatory factors, including VEGF, MCP-1 and ICAM-1 [57]. Since retinal PEDF expression was decreased under diabetic conditions including diabetic situations [28,58], PEDF

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may be a therapeutic target for blocking hyperpermeability and vascular inflammation in diabetic retinopathy as well.

Several researchers have reported that AGEs could augment ADP- or serotonin-induced platelet aggregation via oxidative stress generation [59,60]. Further, AGEs inhibit prostacyclin production and induce plasminogen activator inhibitor-1 (PAI-1) in ECs through an interaction with RAGE [61]. These observations suggest that AGEs have the ability to cause platelet aggregation and fibrin stabilization, which could lead to retinal ischemia and VEGF induction, thereby promoting diabetic retinopathy [62,63]. Since AGEs decrease intracellular cyclic AMP concentrations in ECs and that cyclic AMP agonists such as beraprost sodium and forskolin reduce the AGE-induced PAI-1 production, cyclic AMP elevating agents may also have a therapeutic potential in diabetic retinopathy. In addition, we have found that AGEs directly stimulate growth and tube formation of microvascular ECs, the key steps of angiogenesis, through the interaction with RAGE [64–66]. Our research findings have suggested that AGE–RAGE interaction could increase VEGF gene expression in microvascular ECs by NADPH oxidase-mediated ROS generation and subsequent NF-κB activation via Ras-MAPK pathway [64–66].

ARBs and angiotensin-converting enzyme inhibitors (ACEIs) may block the formation of reactive carbonyl precursors for AGEs *in vitro* by chelating transition metals and inhibiting hydroxyl radicals, at both pre- and post-Amadori steps [67]. In addition, we have found that an ARB, olmesartan inhibits the AGE-evoked inflammatory and angiogenic reactions in ECs by suppressing RAGE expression via its antioxidative properties [68]. These findings suggest that RAS inhibitors may exert beneficial effects on diabetic retinopathy partly via its inhibitory properties on the AGE–RAGE axis.

3. Role of AGEs, RAS and PEDF in diabetic nephropathy

3.1. Mesangial cell loss and dysfunction

As the case in pericytes, AGEs induce apoptotic cell death and VEGF expression in human cultured mesangial cells [69,70]. Mesangial cells occupy a central anatomical position in the glomerulus, playing crucial roles in maintaining structure and function of glomerular capillary tufts [69,70]. They actually provide structural support for capillary loops and modulate glomerular filtration by its smooth muscle activity [70]. Therefore, it is conceivable that the AGE-induced mesangial apoptosis and dysfunction may contribute in part to glomerular hyperfiltration, an early renal dysfunction in diabetes. Several experimental and clinical studies support the pathological role for VEGF in diabetic nephropathy. Indeed, antibodies raised against VEGF have been reported to improve hyperfiltration and albuminuria in streptozotocin-induced diabetic rats [71]. Inhibition of VEGF also prevents glomerular hypertrophy in Zucker diabetic fatty rats, a model animal of type 2 diabetes with obesity [72]. Further, urinary VEGF levels are positively correlated with urinary albumin to creatinine ratio, and inversely associated with creatinine clearance in type 2 diabetic patients [73]. These observations suggest that VEGF overproduction elicited by AGEs may be involved in hyperpermeability and albuminuria at early phase of diabetic nephropathy.

Moreover, we have found that AGEs stimulate MCP-1 expression in mesangial cells as well [69,70]. Increased MCP-1 expression associated with monocyte infiltration in mesangial areas has been observed at early phase of diabetic nephropathy [74]. Plasma MCP-1 was positively correlated with urinary albumin excretion rate in type 1 diabetic patients as well [75]. Therefore, AGE accumulation in the glomerulus could be implicated in the initiation of diabetic nephropathy via MCP-1 induction. Since we have recently found that glucagon-like peptide-1 inhibits AGE-induced vascular cell adhesion molecule-1 (VCAM-1) mRNA levels in ECs and mesangial cells by suppressing RAGE expression via cyclic AMP elevation [76], cyclic AMP may also block the AGE-signaling pathways in mesangial cells.

3.2. Glomerulosclerosis and tubulointerstitial fibrosis

AGEs stimulate insulin-like growth factor-I, -II, platelet-derived growth factor (PDGF) and transforming growth factor-β (TGF-β) in mesangial cells, which in turn mediate production of type IV collagen, laminin and fibronectin [70,77,78]. AGEs induce TGF-β overexpression in both podocytes and proximal tubular cells as well [70,78]. Ziyadeh et al. reported that long-term treatment of type 2 diabetic model mice with blocking antibodies raised against TGF-β suppressed excess matrix gene expression, glomerulosclerosis, and prevented the development of renal insufficiency [79]. These observations suggest that the AGE-induced TGF-β expression plays an important role in the pathogenesis of glomerulosclerosis and tubulointerstitial fibrosis in diabetic nephropathy.

