Association between estimated glomerular filtration rate and asymmetric dimethylarginine concentrations among the elderly in a rural community

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This certifies that the master's thesis of

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ABSTRACT

Association between estimated glomerular filtration rate and asymmetric dimethylarginine concentrations among the elderly in a rural community

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(Directed by Professor Hyeon Chang Kim, MD, PhD)

Background:

Reduction of glomerular filtration rate is one of common disorders in elderly people. The high concentrations of asymmetric dimethylarginine (ADMA) is also prevalent in the

elderly and have been reported as a risk factor of cardiovascular disease (CVD). However, most of studies that examined the association between the two conditions were performed in patients with renal dysfunction, but not for general healthy population. Thus, this study investigated an association between eGFR and ADMA concentration among community-dwelling older Koreans.

Method:

A cross-sectional study was conducted on 269 men and 382 women (mean age, 71.6 years) enrolled in the Korean Social Life, Health, and Aging Project (KSHAP), a population-based longitudinal study of health determinants in elderly Koreans. I classified participants into three statuses according to estimated glomerular filtration rate (eGFR) reduction: normal to minimally-reduced (≥60 mL/min/1.73m², n=198), moderately-reduced (30-<60 mL/min/1.73m², n=407), and severely-reduced eGFR(<30 mL/min/1.73m², n=46). Plasma ADMA concentration was divided into two groups by 75 percentile. The association between eGFR reduction and ADMA elevation was analyzed by multivariable logistic regression models. A multiple linear regression analyses was performed to confirm the association of eGFR and ADMA concentrations in the general elderly after excluding severe eGFR reduction group.

Results:

The mean ADMA level was significantly higher in the severely-reduced eGFR (0.715 ㎛ol/L, p=0.002) than in the normal to minimally-reduced eGFR reduction (0.659 ㎛ol/L). The negative association between eGFR and ADMA concentrations was significant in general participants, excluding those with severely-reduced eGFR (β=-0.0016, p<0.01). Compared to people with normal to minimally-reduced eGFR, the unadjusted odds ratio (OR) for having ADMA elevation (95% CI) was 2.4 (1.2-4.7) in people with the severely-reduced eGFR. Even after adjusting for sex, age, body mass index, blood pressure, total and HDL cholesterol, diabetes, smoking, and drinking, the adjusted OR for the ADMA elevation was 3.6 (1.5-8.9) in people with severely-reduced eGFR, compared with normal to minimally-reduced eGFR.

Conclusion:

The findings of this study suggest that an inverse association between eGFR and ADMA concentrations among the Korean elderly in a rural community.

Keywords: eGFR, kidney, ADMA, CVD, the general elderly

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Ⅰ. INTRODUCTION

The prevalence of chronic kidney disease is increasing among elderly people, because kidney is one of organs that are affected by aging (Prakash and O'Hare 2009). Arteries are progressively stiffening with age (Avolio, Chen et al. 1983). Therefore, the cells of kidney cannot be protected by constricted arteries because advanced aortic stiffening remains arterial vessels expanded (O'Rourke and Safar 2005). Asymmetric dimethylarginine

(ADMA) is an endogenous nitric oxide (NO) synthase inhibitor (Böger, Bode-Böger et al. 1998). ADMA is eliminated through renal excretion and is metabolized by a dimethylarginine dimethylaminohydrolase (DDAH), found in tissues of kidney, pancreas, and blood vessels (Fleck, Janz et al. 2001). Therefore, kidney plays an important role in maintaining reduced plasma ADMA concentrations. However, in the elderly people, DDAH secretion is decreased and ADMA concentration is increased because of reduced kidney function with aging. Inhibiting NO synthase impairs endothelium-dependent vasodilation, resulting in endothelial dysfunction (Böger, Sydow et al. 2000).

Moreover, various previous papers suggested that elevated ADMA causes CVD and increases mortality in patients with CKD. ADMA is independently and significantly associated with cardiovascular risk factors, such as intima-media thickness (IMT), C-reactive protein (CRP), age, homocysteine, arterial pressure, and glucose tolerance (Böger, Bode-Böger et al. 1998, Miyazaki, Matsuoka et al. 1999, Böger 2003). Since ADMA is one of factors that affect vascular disease, carotid IMT is strongly related to ADMA concentration and increased IMT also results in CVD (Hodis, Mack et al. 1998). The significant interaction between ADMA and CRP for predicting IMT progression suggests that inflammatory condition affect control ADMA concentration in patients with renal disease (Zoccali, Benedetto et al. 2002). This evidences lead to present the association of ADMA elevation and cardiovascular disease or mortality. However, even though there are many previous studies, most of them investigated whether ADMA concentration was associated with other diseases or risk factors not in general population, but in patients with

CKD or diabetes. Furthermore, there is no available data on the association between eGFR and ADMA concentration in the elderly population. As this study aims to find possible association between eGFR and plasma ADMA concentrations in general older adults, the findings might be able to affect health behavior of not only renal patients but also general healthy people.

Hence, I hypothesized that eGFR reduction would elevate plasma ADMA concentrations in elderly people. In the study, I investigate the association between eGFR and plasma ADMA concentrations among the elderly in a rural community.

Ⅱ. METHODS

1. Study population

Data of this study was collected from the Korean Social Life, Health, and Aging Project (KSHAP) cohort study, which had been conducted since 2011. The KSHAP study recruited individuals aged 60 years or older and their spouses living in a rural township of Ganghwa Island, South Korea. A total of 814 of the 860 community-dwelling adults (response rate, 94.7%) participated in the study and finished questionnaire surveys from December 2011 to July 2012 (Baek, Hur et al. 2016). The KSHAP-Health Examination (KSHAP-HE) cohort was a subcohort of 698 people who completed additional health examinations at a public health center (n=533) or at home (n=165) (Lee, Lee et al. 2014).

