

Original article

Angiotensin receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, and statins as anti-glycation agents

Lanny Parengkuan¹⁾, Masayuki Yagi¹⁾, Moniruzzaman Mohammad¹⁾, Shin-ichi Asahi²⁾, Yoshikazu Yonei¹⁾

1) Anti-Aging Medical Research Center and Glycation Stress Research Center, Graduate School of Life and Medical Sciences, Doshisha University, Kyoto, Japan

2) Hibiya Park Clinic, Minato-ku, Tokyo

Abstract

Background: Angiotensin receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, and statins are widely used for the treatment of cardiovascular and diabetic complications. Recently, advanced glycation end products (AGEs) have been shown to play a role in promoting and accelerating these diseases. ARBs and ACE inhibitors decrease the formation of AGEs via radical scavenging and transition metal chelation both *in-vitro* and in animal models. Statins may decrease the formation of AGEs and slow the aging process through several potential mechanisms.

Objective: The purpose of this study was to evaluate the inhibitory activity of ARBs, ACE inhibitors, and statins against human serum albumin (HSA) glycation.

Methods: Test samples were prepared in dimethyl sulfoxide. An HSA glycation model was generated by incubating HSA and test samples with and without glucose at 60 °C for 40 h. The fluorescence (excitation, 370 nm; detection, 440 nm) of each sample was measured using a Spectra Max paradigm multimode detection platform.

Results: Among the tested statins, only fluvastatin, Lochol (fluvastatin), and Lipovas (simvastatin) displayed weak anti-glycation activity, with pure fluvastatin ($IC_{50} = 1.84$ mg/nL) having the highest inhibitory activity. Among ARBs, only valsartan and olmesartan exhibited weak anti-glycation activity, with valsartan showing stronger activity ($IC_{50} = 2.28$ mg/mL). These effects were weaker than aminoguanidine ($IC_{50} = 0.063$ mg/mL). In contrast, none of the examined ACE inhibitors had detectable anti-glycation activity.

Conclusion: A part of ARBs and statins seems to possess anti-glycation activity, however it is weak compared to aminoguanidine.

KEY WORDS: aging, angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, glycation, statins

Introduction

Aging is a complex process for which many theories have been proposed. For example, in the glycation theory of aging, toxic byproducts, particularly advanced glycation end products (AGEs), generated during energy production cause cellular damage and lead to reduced longevity. AGEs are proteins and lipids that are formed through the non-enzymatic reaction between proteins and reducing sugars, such as fructose and glucose. Inhibition of AGEs formation and therapeutic intervention to reduce AGEs may slow the aging process and treating age-related diseases.

Aminoguanidine is a widely used AGEs inhibitor that was first discovered in 1986^{1,2)} as a nucleophilic hydrazine derivative that binds irreversibly to reactive intermediates of early glycated products, particularly 3-deoxyglucosone.

Although aminoguanidine prevents AGEs formation and AGE-induced protein cross-linking³⁾, this compound has toxic effects, thus limiting its therapeutic potential. The adverse toxic effects associated with aminoguanidine include drug-induced systemic lupus erythematosus, abnormal liver function, flu-like syndromes, and vasculitis⁴⁾. Aminoguanidine can also damage DNA through hydroxyl- and hydrogen peroxide-formation in the presence of Fe^{+3} ⁵⁾. Side effects related to the trapping of pyridoxal leading to a vitamin B6 deficiency have also been reported⁶⁾. Due to the numerous potential toxic effects of aminoguanidine, other drugs with demonstrated AGEs inhibitory efficacy in the clinical setting are needed.

Here, we evaluated the AGEs inhibitory activity of several well-tolerated anti-hypertensive drugs and statins

Contact Address: Professor Yoshikazu Yonei
Anti-Aging Medical Research Center, Graduate School of Life and Medical Sciences, Doshisha University
1-3, Tataramiyakodani, Kyotanabe-shi, Kyoto, 610-0321 Japan
Phone/Fax: +81-774-65-6394 Email: yyonei@mail.doshisha.ac.jp
Co-authors; Parengkuan L, lannyparengkuan@ymail.com,
Yagi M, myagi@doshisha.ac.jp, Asahi S, asahi777@gmail.com.

against human serum albumin (HSA) to assess their potential as anti-glycation agents.