AGE formation on extracellular matrix proteins alters both matrix–matrix and cell–matrix interactions, which is also involved in the pathogenesis of diabetic glomerulosclerosis. For example, non-enzymatic glycation of type IV collagen and laminin reduce their ability to interact with negatively charged proteoglycans, increasing vascular permeability to albumin [70]. Furthermore, AGE formation on various types of matrix proteins impairs their degradation by matrix metalloproteinases, contributing to basement membrane thickening and mesangial expansion, hallmarks of diabetic nephropathy [54]. AGEs including glycoxidation or lipoxidation products such as carboxymethyllysine (CML), pentosidine, malondialdehyde-lysine accumulate in the expanded mesangial matrix and thickened glomerular basement membranes of early diabetic nephropathy, and in nodular lesions of advanced disease, thus further suggesting the active involvement of AGEs for advanced diabetic nephropathy [80].

In vivo, administration of AGE-albumin to normal healthy mice for 4 weeks induces glomerular hypertrophy with overexpression of type IV collagen, laminin B1 and TGF-β genes [81]. Chronic infusion of AGE-albumin to otherwise healthy rats leads to focal glomerulosclerosis, mesangial expansion, and albuminuria [82]. Further, diabetic RAGE-overexpressing mice have been found to show progressive glomerulosclerosis with renal dysfunction, compared with diabetic littermates lacking the RAGE transgene [83]. AGEs and RAGE were present to enhanced degrees in the diabetic kidney, and blockade of the AGE–RAGE interaction decreased podocyte VEGF expression and albuminuria, which was associated with decreased numbers of inflammatory cells to, and reduced TGF-β expression, in the glomerulus [84]. In addition, diabetic homozygous RAGE null mice failed to develop significantly increased mesangial matrix expansion or thickening of the glomerular basement membrane [84]. Deletion of RAGE is also reported to prevent diabetic nephropathy in the OVE26 type 1 mouse, a model of progressive glomerulosclerosis and decline of renal function [85]. Taken together, these findings suggest that activation of AGE–RAGE system contributes to expression of VEGF and enhanced attraction/activation of inflammatory cells in the diabetic glomerulus, thereby setting the stage for mesangial activation and TGF-β production; processes which converge to cause albuminuria and glomerulosclerosis.

3.3. Crosstalk of the AGE–RAGE system with the RAS

Since Ang II increases intracellular ROS generation in renal cells, it may stimulate the production of AGEs and further augment the AGE–RAGE system in diabetic kidney [86,87]. There is accumulating *in vitro*- and *in vivo*-evidence to suggest the pathophysiological crosstalk between the RAS and AGE–RAGE axis in diabetic nephropathy. Indeed, AGEs activate mesangial TGF-β–Smad system in cultured mesangial cells via autocrine production of angiotensin II and subsequent activation of type 1 receptor, which could probably lead to mesangial cell hypertrophy and glomerular sclerosis in diabetic nephropathy [77]. Further, we have found that an ARB, irbesartan blocks the AGE–

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RAGE-induced ROS generation, apoptosis, MCP-1, PAI-1 and TGF-β overexpression in proximal tubular cells, thus protecting against tubulointerstitial inflammation, fibrosis and atrophy in diabetic nephropathy [88] (Fig. 2). In addition, irbesartan was recently found to prevent the AGE-induced podocyte apoptosis and injury as well; anti-apoptotic effect of irbesartan on AGE-exposed podocytes was stronger than that of valsartan (Fig. 3). Since there is accumulating evidence that podocyte apoptosis and injury are implicated in the progression of diabetic nephropathy [89], blockade of the crosstalk between the AGE–RAGE system and the RAS by RAS inhibitors such as irbesartan is a therapeutic target for preventing diabetic nephropathy.

In animal models, Forbes et al. have reported that an ACEI, ramipril decreases circulating and renal tissue levels of AGEs in experimental diabetic nephropathy [86]. Candesartan, an ARB, reduces AGEs accumulation and subsequent albuminuria by down-regulating the NADPH oxidase p47phox component and inducible NOS expression and by attenuating RAGE expression in type 2 diabetic KK/Ta mouse kidneys [90]. Thomas et al. reported that valsartan, other ARB reduced renal levels of AGEs in AGE-injected animals, whereas Ang II infusion accelerated the formation and accumulation of AGEs in both glomeruli and renal tubules in their models [87]. In addition, we have found that administration of olmesartan medoxomil inhibits the increase of systolic and diastolic blood pressure and urinary *N*-acetyl-beta-D-glucosaminidase activity and prevent glomerulosclerosis in exogenously AGE-injected rats [91]. In humans, an ACEI, ramipril treatment has been shown to result in a mild decline of fluorescent non-CML-AGEs and malondialdehyde concentrations in non-diabetic nephropathy patients [92]. In type 2 diabetic subjects, a low-dose of valsartan treatment was reported to decrease serum AGE levels in a blood pressure-independent manner [93]. These observations suggest that there could exist a pathophysiological crosstalk between the AGE–RAGE system and the RAS in diabetic nephropathy. Blood pressure-lowering independent beneficial effects of RAS inhibitors on diabetic nephropathy [94] could be ascribed at least in part to its inhibitory effects of the AGE–RAGE–oxidative stress system.