In this paper, 47 were excluded for missing key variables, such as eGFR (n=23), plasma ADMA concentration (n=19), and body mass index (BMI) (n=5), among the 698 participants who underwent the KSHAP-HE. Therefore, a total of 651 participants (269 men and 382 women) were included for this cross-sectional study. All participants provided written informed consent forms.

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2. Measurements

Our trained personnel interviewed participants by using standardized questionnaire surveys according to a predefined protocol. The standardized questionnaire was conducted to obtain socio-demographic characteristics such as age, education, economic and marital status, and health behaviors. Health behaviors contained medical history, cigarette smoking, alcohol consumption, and sleep duration.

We measured every participant's height and weight while he/she wore light clothing. Standing height was measured to the nearest 0.1 cm with a stadiometer. Body weight was also measured to the nearest 0.1 kg with a digital scale according to the predefined manual. BMI was calculated as an individual's body weight divided by squared height (kg/m^2). Blood pressure was measured two or three times using an automatic sphygmomanometer

(Dinamap 1846 SX/P; GE Healthcare, Waukesha, WI, USA) after participants rested for at least 5 minutes in a seated position. If the two measurements differed by 10 mmHg or more, additional measurements were performed after 5 minutes. I used the average of the last two measurements in this study.

Individual's blood sample was collected after at least an 8 hour fast. Fasting concentrations of blood glucose, creatinine, and blood urea nitrogen (BUN) were analyzed using a colorimetry-based method (ADVIA1800 Auto Analyzer, Siemens Medical Sol., Deerfield, IL, USA). Fasting insulin concentration was measured by using an immunoradiometric assay (SR-300, Stratec, Germany). Total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride (TG) levels were assayed by enzymatic methods (ADVIA1800 Auto Analyzer, Siemens Medical Sol., Deerfield, IL, USA). I analyzed participants' kidney function using estimated glomerular filtration rate (eGFR), because it was hard to measure GFR directly. The eGFR was calculated by Cockcroft-Gault equation which was developed to predict creatinine clearance: (140-age) x (body weight)/plasma creatinine x 72 (x 0.85 if female) (Cockcroft and Gault 1976). Furthermore, all participants were classified into the three eGFR reduction groups according to National Kidney Foundation criteria for renal failure: (1) normal to minimally-reduced eGFR, ≥60 ml/min /1.73m^2; (2) moderately-reduced eGFR, 30-<60 ml/min /1.73m^2; and (3) severely-reduced eGFR, <30 ml/min /1.73m^2 (Levey, Coresh et al. 2003). In addition, ADMA concentration was measured by an enzyme-linked immunosorbent assay (Spectramax190, Molecular Devices, USA). I decided that ADMA elevation is the

group over 75th percentile of ADMA concentrations.

3. Definition of Diseases

Hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg, diastolic blood pressure (DBP) ≥90 mmHg, or current use of anti-hypertensive medicine. Diabetes was defined as fasting glucose ≥126 mg/dL or current use of oral anti-diabetic medicine or insulin. Hyperlipidemia was defined as total cholesterol ≥240 mg/dL, HDL cholesterol <40 mg/dL or current treatment by anti-hyperlipidemic agents.

4. Statistical analysis

Sex differences of general characteristics were presented using independent t-test and the Wilcoxon rank-sum test for continuous variables, and chi-square test for categorical variables. Continuous variables that followed a normal distribution are shown as mean and standard deviation, whereas skewed variables are expressed as median and interquartile range. Categorical variables were described as numbers and percentages. Fasting glucose and insulin, TG, Serum creatinine, and BUN were log-transformed for parametric analysis due to the right-skewed distributions. I compared to the demographic characteristics according to the three groups of eGFR reduction. Differences of general characteristics among eGFR reduction statuses were analyzed using analysis of variance (ANOVA) for continuous variables and Chi-square test for categorical variables. I also used the general

linear models with contrast coefficients for linear trend test for continuous variables. The Cochran-Armitage test was performed for linear trend for categorical variables.

Correlation between eGFR and ADMA concentrations was assessed by Pearson's coefficients in men, and women. To evaluate independent associations between eGFR status (including eGFR level) and plasma ADMA concentration, I carried out multiple linear regression analyses in three adjusted models: model 1 was unadjusted analyses; model 2 was adjusted for blood pressure, diabetes, total cholesterol, HDL cholesterol, smoking status, and drinking status; and model 3 was adjusted for sex, age, BMI, blood pressure, diabetes, total cholesterol, HDL cholesterol, smoking status, and drinking status. I also tested multiple logistic regression analyses in order to assess the association of eGFR reduction and ADMA elevation in three adjusted models.

All analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC, USA), and statistical significance was defined as a two-sided p value less than 0.05.

Ⅲ. RESULTS

1. Characteristics of study population

Table 1 shows the demographic and clinical characteristics of 651 participants. The study consisted of 269 men and 382 women. The mean age was 71.6 years old (men, 72.2 years old; women, 71.1 years old). Mean eGFR in men was significantly higher than in women (55.1 vs. 50.3 mL/min/1.73m^2, $p<0.001$). Furthermore height, weight, diastolic blood pressure, fasting glucose, serum creatinine and BUN were significantly higher in men then in women. Whereas BMI, pulse pressure (PP), fasting insulin, total and low density lipoprotein (LDL) cholesterol, and TG had significant high level of mean in women, compared to men. However, the mean ADMA concentrations was not significantly different between men and women (0.677 vs. 0.671 ㎛ol/L; p=0.542).