Methods

In-vitro models of glycation using glucose and HSA were used to test the inhibitory activity of anti-hypertensive drugs and statins against AGEs formation⁷⁾.

The tested compounds included 12 statins: atorvastatin, simvastatin, pitavastatin, pravastatin, fluvastatin, lovastatin (Wako Pure Chemical Industries, Chuo-ku, Osaka, Japan), Lipitor/atorvastatin (Astellas, Itabashi-ku, Tokyo, Japan), Lipovas/simvastatin (MSD, Chiyoda-ku, Tokyo, Japan), Livalo/pitavastatin (Kowa, Chuo-ku, Tokyo, Japan), Mevalotin/pravastatin (Daiichi Sankyo, Chuo-ku, Tokyo, Japan), Lochol/fluvastatin (Novartis, Minato-ku, Tokyo, Japan), and Crestor/rosuvastatin (Astra Zeneca, Kita-ku, Osaka, Japan); 11 angiotensin II receptor blockers (ARBs): valsartan, telmisartan (Tokyo Chemical Industry, Kita-ku, Tokyo, Japan), candesartan (Sigma-Aldrich, St. Louis, MO, USA), losartan (LKT Laboratories, Inc., St. Paul, MN, USA), Nu-lotan/losartan (MSD); Diovan/valsartan (Novartis), Blopess/candesartan (Takeda Pharmaceutical, Chuo-ku, Osaka, Japan), Micardis/telmisartan (Astellas); Olmetec/olmesartan (Daiichi Sankyo), Avapro/irbesartan (Dainippon Sumitomo, Chuo-ku, Osaka, Japan), and Irbetan/irbesartan (Shionogi, Chuo-ku, Osaka, Japan); 10 angiotensin converting enzyme (ACE) inhibitors: Coversyl/perindopril (Kyowa-Hako Kirin Servier, Chiyoda-ku, Tokyo, Japan), Adecut/delapril (Takeda Pharmaceutical), Captoril/captopril (Daiichi Sankyo), Renivace/enalapril (MSD), Longes/lisinopril (Shionogi), Zestril/lisinopril (Astra Zeneca), Cibacen/benazepril (Novartis), Tanatril/imidapril (Mitsubishi Tanabe Pharma Corp., Chuo-ku, Osaka, Japan), Preran/trandolapril (Sanofi Aventis, Shinjuku-ku, Tokyo, Japan), and Odric/trandolapril (Nippon Shinyaku, Minami-ku, Kyoto, Japan). Test compounds were dissolved in dimethyl sulfoxide (DMSO; Wako Pure Chemical Industries) prior to use.

The HSA model was used to assay the AGEs inhibitory activity of the test compounds as previously reported⁷⁾. For the assay, 100 μ L of each test sample (anti-hypertensive drugs, statins, or DMSO [control]) was added to 900 μ L of glucose (+) or glucose (-) HSA solution, and the resulting reaction mixtures were incubated at 60 °C for 40 h. The glucose (+) reaction solution contained 0.1 M phosphate buffer (pH 7.4), 40 mg/mL HSA (Sigma Chemical Ltd., Perth, WA, USA), 2.0 M glucose, and distilled water at a 5:2:1:1 volume ratio. The glucose (-) reaction solution contained 0.1 M phosphate buffer (pH 7.4), 40 mg/mL HSA, and distilled water at a 5:2:2 volume ratio.

After the 40-h incubation, sample solution (200 μ L), distilled water (200 μ L), and 5 μ g/mL quinine sulfate (200 μ L) were dispensed into a well of black microplate, and the fluorescence (excitation, 370 nm; detection, 440 nm) was measured using the Spectra Max paradigm multimode detection platform (Molecular Devices, Sunnyvale, CA, USA)^{7, 8)}.