3.4. Role of peroxisome proliferator-activated receptor-γ (PPARγ)

Several papers have shown that PPARγ agonists block the deleterious effects of AGEs and exert beneficial actions on diabetic nephropathy [95,96]. Indeed, activation of PPARγ by rosiglitazone inhibited AGE-induced inducible NOS expression, nitrite release, fibronectin and type IV collagen production by mesangial cells [95,96]. Rosiglitazone also attenuated the AGE-induced interleukin-8 and soluble ICAM-1 generation by proximal tubular epithelial cells through the suppression of signal transducer and activator of transcription [97]. Further, rosiglitazone was reported to inhibit renal extracellular matrix accumulation, fibronectin, type IV collagen and PAI-1 production and subsequently reduce proteinuria in AGE-injected rats [97].

Suppression of RAGE expression may be a molecular target of PPARγ agonists [19,97–106]. Marx et al. reported that stimulation of human ECs with PPARγ agonists such as rosiglitazone and pioglitazone decreased basal as well as tumor necrosis factor-alpha-induced RAGE expression via suppression of NF-κB activation. They also showed that PPARγ agonists decreased AGE-induced MCP-1 expression in ECs [98]. Further, we have found that telmisartan, an ARB, down-regulates RAGE expression and suppresses its downstream signalings in various cell types through its unique PPARγ-modulating ability [100–104]. Indeed, telmisartan was found to reduce RAGE mRNA levels and subsequently inhibit superoxide generation as well as MCP-1 expression in mesangial cells, all of which were prevented by GW9662, an inhibitor of PPARγ [102]. In addition, we have recently found that nifedipine, but not amlodipine, a control calcium channel blocker, decreased RAGE mRNA levels and subsequently reduced ROS generation, and VCAM-1 and MCP-1 expression in AGE-exposed mesangial cells, all of which were blocked by the simultaneous treatment of GW9662 [106]. Although nifedipine did not affect expression levels of PPARγ, they increased the PPARγ transcriptional activity in mesangial cells. Taken together, these observations provide unique beneficial aspect of telmisartsan and nifedipine on diabetic nephropathy; it could work as an anti-inflammatory agent against AGEs by suppressing RAGE expression in cultured mesangial cells via PPARγ activation.

There are a couple of papers to suggest the protective effects of PEDF against diabetic nephropathy. PEDF was decreased at both mRNA and protein levels in the kidney of diabetic rats, whereas TGF-β and fibronectin levels were increased in the same diabetic kidneys [107]. *In vitro*-studies showed that high concentrations of glucose significantly decreased PEDF secretion in human mesangial cells, thus suggesting that hyperglycemia is a direct cause of the PEDF decrease in the kidney. Further, PEDF blocked the high-glucose-induced overexpression of TGF-β, a major pathogenic factor in diabetic nephropathy, and fibronectin in mesangial cells [107]. Therefore,

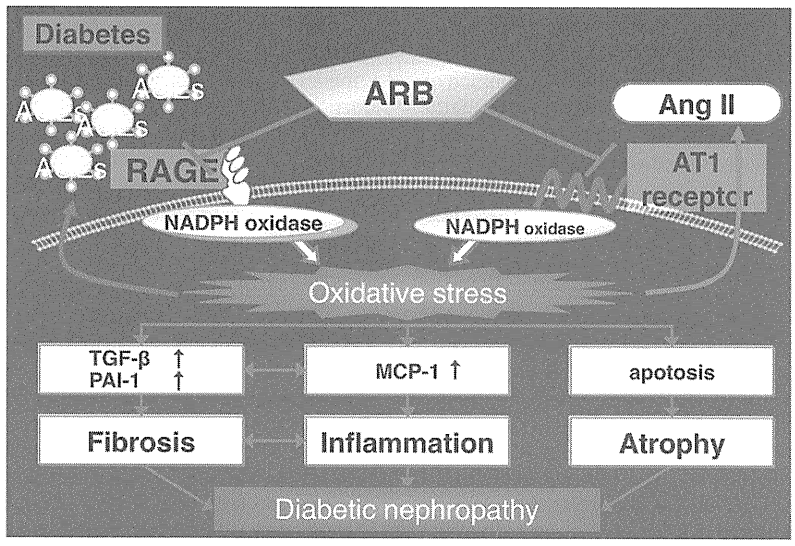

Fig. 2. Role of AGE–RAGE axis and RAS in tubular injury in diabetic nephropathy.

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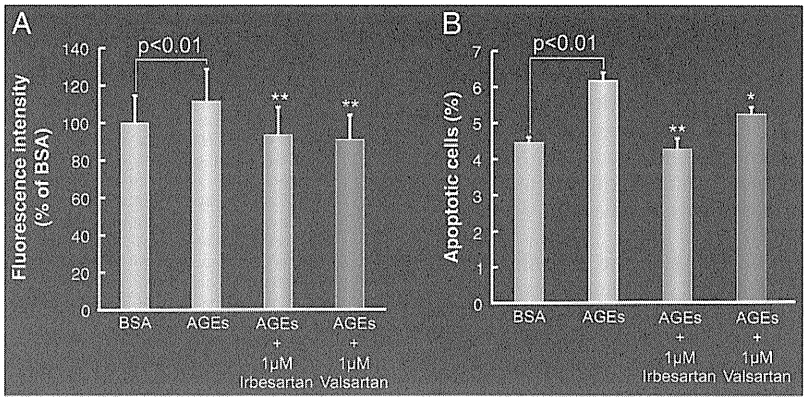