Table 1. General characteristics of study population in total, men, and women

Variables	Total (n=651)	Men (n=269)	Women (n=382)	p-value
eGFR, mL/min/1.73m²	52.3 ± 15.6	55.1 ± 14.9	50.3 ± 15.7	<0.001
Age, yr	71.6 ± 7.5	72.2 ± 6.8	71.1 ± 7.9	0.061
Height, cm	155.1 ± 9.2	162.7 ± 6.3	149.7 ± 6.8	<0.001
Weight, kg	57.9 ± 10.5	62.5 ± 10.1	54.6 ± 9.5	<0.001
Body mass index, kg/m²	24.0 ± 3.4	23.6 ± 3.4	24.3 ± 3.4	0.007
Systolic BP, mmHg	134.2 ± 20.1	132.9 ± 19.8	135.1 ± 20.3	0.165
Diastolic BP, mmHg	72 ± 10.1	73.1 ± 10.4	71.2 ± 9.9	0.023
Pulse pressure, bpm	62.2 ± 16.9	59.9 ± 15.8	63.9 ± 17.5	0.003
Fasting glucose, mg/dL	90 [83, 101]	91 [83, 106]	89 [83, 98]	0.034
Fasting insulin, uIU/mL	7.6 [5.9, 10.3]	7.0 [5.5, 10.4]	7.9 [6.2, 10.2]	0.006
Total cholesterol, mg/dL	181.9 ± 36	172.2 ± 34.6	188.7 ± 35.5	<0.001
LDL cholesterol, mg/dL	99.2 ± 32.7	90.7 ± 31.9	105.1 ± 32	<0.001
HDL cholesterol, mg/dL	50.9 ± 12.7	50.1 ± 13.3	51.5 ± 12.3	0.147
Triglycerides, mg/dL	136 [102, 188]	129 [94, 178]	141 [105, 193]	0.029
BUN, mg/dL	15.8 [13.1, 19.1]	16.6 [13.9, 19.3]	15.2 [12.7, 18.7]	0.001
Creatinine, mg/dL	0.95 [0.85, 1.09]	1.06 [0.97, 1.19]	0.88 [0.81, 0.98]	<0.001
ADMA, μmol/L	0.674 ± 0.111	0.677 ± 0.109	0.671 ± 0.112	0.542
ADMA elevation *	182 (28.0)	80 (12.3)	102 (15.7)	0.396
Diabetes, %	62 (9.5)	33 (12.3)	29 (7.6)	0.047
Hypertension, %	420 (64.5)	163 (60.6)	257 (67.3)	0.080
Hyperlipidemia, %	181 (27.8)	75 (27.9)	106 (27.8)	0.970
Smoking				
Non-smoker	456 (70.0)	82 (30.5)	374 (97.9)	<0.001
Past smoker	117 (18.0)	117 (43.5)	0 (0.0)	
Current smoker	78 (12.0)	70 (26.0)	8 (2.1)	
Drinking				
Non-drinker	512 (78.7)	154 (57.3)	358 (93.7)	<0.001
Current drinker	139 (21.3)	115 (42.7)	24 (6.3)	

Values are shown as mean±SD, median[IQR], or number (%).

eGFR, estimated glomerular filtration rate; BP, blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; BUN, blood urea nitrogen; ADMA, asymmetric dimethylarginine.

* ADMA elevation, people with ADMA concentrations >75th percentile

2. General characteristics according to eGFR reduction status

Table 2, 3, and 4 present the general characteristics according to eGFR reduction status in total group, men, and women, respectively. In table 2, participants with normal to minimally-reduced eGFR (≥60 mL/min/1.73m^2) were 198 (30.4%), people with moderately-reduced eGFR (30-60< mL/min/1.73m^2) were 407 (62.5%), and severely-reduced eGFR group was consisted of 46 (7.1%) among total study population. The mean of ADMA concentrations was significantly higher in people with moderately-reduced eGFR (0.676 ㎛ol/L) and severely-reduced eGFR (0.715 ㎛ol/L) compared to people with normal to minimally-reduced eGFR (0.659 ㎛ol/L, p=0.007). The trend of SBP was significantly increased as eGFR reduction was become severe. Whereas, the trends of BMI, DBP, and TG were significantly decreased as eGFR was severely reduced.

Table 2. General characteristics according to eGFR reduction status in total participants

Variables	eGFR status			*p-value*
	Normal to minimally-reduced (≥60, n=198)	Moderately-reduced (30-<60, n=407)	Severely-reduced (<30, n=46)	
eGFR, mL/min/1.73m²	70.0 ± 9.7	47.0 ± 7.7	22.9 ± 6.4	<0.001
Age, yr	66.1 ± 5.4	73.0 ± 6.4	82.2 ± 6.5	<0.001
Body mass index, kg/m²	26.0 ± 3.3	23.3 ± 19.4	21.1 ± 3.1	<0.001
Systolic BP, mmHg	133.1 ± 19.6	133.8 ± 9.7	142.2 ± 16.1	0.017
Diastolic BP, mmHg	74.5 ± 9.9	71.3 ± 9.7	67.5 ± 12.2	<0.001
Fasting glucose, mg/dL	91 [83, 105]	89 [83, 99]	90 [85, 103]	0.020
Fasting insulin, uIU/mL	8.2 [6.5, 11.3]	7.3 [5.6, 9.9]	6.5 [5.4, 9.1]	0.628
Total cholesterol, mg/dL	183.6 ± 36.1	182.2 ± 35.7	171.2 ± 37.7	0.101
HDL cholesterol, mg/dL	50.0 ± 12.4	51.7 ± 12.6	48.5 ± 14.8	0.123
Triglycerides, mg/dL	143 [109, 203]	133 [98, 176]	130 [89, 193]	0.002
ADMA, μmol/L	0.659 ± 0.110	0.676 ± 0.108	0.715 ± 0.127	0.007
ADMA elevation *	48 (24.2)	114 (28.0)	20 (43.5)	0.025
Diabetes, %	15 (7.6)	40 (9.8)	7 (15.2)	0.127
Hypertension, %	128 (64.7)	258 (63.4)	34 (73.9)	0.556
Hyperlipidemia, %	63 (31.8)	103 (25.3)	15 (32.6)	0.184
Men, sex	101 (51.0)	154 (37.8)	14 (30.4)	0.001
Smoking				
Non-smoker	172 (86.9)	361 (88.7)	40 (87.0)	0.703
Current smoker	26 (13.1)	46 (11.3)	6 (13.0)	
Drinking				
Non-drinker	141 (71.2)	330 (81.1)	41 (89.1)	0.001
Current drinker	57 (28.8)	77 (18.9)	5 (10.9)	

Values are shown as mean±SD, median[IQR], or number (%).

eGFR, estimated glomerular filtration rate; BP, blood pressure; HDL, high-density lipoprotein; ADMA, asymmetric dimethylarginine.