The AGEs inhibitory activity of each sample was calculated using the following formula:

$$\text{Inhibitory activity against AGEs fluorescence, (\%)} = \frac{(1 - \text{Glu (+) sample} - \text{Glu (-) sample}) / (\text{Glu (+) control} - \text{Glu (-) control}) \times 100}{\text{(Glu means glucose in this formula)}}$$

The 50% inhibitory concentration (IC₅₀) against AGEs fluorescence, was calculated from a regression curve of the inhibitory activity for three concentrations of each sample (n = 3). The activity of each extract was compared with the activity of aminoguanidine⁸⁾.

Results

The results of the HSA assay for each test compound are presented in [Table 1](#). In the statin group, only fluvastatin, Lochol/fluvastatin, and Lipovas/simvastatin showed anti-glycation activity, with pure fluvastatin having the highest inhibition rate. Among ARBs, Diovan/valsartan and Olmetec/olmesartan displayed anti-glycation activity, with Diovan/valsartan showing stronger anti-glycation activity. In contrast, no ACE inhibitor had detectable anti-glycation activity.

Discussion

Our findings show that the ARBs valsartan/Diovan and olmesartan/Olmetec, and the statins fluvastatin and simvastatin/Lipovas have anti-glycation activity. Notably, none of the examined ACE inhibitors had detectable anti-glycation activity. Although the anti-glycation activities of the ARBs and statins are not as high as that of aminoguanidine (IC₅₀ = 0.063 mg/mL)⁹⁾, these findings suggest that treatment with these drugs may be effective in preventing AGE-related complications with a reduced risk of adverse effects in diabetic and cardiovascular patients. However these result may be different from the *in vivo* reaction considering the glucose absorbent mechanism and the possibility of enhance insulin reaction are different for each compounds.

Anti-hypertensive drugs such as ARBs and ACE inhibitors decrease the formation of AGEs via radical scavenging and transition metal chelation¹⁰⁾ both *in-vitro* and in animal models of diabetes^{11,12)}. Furthermore, the results of *in-vitro* experiments and preclinical and clinical studies suggest that ACE inhibitors prevent AGEs formation by promoting expression of the receptor of AGE (RAGE)¹¹⁾. Sebekova *et al.*¹³⁾ reported that treatment with the ACE inhibitor ramipril for 2 months significantly decreased the fluorescent AGE level in 12 subjects with nondiabetic nephropathy. It is conceivable that blockade of the renin-angiotensin system (RAS) with drugs such as ACE inhibitors may affect AGEs accumulation by either improving renal function or reducing oxidative stress. Culture experiments using NRK-49F cells exposed to AGEs demonstrated that the ACE inhibitor captopril blocks AGE-induced collagen production¹⁴⁾. In addition, increased protein expression of RAGE was also attenuated by ACE inhibition¹⁴⁾.

ARBs have protective effects against kidney damage and can reduce renal AGEs accumulation and proteinuria in diabetic rodents *in vivo*^{12,15-17)} to a similar degree to that of ACE inhibitors¹⁸⁾. For example, *in-vivo* studies using a renal ablation model showed that treatment with the ARBs, losartan, decreased serum AGEs concentrations and improved renal function independent of changes in the profibrotic cytokine transforming growth factor- β ¹⁹⁾. Here, in contrast, we found that losartan, in both its pure and commercially produced forms, did not display anti-glycation activity. These apparently contrasting results may be explained by the fact that the previous study found that AGEs were reduced in

Anti-glycative effect of ARBs, ACEIs, and statins

Table 1. Inhibition of formation of fluorescence AGEs by ARBs, ACE inhibitors and statins.