Fig. 3. Effects of irbesartan on ROS generation (A) and apoptotic cell death (B) in immortalized mouse podocytes [126]. Differentiated podocytes were treated with 100 μg/ml AGE–bovine serum albumin (BSA) (AGEs) or non-glycated BSA (BSA) in the presence or absence of 1 μM irbesartan (a generous gift from Dainippon Sumitomo Pharma, Tokyo, Japan) or valsartan (Toronto Research Chemicals Inc., Ontario, Canada) for 16 h (A) or 24 h (B). (A) Then the cells were incubated with phenol red free Dulbecco's Modified Eagle Medium containing 3 μM dihydroethidium (DHE) (Molecular Probes Inc., Eugene, OR, USA) as described previously [109]. Intensity of DHE staining in 5 different field of each sample was analyzed by microcomputer-assisted image J. (B) Apoptotic cells were measured by flow cytometry as described previously [109]. For every histogram, 5000 podocytes were counted to evaluate the percentage of apoptotic cells. * and **, $p<0.05$ and $p<0.01$ compared to the value with AGEs alone, respectively.

decreased expression of PEDF in diabetic kidneys may contribute to extracellular matrix overproduction and the development of diabetic nephropathy. *In vivo*, overexpression of PEDF was found to alleviate microalbuminuria, to prevent the expression of two major fibrogenic factors, TGF-β and connective tissue growth factor (CTGF), and to significantly reduce the production of an extracellular matrix protein in the diabetic kidney [108]. These findings suggest that PEDF functions as an endogenous anti-TGF-β and anti-fibrogenic factor in the kidney. A therapeutic potential of PEDF in diabetic nephropathy is supported by its down-regulation in diabetes; its prevention of the overexpression of TGF-β, CTGF, and extracellular matrix proteins in diabetic kidney; and its amelioration. Moreover, we have recently found that PEDF inhibits the AGE-induced RAGE gene expression and reduced ROS generation, inflammatory and fibrogenic gene expression (MCP-1, TGF-β, fibronectin and type IV collagen gene expression) in cultured human proximal tubular cells [109]. PEDF administration inhibited oxidative stress generation and RAGE, MCP-1 and TGF-β gene induction in diabetic kidneys as well [109]. Given that RAGE is a cell receptor for AGEs that mainly mediates the biological effects of these macroproteins and that ROS generation works as a second messenger of RAGE-downstream pathways for MCP-1 and TGF-β gene induction [1,17,88,106], the results suggest that RAGE gene suppression in tubular cells would be a central mechanism by which PEDF inhibited inflammatory and fibrogenic reactions in early phase of diabetic nephropathy. Since PEDF activates PPARγ signaling in variety of cells [110,111], PEDF may reduce RAGE gene expression in diabetic kidney via PPARγ.

3.5. Clinical trial

Double-blinded, placebo-controlled, randomized clinical trials of aminoguanidine (Pimagedine®), a prototype therapeutic agent for the prevention of AGE formation (ACTION; A Clinical Trial In Overt Nephropathy), were designed to evaluate the safety and efficacy of aminoguanidine in retarding the rate of progression of renal disease in patients with overt diabetic nephropathy. Pimagedine® therapy reduced the 24-h total urinary proteinuria and prevented the decrease in glomerular filtration rate and the progression of diabetic retinopathy in patients with type 1 diabetes [112]. The effects of Pimagedine® on serum creatinine doubling were found not to be significant; serum creatinine doubled in 26% of the placebo-treated patients and in 20% of those who received Pimagedine ($p=0.099$). However, this study is noteworthy in providing the first clinical proof of the concept that inhibiting AGE formation can result in a clinically important attenuation of the serious complication of diabetes. Reported side effects of aminoguanidine in clinical therapy were gastrointestinal disturbance, abnormalities in liver function tests, flu-like symptoms, and a rare vasculitis [112]. Further clinical trials of aminoguanidine were terminated due to safety concerns.

4. Role of AGEs and RAS in diabetic macroangiopathy

AGEs formed on the extracellular matrix result in decreased elasticity of vasculatures, and quench NO, which could mediate defective endothelium-dependent vasodilatation in diabetes [113]. Indeed, increased oxidative stress generation induced by AGEs inactivates NO to form peroxynitrite. AGE modification of low-density lipoprotein (LDL) exhibits impaired plasma clearance and contributes significantly to increased LDL *in vivo*, thus being involved in atherosclerosis [114]. Binding of AGEs to RAGE results in generation of intracellular ROS generation and subsequent activation of the redox-sensitive transcription factor NF-κB in vascular wall cells, which promotes the expression of a variety of atherosclerosis-related genes, including ICAM-1, VCAM-1, MCP-1, PAI-1, tissue factor, VEGF, and RAGE [1,17].