* ADMA elevation, people with ADMA concentrations >75th percentile

Table 3 shows the demographic characteristics in men according to eGFR reduction status. The eGFR statuses were consisted of 101 men with normal to minimally-reduced eGFR (37.6%), 154 men with moderately-reduced eGFR (57.2%), and 14 men with severely-reduced eGFR (5.2%). As the eGFR was reduced, plasma ADMA concentrations were significantly increased in men. On the other hand, BMI, DBP, and TG were significantly lower in men with severely-reduced eGFR, compared with normal to minimally-reduced eGFR.

Table 3. General characteristics according to eGFR reduction status in men

Variables	eGFR status			*p-value*
	Normal to minimally-reduced (≥60, n=101)	Moderately-reduced (30-<60, n=154)	Severely-reduced (<30, n=14)	
eGFR, mL/min/1.73m²	69.8 ± 8.6	48.3 ± 7.3	23.4 ± 6.4	<0.001
Age, yr	67.5 ± 4.9	74.3 ± 5.7	82.9 ± 6.5	<0.001
Body mass index, kg/m²	25.5 ± 3.4	22.5 ± 2.9	21.0 ± 3.1	<0.001
Systolic BP, mmHg	134.0 ± 20.7	132.2 ± 19	132.3 ± 16.1	0.779
Diastolic BP, mmHg	77.1 ± 9.8	71.1 ± 9.7	65.0 ± 12.2	<0.001
Fasting glucose, mg/dL	94 [85, 108]	92 [83, 105]	88 [76, 90]	0.174
Fasting insulin, uIU/mL	7.6 [6.1, 11.7]	6.8 [5.2, 10.3]	5.2 [4.5, 6.3]	0.189
Total cholesterol, mg/dL	173.2 ± 37.8	173.2 ± 32.4	154.7 ± 31	0.152
HDL cholesterol, mg/dL	49.1 ± 13.6	50.9 ± 13.3	47.6 ± 9.8	0.451
Triglycerides, mg/dL	146 [109, 203]	120 [85, 161]	99 [78, 167]	0.001
ADMA, μmol/L	0.655 ± 0.111	0.681 ± 0.104	0.786 ± 0.786	<0.001
ADMA elevation *	23 (22.8)	47 (30.5)	10 (71.4)	0.003
Diabetes, %	11 (10.9)	22 (14.3)	0 -	0.915
Hypertension, %	68 (67.3)	86 (55.8)	9 (64.3)	0.168
Hyperlipidemia, %	32 (31.7)	40 (26.0)	3 (21.4)	0.524
Smoking				
Non-smoker	76 (75.2)	114 (74.0)	9 (64.3)	0.519
Current smoker	25 (24.8)	40 (26.0)	5 (35.7)	
Drinking				
Non-drinker	52 (51.5)	91 (59.1)	11 (78.6)	0.056
Current drinker	49 (48.5)	63 (40.9)	3 (21.4)	

Values are shown as mean±SD, median[IQR], or number (%).

eGFR, estimated glomerular filtration rate; BP, blood pressure; HDL, high-density lipoprotein; ADMA, asymmetric dimethylarginine.

* ADMA elevation, people with ADMA concentrations >75th percentile

Table 4 presents the baseline characteristics in women regarding eGFR reduction status. Each status in eGFR reduction accounted for 25.4%, 66.2%, and 8.4% in normal to minimally-reduced, moderately-reduced, and severely-reduced eGFR, respectively. Women with severely-reduced eGFR had significantly lower BMI, compared to those with normal to minimally-reduced eGFR. However, the trends of SBP and fasting glucose were increased significantly as the function of eGFR was reduced. Furthermore, mean ADMA concentrations had no significant difference among three groups of eGFR reduction.

Table 4. General characteristics according to eGFR reduction status in women

Variables	eGFR status			*p-value*
	Normal to minimally-reduced (≥60, n=97)	Moderately-reduced (30-<60, n=253)	Severely-reduced (<30, n=32)	
eGFR, mL/min/1.73m²	70.1 ± 10.8	46.2 ± 7.8	22.6 ± 6.1	<0.001
Age, yr	64.6 ± 5.6	72.3 ± 6.7	81.9 ± 6.4	<0.001
Body mass index, kg/m²	26.6 ± 3.1	23.7 ± 3.0	21.2 ± 3.3	<0.001
Systolic BP, mmHg	132.2 ± 18.5	134.8 ± 19.6	146.6 ± 26.6	0.002
Diastolic BP, mmHg	71.7 ± 9.3	71.4 ± 9.7	68.6 ± 12.8	0.281
Fasting glucose, mg/dL	89 [82, 99]	89 [83, 97]	94 [86, 114]	<0.001
Fasting insulin, uIU/mL	8.3 [7.0, 11.1]	7.7 [5.9, 9.8]	7.7 [6.2, 10.7]	0.297
Total cholesterol, mg/dL	194.5 ± 30.9	187.8 ± 36.5	178.3 ± 38.5	0.065
HDL cholesterol, mg/dL	50.9 ± 11	52.1 ± 12.1	48.8 ± 16.7	0.298
Triglycerides, mg/dL	138 [108, 203]	141 [102, 188]	154 [110, 221]	0.496
ADMA, μmol/L	0.664 ± 0.110	0.673 ± 0.111	0.684 ± 0.131	0.627
ADMA elevation *	25 (25.8)	67 (26.5)	10 (31.3)	0.624
Diabetes, %	4 (4.1)	18 (7.1)	7 (21.9)	0.006
Hypertension, %	60 (61.9)	172 (68.0)	25 (78.1)	0.087
Hyperlipidemia, %	31 (32.0)	63 (24.9)	12 (37.5)	0.191
Smoking				
Non-smoker	96 (99.0)	247 (97.6)	31 (96.9)	0.381
Current smoker	1 (1.0)	6 (2.4)	1 (3.1)	
Drinking				
Non-drinker	89 (91.8)	239 (94.5)	30 (93.7)	0.467
Current drinker	8 (8.2)	14 (5.5)	2 (6.3)	