No	Group	Chemical compound	Product name	Concentration (mg/ml)	Inhibition rate (%)	IC ₅₀
1	Statin	Atorvastatin		0.1	-9.8 ± 5.6	None
				0.01	-5.2 ± 3.1	
				0.001	0.1 ± 6.0	
2	Statin	Simvastatin		0.1	-2.7 ± 5.6	None
				0.01	-5.3 ± 7.5	
				0.001	1.7 ± 4.8	
3	Statin	Pitavastatin		0.1	-10.5 ± 2.4	None
				0.01	-10.4 ± 2.0	
				0.001	-4.4 ± 8.3	
4	Statin	Pravastatin		0.1	-24.0 ± 15.7	None
				0.01	-12.7 ± 1.7	
				0.001	-3.6 ± 1.8	
5	Statin	Fluvastatin		0.1	31.5 ± 4.3	1.84 ± 0.90
				0.01	-7.3 ± 7.8	
				0.001	-8.5 ± 6.3	
6	Statin	Lovastatin		0.1	-19.5 ± 7.4	None
				0.01	-23.2 ± 7.2	
				0.001	-16.3 ± 6.6	
7	ARBs	Valsartan		0.1	-5.1 ± 4.8	None
				0.01	-22.8 ± 7.7	
				0.001	-18.3 ± 6.7	
8	ARBs	Telmisartan		0.1	-12.3 ± 2.8	None
				0.01	-30.1 ± 3.5	
				0.001	-23.7 ± 3.2	
9	ARBs	Candesartan		0.1	11.9 ± 3.9	None
				0.01	7.6 ± 4.3	
				0.001	4.2 ± 3.8	
10	ARBs	Losartan		0.1	7.8 ± 6.0	None
				0.01	1.7 ± 5.2	
				0.001	-2.8 ± 6.0	
11	Statin	Atorvastatin-calcium hydrate	Lipitor*	0.1	6.3 ± 4.7	None
				0.01	3.7 ± 6.4	
				0.001	2.1 ± 6.9	
12	Statin	Simvastatin	Lipovas*	0.1	19.4 ± 3.9	> 100
				0.01	5.2 ± 4.2	
				0.001	1.8 ± 6.5	
13	Statin	Pitavastatin calcium	Livalo*	0.1	18.2 ± 1.3	None
				0.01	5.8 ± 3.5	
				0.001	4.9 ± 3.2	
14	Statin	Pravastatin sodium	Mevalotin*	0.1	9.5 ± 4.8	None
				0.01	7.5 ± 5.6	
				0.001	4.3 ± 5.2	
15	Statin	Fluvastatin sodium	Lochol*	0.1	32.1 ± 4.1	14.07 ± 15.39
				0.01	14.1 ± 4.3	
				0.001	10.4 ± 5.7	
16	Statin	rosuvastatin calcium	Crestor*	0.1	17.3 ± 3.4	None
				0.01	15.6 ± 5.2	
				0.001	13.0 ± 5.9	
17	ARBs	Losartan potassium	Nu-lotan*	0.1	23.5 ± 5.0	None
				0.01	20.9 ± 7.1	
				0.001	17.3 ± 8.9	