Bone marrow-derived circulating endothelial progenitor cells (EPCs) are critical to vascular repair [115]. Diabetes is associated with endothelial dysfunction, decreased EPC function and mobilization, which could contribute to accelerated atherosclerosis and increased risk for CVD in diabetic patients [115]. AGEs enhance apoptosis and suppress migration and tube formation of late EPCs through the interaction with RAGE via down-regulation of Akt and cycloxygenase-2 [116]. AGEs have also been shown to cause a reduction of length growth and EPC incorporation into the sprouts in association with RAGE overexpression and p38 mitogen-activated protein kinase (MAPK) activation [117]. Furthermore, AGE-modification of vascular substrates impair vascular repair by inhibiting EPC adhesion, spreading and migration via glycation of Arg–Gly–Asp (RGD) motif of fibronectin [118]. In addition, C-reactive protein (CRP) has been found to increase oxidative stress generation, alter antioxidant defenses, and subsequently induces apoptosis of EPCs via RAGE induction [119]. These observations suggest that AGE–RAGE axis affects collateral artery formation after myocardial ischemia directly and indirectly by impairing vascular repair and inactivating NO, a mediator of angiogenic signal of VEGF [120]. Recently, skin autofluorescence, an established noninvasive measure of AGE accumulation, but not serum pentosidine, was independently associated with low circulating EPCs in subjects with ESRD [121].

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Further, AGEs have the ability to induce osteoblastic differentiation of microvascular pericytes, which would contribute to the development of vascular calcification in accelerated atherosclerosis in diabetes as well [122]. The interaction of the RAS and the AGE–RAGE system in the development of and progression of diabetic vascular complication has also been proposed. The AGE–RAGE interaction augments angiotensin II-induced smooth muscle cell proliferation and activation, thus being involved in accelerated atherosclerosis in diabetes [123].

Smooth muscle cell proliferation, migration, and neointimal expansion upon arterial injury were strikingly suppressed in homozygous RAGE null mice compared with those observed in wild-type littermates [124]. These data highlight key roles for RAGE in modulating smooth muscle cell properties after injury and suggest that RAGE is a logical target for suppression of untoward neointimal expansion consequent to arterial injury. Diabetic RAGE(−/−)/apoE(−/−) mice had significantly reduced atherosclerotic plaque area, which is associated with attenuation of leukocyte recruitment, decreased expression of pro-inflammatory mediators, reduced oxidative stress and AGE accumulation [125].

5. Conclusion

Inhibition of the AGE formation and blockade of the AGE–RAGE system and its crosstalk with the RAS may become novel therapeutic strategies in vascular complications of diabetes.

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Clinical Investigations

PREVENTION

Beneficial Cardiometabolic Actions of Telmisartan Plus Amlodipine Therapy in Elderly Patients With Poorly Controlled Hypertension

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ABSTRACT

Background: There is a growing body of evidence that blood pressure (BP) level is one of the major determinants of cardiovascular morbidity and mortality in individuals, including elderly people. However, to achieve a target BP level in the elderly is more difficult compared with patients aged <65 years. Current guidelines recommend combination drug therapy with different modes of action for the treatment of elderly patients with moderate hypertension (HT). However, the optimal combination regimen is not well established in elderly HT.

Hypothesis: We hypothesized that combination therapy of telmisartan plus amlodipine would exert favorable cardiometabolic actions in elderly HT.

Methods: Seventeen elderly patients with essential HT who failed to achieve a target home BP level with treatment of 5 mg amlodipine plus 80 mg valsartan or 8 mg candesartan for at least 2 months were enrolled. Then the patients were assigned to replace their valsartan or candesartan with 40 mg telmisartan. The subjects were instructed to measure their own BP at home every day during the study periods.

Results: Replacement of valsartan or candesartan by telmisartan in amlodipine-treated elderly hypertensive patients showed a significant reduction in morning home systolic BP and evening home systolic and diastolic BP at 12 weeks. Switching to telmisartan significantly increased serum adiponectin level.

Conclusions: Our present study suggests that combination therapy with telmisartan plus amlodipine may exert more beneficial cardiometabolic effects in elderly patients with HT compared with valsartan or candesartan plus amlodipine treatment.

Introduction

The number of elderly individuals, defined as persons aged ≥ 65 years, keeps increasing in developed continues.[1,2] Hypertension (HT) is highly prevalent in the elderly population. More than 60% of people aged ≥ 65 years in the United States and Japan have HT.[1,2] There is a growing body of evidence that blood pressure (BP) level is one of the major determinants of cardiovascular morbidity and mortality in individuals, including elderly people.[2–6] Indeed, a positive association between elevation of BP level and increased risk of future cardiovascular events is observed in elderly individuals, and the absolute risk of cardiovascular disease is higher in the aged population.[2–6] Therefore, aggressive control of BP is also desirable in the elderly with HT.