Values are shown as mean±SD, median[IQR], or number (%).

eGFR, estimated glomerular filtration rate; BP, blood pressure; HDL, high-density lipoprotein; ADMA, asymmetric dimethylarginine.

* ADMA elevation, people with ADMA concentrations >75th percentile

3. Correlation between eGFR and plasma ADMA concentrations

Figure 1 shows the correlation of eGFR and plasma ADMA concentrations in men and women. The correlation was described using Pearson's coefficients with scatter plots. The eGFR was negatively correlated with ADMA concentrations among men in unadjusted model ($r=-0.23$, $p<0.01$). However, the inverse correlation between eGFR and ADMA concentrations was not significant in women ($r=-0.05$, $p=0.373$).

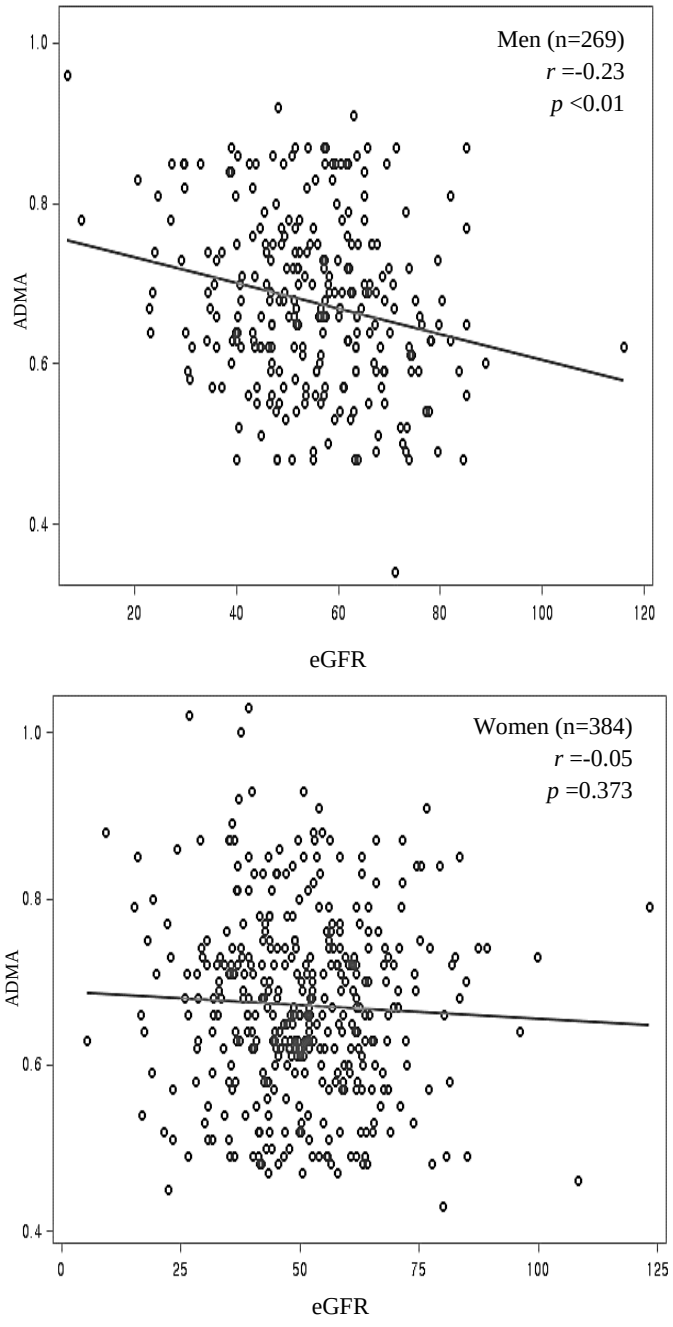

Figure 1. Correlation between eGFR and ADMA concentrations in men and women

4. Association between eGFR and ADMA concentrations

Table 5 outlines the linear association of continuous eGFR and ADMA concentrations from multiple regression analyses in men and women. According to sex-specific analysis in table 5, eGFR was significantly and inversely associated with plasma ADMA concentrations among men in unadjusted model (β= -0.0017, p <0.001). After adjusting for SBP, DBP, total and HDL cholesterol, diabetes, smoking status, and alcohol consumption, the inverse association of continuous eGFR and ADMA concentrations was still significant (β= -0.0014, p= 0.006). Moreover, after additional adjustment for age and BMI, eGFR was significantly and negatively associated with ADMA concentrations in men (β= -0.0022, p= 0.002). On the other hand, in women, the association of eGFR and ADMA concentrations was not significant in unadjusted model. After multiple adjustments for age, BMI, SBP, DBP, total and HDL cholesterol, diabetes, smoking status, and drinking status, eGFR was not significantly associated with plasma ADMA concentrations from statistical point (β= -0.0011, p= 0.077), however, considering sample size, I could suggest that women might have significantly inverse association of eGFR and ADMA concentrations after multiple adjustment.