No	Group	Chemical compound	Product name	Concentration (mg/ml)	Inhibition rate (%)	IC ₅₀
18	ARBs	Valsartan	Diovan*	0.1	40.0 ± 1.0	2.28 ± 2.37
				0.01	24.5 ± 3.4	
				0.001	19.1 ± 5.0	
19	ARBs	Candesartan cilexetil	Blopres*	0.1	14.7 ± 5.5	None
				0.01	3.4 ± 5.4	
				0.001	3.4 ± 5.0	
20	ARBs	Telmisartan	Micardis*	0.1	10.9 ± 4.5	None
				0.01	10.7 ± 3.0	
				0.001	14.8 ± 5.0	
21	ARBs	Olmesartan medoxomil	Olmotec*	0.1	11.8 ± 4.7	> 100
				0.01	-5.7 ± 8.9	
				0.001	-7.0 ± 7.8	
22	ARBs	Irbesartan	Avapro*	0.1	-9.4 ± 7.3	None
				0.01	-11.8 ± 8.1	
				0.001	-6.2 ± 10.0	
23	ARBs	Irbesartan	Irbetan*	0.1	-12.4 ± 1.7	None
				0.01	20.5 ± 52.5	
				0.001	-13.6 ± 16.2	
24	ACE inhibitor	Perindopril erbumine	Coversyl*	0.1	-9.3 ± 5.4	None
				0.01	-6.9 ± 8.1	
				0.001	-5.6 ± 7.0	
25	ACE inhibitor	Delapril hydrochloride	Adecut*	0.1	5.2 ± 0.6	None
				0.01	-8.0 ± 4.8	
				0.001	-6.0 ± 6.3	
26	ACE inhibitor	Trandolapril	Preran*	0.1	-3.8 ± 5.9	None
				0.01	-7.4 ± 3.9	
				0.001	-4.8 ± 5.5	
27	ACE inhibitor	Trandolapril	Odric*	0.1	-6.5 ± 4.6	None
				0.01	-6.6 ± 5.4	
				0.001	-3.4 ± 5.1	
28	ACE inhibitor	Captopril	Captopril*	0.1	-3.3 ± 2.5	None
				0.01	-8.9 ± 2.9	
				0.001	-4.3 ± 4.6	
29	ACE inhibitor	Enalapril maleate	Renivace*	0.1	-3.9 ± 5.3	None
				0.01	-5.2 ± 5.5	
				0.001	-7.0 ± 6.0	
30	ACE inhibitor	Lisinopril hydrate	Longes*	0.1	-1.3 ± 5.8	None
				0.01	-5.7 ± 4.7	
				0.001	-2.3 ± 6.3	
31	ACE inhibitor	Lisinopril hydrate	Zestril*	0.1	3.7 ± 4.8	None
				0.01	7.5 ± 4.2	
				0.001	6.2 ± 8.3	
32	ACE inhibitor	Benazepril hydrochloride	Cibacen*	0.1	13.9 ± 3.0	None
				0.01	6.0 ± 6.4	
				0.001	2.3 ± 4.8	
33	ACE inhibitor	Imidapril hydrochloride	Tanatril*	0.1	7.1 ± 3.7	None
				0.01	-5.0 ± 14.4	
				0.001	-3.9 ± 8.3	

Data are expressed as mean ± standard deviation. None, non-dose dependent; AGEs, advanced glycation end products; ARBs, angiotensin receptor blockers; ACE, angiotensin-converting enzyme; IC₅₀, 50% inhibitory concentration expressed in mg/mL. *Samples were prepared from commercially available tablets that were grounded into powder. Aminoguanidine IC₅₀ was 0.063 mg/mL in our previous study ⁹.

association with improved renal function and reactive oxygen species (ROS) inhibition²⁰ whereas our study was limited to examining the direct inhibitory effect of losartan on *in-vitro* AGEs generation.

The ARB valsartan also has renoprotective effects, which are independent of blood pressure in type 2 diabetes mellitus patients^{16,21}. Valsartan treatment also decreases serum AGEs in type 2 diabetic subjects with hypertension¹⁶ though an unknown mechanism, although the anti-oxidative activity of valsartan may contribute to this response²². Consistent with this finding, valsartan exhibited anti-glycation activity in the present HSA assay. The ARB olmesartan was recently reported to inhibit the formation and accumulation of AGEs *in vitro*¹⁰ and in diabetic rat models^{12,15}. Valsartan treatment also decreases serum AGEs in type 2 diabetic subjects with hypertension¹⁶ through an unknown mechanism, although the anti-oxidative activity of valsartan may contribute to this response²².