Elderly HT is characterized by impairment of fluid volume and electrolyte regulation, decrease in the baroreceptor reflex, and coexistence of atherosclerosis, insulin resistance, and glucose intolerance.[2,3] Therefore, to achieve a target BP level in the elderly is more difficult compared with patients aged <65 years. The Japanese Society of Hypertension recommends calcium channel blockers (CCBs), angiotensin-converting enzyme (ACE) inhibitors, angiotensin II type 1 receptor blockers (ARBs), or low-dose thiazide diuretics as the first-line drugs for the management of elderly HT, and if BP control is insufficient with monotherapy, combination therapy with these agents should be conducted.[2] Combination therapy with ACE inhibitors/ARBs plus CCBs has an advantage in the lack of metabolic adverse effects, whereas diuretics are associated with hyperglycemia, hyperuricemia, dyslipidemia, and

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hypokalemia.[2,3] Furthermore, recently, 2 landmark trials, Avoiding Cardiovascular Events in Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) and Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint (ONTARGET), have revealed that combination therapy with ACE inhibitors/ARBs plus CCBs is also effective and well-tolerated in elderly HT.[7,8] However, an optimal combination regimen is not well established in elderly HT. Because risk of cough from ACE inhibitors is relatively high in East Asian patients compared with white patients,[9] ARBs are more popular than ACE inhibitors in Japan. Therefore, we examined here in elderly patients whose BP level at home was uncontrolled by combination treatment with 5 mg amlodipine plus 80 mg valsartan or 8 mg candesartan for at least 2 months whether additional BP lowering could be achieved by switching to 5 mg amlodipine plus 40 mg telmisartan. We also investigated whether switching from valsartan or candesartan to telmisartan could have favorable metabolic effects in elderly hypertensive patients.

Methods

Subjects

This was a prospective, open-label, 12-week study. Patients aged ≥ 65 years with essential HT not achieving a target home BP level were recruited from multiple centers in Japan.[10,11] All patients were taking 5 mg amlodipine plus 80 mg valsartan (n = 5) or 8 mg candesartan (n = 12) for at least 2 months. A screening period of up to 2 to 4 weeks was used to assess eligibility and to eliminate prior medications. Finally, 17 eligible patients (14 males and 3 females; mean age, 74.5 ± 7.3 y) were assigned to replace their valsartan or candesartan with 40 mg telmisartan. During the study period, subjects were instructed not to change their lifestyles and to continue taking the same dose of any concomitant drugs. We excluded any patients with secondary HT, chronic liver disease, severe chronic heart failure, and those who had recent (<6 mo) acute coronary syndromes, stroke, and any acute infections. Patients who were aged <20 years, whose BP level was $\geq$180/110 mm Hg, or whose serum creatinine (Cr) level was $\geq$1.5 mg/dL were also excluded. Anthropometric and metabolic variables and serum chemistries were measured at baseline and at 12 weeks after telmisartan treatment as described previously.[12] Informed consent was obtained from all the subjects, and the study protocol was approved by the Institutional Ethics Committee of Kurume University School of Medicine.

Study Design

The medical history was ascertained by a questionnaire. Height and weight were measured, and body mass index (kg/m^2) was calculated as an index of the presence or absence of obesity. The subjects were instructed to measure their own BP at home every day by using an automatic device based on the cuff-oscillometric method (HEM-7501-HP; Omron Healthcare, Kyoto, Japan). Blood pressure was measured in a sitting position after at least 5 minutes of rest twice a day: once in the morning within 1 hour of awakening, after micturition, but before taking antihypertensive agents (morning home BP); and once in the evening, just before going to bed (evening home BP). Morning and evening systolic BP (SBP) and diastolic BP (DBP) were averaged in each subject for the final 5 days of the screening period (days −4–0) and for the final 5 days of twelfth week of the treatment period (days 80–84). The mean of these values was used as the BP level at baseline and at 12 weeks after telmisartan treatment, respectively.

Blood was drawn from the antecubital vein in the morning after 12-hour fasting for determination of lipids (high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides), fasting plasma glucose (FPG), insulin, glycated hemoglobin, serum Cr, and adiponectin. Blood chemistries were measured at a commercially available laboratory (SRL Inc., Hachioji, Japan). The homeostasis model assessment of insulin resistance index was calculated from the values of FPG (mg/dL) and insulin (μU/mL) using the following formula: (glucose × insulin) / 405. Estimated glomerular filtration rate was calculated with the modified isotope dilution mass spectrometry-traceable, 4-variable

Table 1. Clinical Variables at Baseline and at 12 Weeks After Telmisartan Treatment

Clinical Variable	Baseline	At 12 Weeks	*P* Value
BMI (kg/m^2)	24.8 ± 1.8	24.9 ± 1.8	0.83
Heart rate (beats/min)	66.4 ± 16.5	61.8 ± 9.1	0.22
Morning SBP (mm Hg)	153.3 ± 14.2	145.9 ± 14.0	<0.05
Morning DBP (mm Hg)	75.1 ± 8.3	74.5 ± 9.3	0.55
Evening SBP (mm Hg)	141.7 ± 14.6	132.6 ± 16.4	<0.01
Evening DBP (mm Hg)	67.8 ± 7.8	65.1 ± 8.7	<0.05
LDL-C (mg/dL)	113.1 ± 28.8	113.1 ± 26.6	0.99
TG (mg/dL)	101.2 ± 33.4	113.4 ± 53.6	0.27
HDL-C (mg/dL)	55.5 ± 8.9	54.8 ± 9.8	0.64
FPG (mg/dL)	100.1 ± 8.5	100.9 ± 10.4	0.80
HbA_{1c} (%)	4.9 ± 0.4	4.9 ± 0.4	0.09
Fasting insulin (μU/mL)	5.1 ± 3.2	5.3 ± 3.7	0.82
HOMA-IR	1.3 ± 0.8	1.3 ± 0.9	0.87
Adiponectin (μg/mL)	13.2 ± 10.0	14.3 ± 11.0	<0.01
Cr (mg/dL)	0.7 ± 0.2	0.8 ± 0.2	0.54
eGFR (mL/min/1.73m^2)	78.7 ± 19.0	77.8 ± 19.7	0.62
DM, n	3	3	NA
Dyslipidemia, n	9	9	NA

Abbreviations: BMI, body mass index; Cr, creatinine; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; NA, not applicable; SBP, systolic blood pressure; TG, triglycerides.