Table 6 describes the relationship of eGFR and ADMA concentrations in study population with normal to moderately-reduced eGFR. I suggested these tables in order to emphasize that the significant association was also shown in general healthy older adults without severely-reduced eGFR through a sensitivity analysis. In table 6 from a sex-specific analysis, low eGFR were significantly associated with high ADMA concentrations

in men (β= -0.0017, p =0.042) and women (β= -0.0016, p =0.034) with normal to moderately-reduced eGFR after adjusted for age, BMI, blood pressure, total and HDL cholesterol, diabetes, smoking habit, and drinking status. According to table 6, I would insist both of general men and women, excluding people with severely-reduced eGFR, are related to eGFR and ADMA concentration.

Table 5. Association between eGFR and ADMA concentrations in men and women

Variables	Model 1		Model 2		Model 3	
	β (㎛ol/L)	p value	β (㎛ol/L)	p value	β (㎛ol/L)	p value
MEN (n=269)						
eGFR (mL/min/1.73m²)	-0.0017	<0.001	-0.0014	0.006	-0.0022	0.002
Systolic BP (mmHg)			0.0001	0.900	-0.0003	0.570
Diastolic BP (mmHg)			-0.0009	0.338	-0.0005	0.587
Total cholesterol (mg/dL)			-0.0001	0.571	-0.0002	0.392
HDL cholesterol (mg/dL)			0.0003	0.612	0.0007	0.184
Diabetes			0.0168	0.409	0.0103	0.610
Current smokers (for non-smokers)			0.0264	0.087	0.0329	0.032
Current drinkers (for non-drinkers)			-0.0040	0.777	-0.0047	0.739
Age (yr)					0.0006	0.673
BMI (kg/m²)					0.0074	0.005
WOMEN (n=382)						
eGFR (mL/min/1.73m²)	-0.0003	0.373	-0.0004	0.360	-0.0011	0.077
Systolic BP (mmHg)			-0.0001	0.676	-0.0001	0.863
Diastolic BP (mmHg)			0.0005	0.431	0.0003	0.652
Total cholesterol (mg/dL)			0.00003	0.886	0.00002	0.930
HDL cholesterol (mg/dL)			-0.0006	0.253	-0.0004	0.408
Diabetes			-0.0085	0.707	-0.0143	0.535
Current smokers (for non-smokers)			0.0485	0.240	0.0488	0.237
Current drinkers (for non-drinkers)			-0.0456	0.062	-0.0447	0.069
Age (yr)					-0.0012	0.279
BMI (kg/m²)					0.0032	0.159

eGFR, estimated glomerular filtration rate; BP, blood pressure; HDL, high-density lipoprotein; BMI, body mass index.

Model 1: unadjusted

Model 2: adjusted for blood pressure, total and HDL cholesterol, diabetes, smoking status, and drinking status.

Model 3: adjusted for age, BMI, blood pressure, total and HDL cholesterol, diabetes, smoking status, and drinking status.

Table 6. Association between eGFR and ADMA concentrations in men and women, after excluding people with severely-reduced eGFR

Variables	Model 1		Model 2		Model 3	
	β (㎛ol/L)	p value	β (㎛ol/L)	p value	β (㎛ol/L)	p value
MEN (n=255)						
eGFR (mL/min/1.73m²)	-0.0011	0.041	-0.0007	0.218	-0.0017	0.042
Systolic BP (mmHg)			0.0000	0.974	-0.0003	0.464
Diastolic BP (mmHg)			-0.0006	0.510	-0.0002	0.812
Total cholesterol (mg/dL)			-0.0001	0.625	-0.0002	0.412
HDL cholesterol (mg/dL)			0.0003	0.585	0.0007	0.173
Diabetes			0.0202	0.323	0.0126	0.536
Current smokers (for non-smokers)			0.0177	0.057	0.0217	0.020
Current drinkers (for non-drinkers)			-0.0075	0.610	-0.0086	0.550
Age (yr)					0.0006	0.695
BMI (kg/m²)					0.0076	0.007
WOMEN (n=350)						
eGFR (mL/min/1.73m²)	-0.0002	0.577	-0.0002	0.593	-0.0016	0.034
Systolic BP (mmHg)			-0.0001	0.846	0.0000	0.948
Diastolic BP (mmHg)			0.0003	0.727	0.0000	0.981
Total cholesterol (mg/dL)			-0.00001	0.968	-0.00003	0.857
HDL cholesterol (mg/dL)			-0.0004	0.448	-0.0002	0.695
Diabetes			-0.0307	0.228	-0.0364	0.154
Current smokers (for non-smokers)			0.0170	0.429	0.0167	0.437
Current drinkers (for non-drinkers)			-0.0456	0.067	-0.0427	0.086
Age (yr)					-0.0020	0.097
BMI (kg/m²)					0.0051	0.033

eGFR, estimated glomerular filtration rate; BP, blood pressure; HDL, high-density lipoprotein; BMI, body mass index.

Model 1: unadjusted

Model 2: adjusted for blood pressure, total and HDL cholesterol, diabetes, smoking status, and drinking status.

Model 3: adjusted for age, BMI, blood pressure, total and HDL cholesterol, diabetes, smoking status, and drinking status.

5. Categories of eGFR and ADMA concentration

Table 7 shows relationships between categories of eGFR and ADMA concentrations in men and women by using multiple linear regression and logistic regression analyses. In men, the significant association of severely-reduced eGFR and higher ADMA concentration was also present in model 1, 2, and 3. The unadjusted OR for having ADMA elevation in severely-reduced eGFR was 8.5 (2.4-29.6). Compared with normal to minimally-reduced eGFR, the adjusted ORs of severely-reduced eGFR were 5.6 (1.3-23.8) and 5.7 (1.2-27.4) in adjusted model 2 and model 3, respectively. On the other hand, for women, the ADMA concentration was not significantly increased in moderately and severely-reduced eGFR regardless of adjustments. Furthermore, the ORs for ADMA elevation of moderately and severely-reduced eGFR were not significant in unadjusted and adjusted model. The fully adjusted ORs in severely-reduced eGFR seemed not significant in a statistical aspect, compared to those in normal to minimally-reduced eGFR. However, when I considered sample size and the length of confidence interval, the multiple adjusted OR of severely-reduced eGFR was significant for ADMA elevation in women.