Statins, which are competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMGCoA) reductase, may decrease the formation of AGEs and slow the aging process through several potential mechanisms. Evidence suggests that statins are involved in a positive feedback regulation mechanism between C-reactive protein and the AGE-RAGE axis, reduce the AGE-induced formation of intracellular reactive oxygen species ROS, and due to their cholesterol-lowering effects, increase the level of soluble RAGE by inducing RAGE shedding²³⁻²⁵. These findings indicate that statins reduce serum levels of AGEs, lower RAGE expression, and increase soluble RAGE levels by inducing RAGE shedding in diabetic patients²⁵. Statins are also reported to play a key role in the treatment of AGE-induced diabetic vasculopathy by blocking RAGE-AGE interaction and inhibiting ROS generation²⁴. Our present findings demonstrate that statins (fluvastatin and simvastatin/Lipovas) directly inhibit glycation *in vitro*, and suggest that these compounds may also reduce AGEs formation *in vivo*.

In the present HSA assay results, several differences in

the inhibitory rates between pure chemical compounds and the corresponding commercial product were observed. These differences may be attributable to the presence of inactive compounds in the commercial products, which may lower or accelerate the relative activity of the test compound.

The anti-glycation activity results for the ACE inhibitor compounds tested here differ from those reported by Miyata *et al.*¹⁰, who showed that ACE inhibitors reduce the production of AGEs, such as pentosidine and *N*^ε-(carboxymethyl) lysine, and those reported by Forbes *et al.*¹¹, who found that ACE inhibitors have AGE-binding ability. These differences may be attributable to the experimental conditions of each study, such as the medium used for the assays and the incubation period.

Conclusion

We have shown that ARBs and statins possess anti-glycation activity *in vitro*, suggesting that these anti-hypertensive drugs may have AGEs inhibitory activity and therefore be effective for preventing AGE-related complications in diabetic and cardiovascular patients. However, because the difference in chemical structures and glucose absorbance mechanism of tested compounds, their *in-vivo* effects may differ from the *in-vitro* activities determined using the HSA. Therefore, although promising, caution is needed when interpreting the present results, and further study is necessary to fully understand the action of these compounds *in vivo*.

Conflicts of interest statement

The authors have no conflicts of interest related to this study to declare.

References

- 1) Brownlee M, Vlassara H, Kooney A, et al. Aminoguanidine prevents diabetes-induced arterial wall protein cross-linking. *Science*. 1986; 232: 1629-1632.
- 2) Indu D, Kaushik D. Aging: Drugs to eliminate methylglyoxal, a reactive glucose metabolite, and advanced glycation endproducts. *Pharmacology*. 2012; 30: 681-708.
- 3) Edelstein D, Brownlee M. Mechanistic studies of advanced glycosylation end product inhibition by aminoguanidine. *Diabetes*. 1992; 41: 26-29.
- 4) Freedman BI, Wuerth JP, Cartwright K, et al. Design and baseline characteristics for the aminoguanidine clinical trial in overt type 2 diabetic nephropathy (ACTION II). *Control Clin Trials*. 1999; 20: 493-510.
- 5) Suji G, Sivakami S. DNA damage by free radical production by aminoguanidine. *Ann N Y Acad Sci*. 2006; 1067: 191-199.
- 6) Taguchi T, Sugiura M, Hamada Y, et al. *In vivo* formation of a Schiff base of aminoguanidine with pyridoxal phosphate. *Biochem Pharmacol*. 1998; 55: 1667-1671.
- 7) Hori M, Yagi M, Nomoto K, et al. Experimental models for advanced glycation end product formation using albumin, collagen, elastin, keratin and proteoglycan. *Anti-Aging Medicine*. 2012; 9: 125-134.
- 8) Hori M, Yagi M, Nomoto K, et al. Inhibition of advanced glycation end product formation by herbal teas and its relation to anti-skin aging. *Anti-Aging Medicine*. 2012; 9: 135-148.
- 9) Parengkuan L, Yagi M, Matsushima M, et al. Anti-glycation activity of various fruits. *Anti-Aging Medicine*. 2013; 10: 70-76.
- 10) Miyata T, van Ypersele de Strihou C, Ueda Y, et al. Angiotensin II receptor antagonists and angiotensin-converting enzyme inhibitors lower *in vitro* the formation of advanced glycation end products: Biochemical mechanisms. *J Am Soc Nephrol*. 2002; 13: 2478-2487.
- 11) Forbes JM, Thorpe SR, Thallas-Bonke V, et al. Modulation of soluble receptor for advanced glycation end products by angiotensin-converting enzyme-1 inhibition in diabetic nephropathy. *J Am Soc Nephrol*. 2005; 16: 2363-2372.