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Modification of Diet in Renal Disease Study equation for Japanese.[13]

Statistical Methods

Data were expressed as mean ± SD. To compare the parameter changes between baseline and after the telmisartan treatment, we used the paired t test. Statistical significance was defined as $P < 0.05$. All statistical analyses were performed with SAS software, version 9.2 (SAS Institute Inc., Cary, NC).

Results

Demographic data of the subjects are presented in the Table 1. As shown in Figure 1, replacement of valsartan or candesartan with telmisartan in amlodipine-treated elderly hypertensive patients showed a significant reduction in morning home SBP and evening home SBP and DBP at 12 weeks; morning and evening BP level decreased from 153.3/75.1 mm Hg and 141.7/67.8 mm Hg at baseline to 145.9/74.5 mm Hg and 132.6/65.1 mm Hg at 12 weeks after the telmisartan treatment, respectively. As shown in Figure 2, serum adiponectin level was significantly increased after switching to telmisartan therapy. However, the changes in serum adiponectin level were not correlated with those in mean BP levels (MBP; Figure 3). There were no significant differences in values of body mass index, low-density lipoprotein cholesterol, triglycerides, high-density lipoprotein cholesterol, FPG, glycated hemoglobin, homeostasis model assessment of insulin resistance index, Cr, and estimated glomerular filtration rate before and after the treatment of telmisartan (Table).

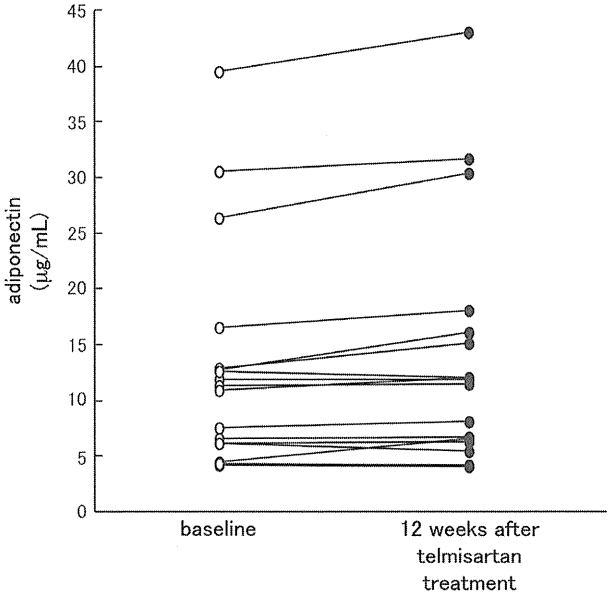

Figure 2. Serum adiponectin levels of each subject at baseline and after telmisartan treatment. Replacement of valsartan or candesartan with telmisartan showed a significant increase in serum adiponectin levels at 12 weeks.

Discussion

Recent analysis by the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) revealed that any commonly used BP-lowering regimen reduced the risk of total major cardiovascular events, and larger lowering in BP level produced larger reductions in the risk.[4] These observations suggest that most of the differences among treatment regimens in their effects on cardiovascular outcomes could be explained by the differences in achieved BP level. However, it may also be true that a particular treatment regimen may be superior or inferior to others with regard to reduction of risk of cardiovascular events.[7,8,14–16] Further, to achieve a target BP level is often difficult in the elderly on single-drug therapy.[2,3] Therefore, current Japanese guidelines recommend combination drug therapy

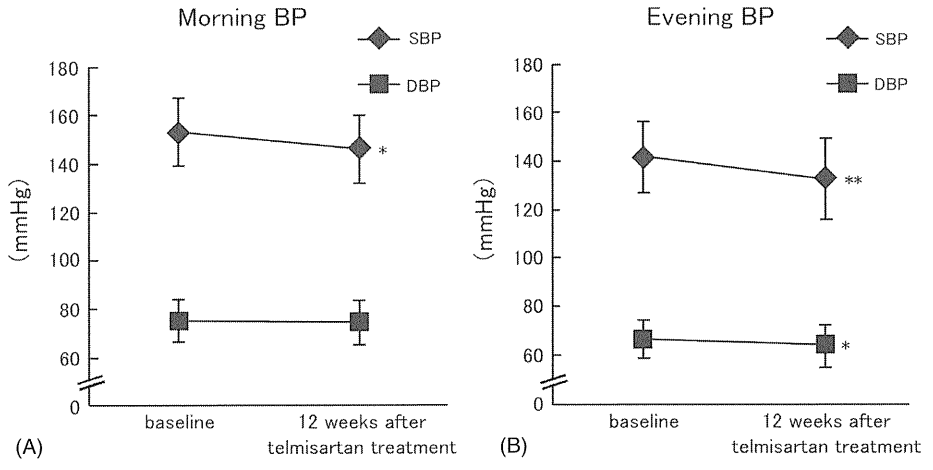

Figure 1. Morning (A) and evening (B) home BP levels at baseline and after telmisartan treatment. Replacement of valsartan or candesartan with telmisartan showed a significant reduction in morning SBP and evening SBP and DBP at 12 weeks. Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

[a] The * indicates $P < 0.05$ compared with baseline values.