Table 7. Categories of eGFR and ADMA concentrations in men and women

eGFR reduction	Adjusted mean ADMA concentration	β (㎛ol/L)	p-value	Case / no. of participants (%)	OR for ADMA elevation*
Men (n=269)					
Model 1					
Normal to minimally-reduced (≥60)	0.6554	reference	-	23 / 101 (22.8)	1.0 (reference)
Moderately-reduced (30-<60)	0.6808	0.0254	0.062	47 / 154 (30.5)	1.5 (0.8-2.7)
Severely-reduced (<30)	0.7857	0.1303	<0.001	10 / 14 (71.4)	8.5 (2.4-29.6)
Model 2					
Normal to minimally-reduced (≥60)	0.6619	reference	-	23 / 101 (22.8)	1.0 (reference)
Moderately-reduced (30-<60)	0.6777	0.0157	0.281	47 / 154 (30.5)	1.2 (0.6-2.4)
Severely-reduced (<30)	0.7742	0.1116	<0.001	10 / 14 (71.4)	5.6 (1.3-23.8)
Model 3					
Normal to minimally-reduced (≥60)	0.6584	reference	-	23 / 101 (22.8)	1.0 (reference)
Moderately-reduced (30-<60)	0.6800	0.0217	0.211	47 / 154 (30.5)	1.2 (0.6-2.6)
Severely-reduced (<30)	0.7736	0.1147	0.002	10 / 14 (71.4)	5.7 (1.2-27.4)
Women (n=382)					
Model 1					
Normal to minimally-reduced (≥60)	0.6635	reference	-	25 / 97 (25.8)	1.0 (reference)
Moderately-reduced (30-<60)	0.6727	0.0092	0.493	67 / 253 (26.5)	1.0 (0.6-1.8)
Severely-reduced (<30)	0.6844	0.0209	0.364	10 / 32 (31.3)	1.3 (0.6-3.1)
Model 2					
Normal to minimally-reduced (≥60)	0.6622	reference	-	25 / 97 (25.8)	1.0 (reference)
Moderately-reduced (30-<60)	0.6729	0.0090	0.510	67 / 253 (26.5)	1.3 (0.7-2.4)
Severely-reduced (<30)	0.6871	0.0235	0.333	10 / 32 (31.3)	2.3 (0.8-6.7)
Model 3					
Normal to minimally-reduced (≥60)	0.6538	reference	-	25 / 97 (25.8)	1.0 (reference)
Moderately-reduced (30-<60)	0.6746	0.0188	0.253	67 / 253 (26.5)	1.5 (0.8-2.8)
Severely-reduced (<30)	0.6992	0.0433	0.158	10 / 32 (31.3)	2.9 (0.9-9.6)

eGFR, estimated glomerular filtration rate; ADMA, asymmetric dimethylarginine; OR, odds ratio; BMI, body mass index.

Model 1: unadjusted

Model 2: adjusted for blood pressure, total and HDL cholesterol, diabetes, smoking and drinking status.

Model 3: adjusted for age, BMI, blood pressure, total and HDL cholesterol, diabetes, smoking and drinking status.

* ADMA elevation, people with ADMA concentrations >75th percentile

Ⅳ. DISCUSSION

1. Summary of findings

This cross-sectional study assessed to the association between eGFR and plasma ADMA concentrations in general older adults. In a sex-specific analyses, the inverse association was significant in men before and after adjusted for sex, age, BMI, SBP, DBP, total and HDL cholesterol, diabetes, and smoking and drinking status. In women, the association was not seemed significant at the view of statistics however, considering the sample size, p-value was in borderline of statistical significance level. Therefore, the association of eGFR and ADMA concentration among women might have a significant meaning after multiple adjustments. Even after excluded participants with severely-reduced eGFR, the relationship remained significant among normal to moderately-reduced eGFR groups. Besides, after fully adjusting, men and women with normal to moderately-reduced eGFR had the significantly inverse associations between eGFR and ADMA concentrations. According to this result, the association between low eGFR and high ADMA concentration was significant in general elderly participants without severely-reduced eGFR.

In addition, men showed the higher ORs for ADMA elevation of severely-reduced eGFR than of normal to minimally-reduced eGFR. In case of women, the unadjusted ORs for ADMA elevation remained not significantly in moderately and severely-reduced eGFR, compared to normal to minimally-reduced eGFR. However, after adjusted potential

confounders, the OR for having high ADMA concentrations seemed almost significantly in severely-reduced eGFR, considering the length of confidence interval and sample size.