- 12) Nangaku M, Miyata T, Sada T, et al. Anti-hypertensive agents inhibit *in vivo* the formation of advanced glycation end products and improve renal damage in a type 2 diabetic nephropathy rat model. *J Am Soc Nephrol*. 2003; 14: 1212-1222.
- 13) Sebeková K, Gazdíková K, Syrová D, et al. Effects of ramipril in nondiabetic nephropathy: Improved parameters of oxidative stress and potential modulation of advanced glycation end products. *J Hum Hypertens*. 2003; 17: 265-270.
- 14) Huang JS, Guh JY, Chen HC, et al. Role of receptor for advanced glycation end-product (RAGE) and the JAK/STAT- signaling pathway in AGE-induced collagen production in NRK-49F cells. *J Cell Biochem*. 2001; 81: 102-113.
- 15) Izuhara Y, Nangaku M, Inagi R, et al. Renoprotective properties of angiotensin receptor blockers beyond blood pressure lowering. *J Am Soc Nephrol*. 2005; 16: 3631-3641.
- 16) Komiya N, Hirose H, Saisho Y, et al. Effects of 12-month valsartan therapy on glycation and oxidative stress markers in type 2 diabetic subjects with hypertension. *Int Heart J*. 2008; 49: 681-689.
- 17) Fan Q, Liao J, Kobayashi M, et al. Candesartan reduced advanced glycation end-products accumulation and diminished nitro-oxidative stress in type 2 diabetic KK/Ta mice. *Nephrol Dial Transplant*. 2004; 19: 3012-3020.
- 18) Forbes JM, Cooper ME, Thallas V, et al. Reduction of the accumulation of advanced glycation end products by ACE inhibition in experimental diabetic nephropathy. *Diabetes*. 2002; 51: 3274-3282.
- 19) Sebeková K, Schinzel R, Münch G, et al. Advanced glycation end-product levels in subtotaly nephrectomized rats: Beneficial effects of angiotention II receptor I antagonist losartan. *Miner Electrolyte Metab*. 1999; 25: 380-383.
- 20) Rajagopalan S, Kurz S, Munzel T, et al. Angiotensin II-mediated hypertension in the rat increases vascular superoxide production via membrane NADH/NADPH oxidase activation: Contribution to alterations of vasomotor tone. *J Clin Invest*. 1996; 97: 1916-1923.
- 21) Viberti G, Wheeldon NM. Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus: A blood pressure-independent effect. *Circulation*. 2002; 106: 672-678.
- 22) Monacelli F, Poggi A, Storace D, et al. Effects of valsartan therapy on protein glycoxidation. *Metabolism*. 2006; 55: 1619-1624.
- 23) Paradelo-Dobarro B, Raposeiras-Roubín S, Rodiño-Janeiro BK, et al. Statins modulate feedback regulation mechanisms between advanced glycation end-products and C-reactive protein: Evidence in patients with acute myocardial infarction. *Eur J Pharm Sci*. 2013; 49: 512-518.
- 24) Yoon SJ, Yoon YW, Lee BK, et al. Potential role of HMG CoA reductase inhibitor on oxidative stress induced by advanced glycation endproducts in vascular smooth muscle cells of diabetic vasculopathy. *Exp Mol Med*. 2009; 41: 802-811.
- 25) Quade-Lyssy P, Kanarek AM, Baiersdörfer M, et al. Statins stimulate the production of a soluble form of the receptor for advanced glycation end products. *J Lipid Res*. 2013; 54: 3052-3061.