[b] The ** indicates $P < 0.001$ compared with baseline values.

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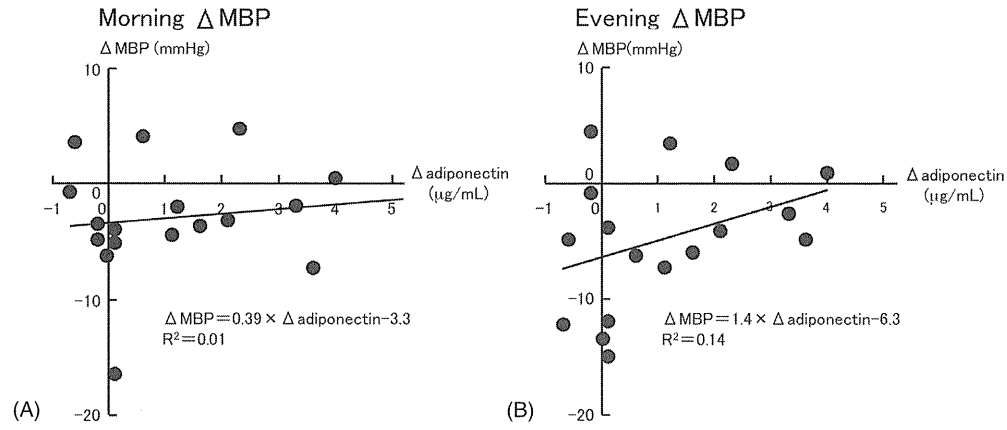

Figure 3. Correlation of the changes in serum adiponectin (△adiponectin) obtained by switching from valsartan or candesartan to telmisartan therapy with those in morning (A) and evening (B) MBP (△MBP). △adiponectin was not correlated with morning (A) or evening (B) △MBP. Abbreviations: MBP, mean blood pressure; R^2, coefficient of determination.

with different modes of action for the treatment of elderly patients with moderate HT.[2]

In this study, we demonstrated for the first time that in elderly hypertensive patients uncontrolled by the combination treatment of 5 mg amlodipine plus 80 mg valsartan or 8 mg candesartan, additional morning and evening home BP lowering was achieved by switching to 5 mg amlodipine plus 40 mg telmisartan. Morning home SBP and evening home SBP and DBP levels were significantly decreased at 12 weeks after the telmisartan treatment. Several clinical studies have shown that home BP is superior to office BP in predicting the risk of cardiovascular mortality in hypertensive patients.[17–19] Furthermore, cardiovascular events often occur in the early morning,[20,21] and there is a strong correlation between early-morning HT and the risk of future cardiovascular events.[22,23] Therefore, our present findings suggest that combination therapy with telmisartan plus amlodipine may exert more cardioprotective effects in elderly patients with HT by reducing home BP, especially morning BP, compared with valsartan or candesartan plus amlodipine treatment. Nishimura et al reported that the antihypertensive effects of telmisartan on morning and evening home BP level were greater than those of candesartan or valsartan in patients with essential HT,[24] thus supporting our observations. Telmisartan has the strongest binding affinity to angiotensin II type 1 receptor and the longest elimination half-life among various ARBs.[25,26] These characteristics of telmisartan may explain the long-lasting home BP-lowering effects in our uncontrolled elderly hypertensive patients.

In this study, switching to telmisartan significantly increased serum adiponectin levels (Figure 2). Furthermore, the changes in serum adiponectin (△adiponectin) obtained by switching from valsartan or candesartan to telmisartan therapy were not correlated with those in morning MBP or evening MBP (△MBP) (Figure 3). These findings suggest that telmisartan may increase serum adiponectin level in a BP-lowering–independent manner. Recently, telmisartan was reported to act as a partial agonist of peroxisome proliferator-activated receptor-γ (PPAR-γ),[15,27] which promotes differentiation of preadipocytes by activating adipose-specific gene expression.[15,28] Telmisartan treatment was shown to decrease weight of visceral adipose tissue and increase serum adiponectin level in diet-induced obese mice.[29] In addition, Miura et al reported that replacement of valsartan or candesartan with telmisartan in hypertensive patients with type 2 diabetes resulted in a significant increase in serum adiponectin level.[30] These findings suggest that telmisartan could increase serum adiponectin level via PPAR-γ –modulating activity.

Conclusion

Although switching to telmisartan did not affect other anthropometric and metabolic variables in our subjects, given the insulin-sensitizing and anti-inflammatory properties of adiponectin,[28,31] telmisartan plus amlodipine therapy may exert favorable cardiometabolic actions in elderly HT. Further longitudinal study is needed to clarify the issue.

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