2. Comparison with previous studies

I observed whether there is the inverse association of eGFR and ADMA concentrations in general elderly people. My results are in consistent with various previous studies (Fleck, Schweitzer et al. 2003, Safar, London et al. 2004, Fliser, Kronenberg et al. 2005, Wang, Sim et al. 2006, Townsend, Wimmer et al. 2010). According to a prospective study, which was conducted for 227 patients with the mild to moderate kidney disease from Germany, Austria, and South Tyrol, ADMA concentrations were significantly and negatively correlated with GFR, and positively correlated with age and serum creatinine. Mean ADMA concentrations in advanced CKD patients with GFR <30 ml/min/1.73 m^2 were significantly higher than in CKD patients with GFR ≥90 ml/min/1.73 m^2. Furthermore, this study suggested that ADMA elevation was one of factors which promote progression of CKD (Fliser, Kronenberg et al. 2005). A cross-sectional study in Australia was conducted for 145 patients aged 40 to 74 with coronary artery disease. Although this study included only patients with GFR≥45 ml/min/1.73 m^2, patients in low GFR group (GFR<81 ml/min/1.73 m^2) had significantly higher ADMA concentrations, compared to high GFR group (GFR≥81 ml/min/1.73 m^2). The association of GFR and ADMA concentrations was also independent of sex, age, and cigarette smoking habit (Wang, Sim et al. 2006). In the

Chronic Renal Insufficiency Cohort (CRIC) study, the arterial stiffness, measured using aortic pulse wave velocity (PWV), was investigated to assess the effects of aortic PWV on CKD. The degree of kidney function was significantly negative associated with aortic PWV even after adjusted for potential confounders. Because arterial stiffness is one of factors that promote endothelial dysfunctions, the reduced kidney function might be related to elevated ADMA concentrations (Townsend, Wimmer et al. 2010). According to a review paper, the association between increased aortic PWV and reduced creatinine clearance was significant in normal participants and in people with high blood pressure, even though the association was not significant in experimental rat models of moderate renal insufficiency. Furthermore, age, blood pressure, and diabetes mellitus were factors that have independently effects on the level of PWV (Safar, London et al. 2004). One of previous paper observed the differences of mean ADMA concentrations among patients with CKD. In results, CKD and dialysis patients had significant higher ADMA concentrations compared to control group (Fleck, Janz et al. 2001).

Moreover, my study targeted to elderly people, old-age might be a factor that affected the association of kidney function and ADMA concentrations. In American's paper, decline of eGFR in the elderly was an independent predictor for adverse outcomes because eGFR considers age, sex, and body size in the equation (Levey, Coresh et al. 2003). In addition, even though there were more women than men, the significant association of eGFR and ADMA concentration was weaker in women than in men. Same as our findings which have weak associations in women, there are several sex-specific studies that investigated the

renal function (Coggins, Breyer Lewis et al. 1998, Swedko, Clark et al. 2003, Cirillo, Anastasio et al. 2005, Kielstein, Martens-Lobenhoffer et al. 2008). According to the papers, serum creatinine, which one of factors that consist of eGFR, was determined by muscle mass. Hence, sex difference was occurred because women and elderly people have relative low muscle mass compared to men and young people. In a case of elderly women, the creatinine concentrations were within normal ranges compared to low muscle mass, although their kidney was quite impaired. Thus, several researchers suggested that eGFR might underestimate the renal function in women, especially elderly people. However, the potential reasons why women had a weaker association compared to men, despite of the large sample size are not explained yet and the possible mechanism of sex difference is remained unclear. It is also hard to compare my results with other study findings because few papers have investigated sex-specific research. Further studies should investigate the reason of sex bias in a kidney function.

However, a few previous studies are contrasted with my findings. According to the Multi-Ethnic Study of Atherosclerosis (MESA), there is no significant association between endothelial dysfunction, measured as flow-mediated dilation (FMD), and differences in eGFR decline among 2,997 participants with eGFR >60 ml/min/1.73 m^2. Arterial stiffness also accelerates kidney dysfunction (Peralta, Jacobs et al. 2012). However, this MESA study had some limitations that it was conducted for persons with eGFR > 60 ml/min/1.73 m^2 and FMD may not be able to accurately measure the relationship of endothelial dysfunction and kidney function. In the Framing Heart Study, they could not found a

significant association between endothelial dysfunction and CKD status for 2,301 participants. Especially moderate CKD patients were not correlated with endothelial dysfunction (Foster, Keyes et al. 2008). However, this study also measured endothelial function by using FMD and conducted for only white. Therefore, the study might have measurement errors and has limitation to generalize the results to Asians.

3. Possible explanations

In this study, I could observed the inverse association of eGFR and ADMA concentrations among the Korean elderly in a rural community. Although the mechanisms underlying the association are unclear, several previous papers suggest a couple of possible mechanisms that support the link between kidney function and ADMA concentrations.

According to previous studies, ADMA is degraded by the dimethylarginine dimethlylaminohydrolase (DDAH) enzyme (MacAllister, Fickling et al. 1994, Böger and Bode-Böger 2000). The tissues of kidney, blood vessels, and pancreas produce the DDAH enzyme (Ito, Tsao et al. 1999, Alpoim, Sousa et al. 2015). According to animal study, kidney takes a major part in DDAH expression (Ito, Tsao et al. 1999). Besides, the excretion of ADMA is conducted through urine (Fleck, Schweitzer et al. 2003). After hemodialysis treatments, patients with renal failure have significantly reduced ADMA concentrations and improved endothelial function (Cross, Donald et al. 2001). Thus, the lower kidney function can lead to elevation of ADMA concentration (Safar, London et al. 2004, Lücke,

Kanzelmeyer et al. 2008), because the ADMA is metabolized by DDAH activity from kidney and removed via renal excretion (Figure 2). However, due to limitations of a cross-sectional study design, investigating a causal relationship between eGFR and ADMA concentration is difficult. Therefore, contrary to the explanation that I suggested, ADMA elevation might be able to cause eGFR reduction. If so, ADMA elevation would be one of risk factors for renal diseases.

According to a disease-stratified analysis, the association of low eGFR and high ADMA concentration in people with hypertension was significantly showed after fully adjusted. However, people without hypertension did not have the significant inverse association of eGFR and ADMA concentrations (Table S1). On the other hand, even after excluding people with diabetes or hyperlipidemia, the significant association was remained unchanged. According to these results, hypertension has a possibility that might be a major confounder or mediator which can affect the association of eGFR and ADMA concentration, unlike diabetes and hyperlipidemia. Thus, further studies should be performed for finding the possible association among eGFR, ADMA concentrations, and hypertension.

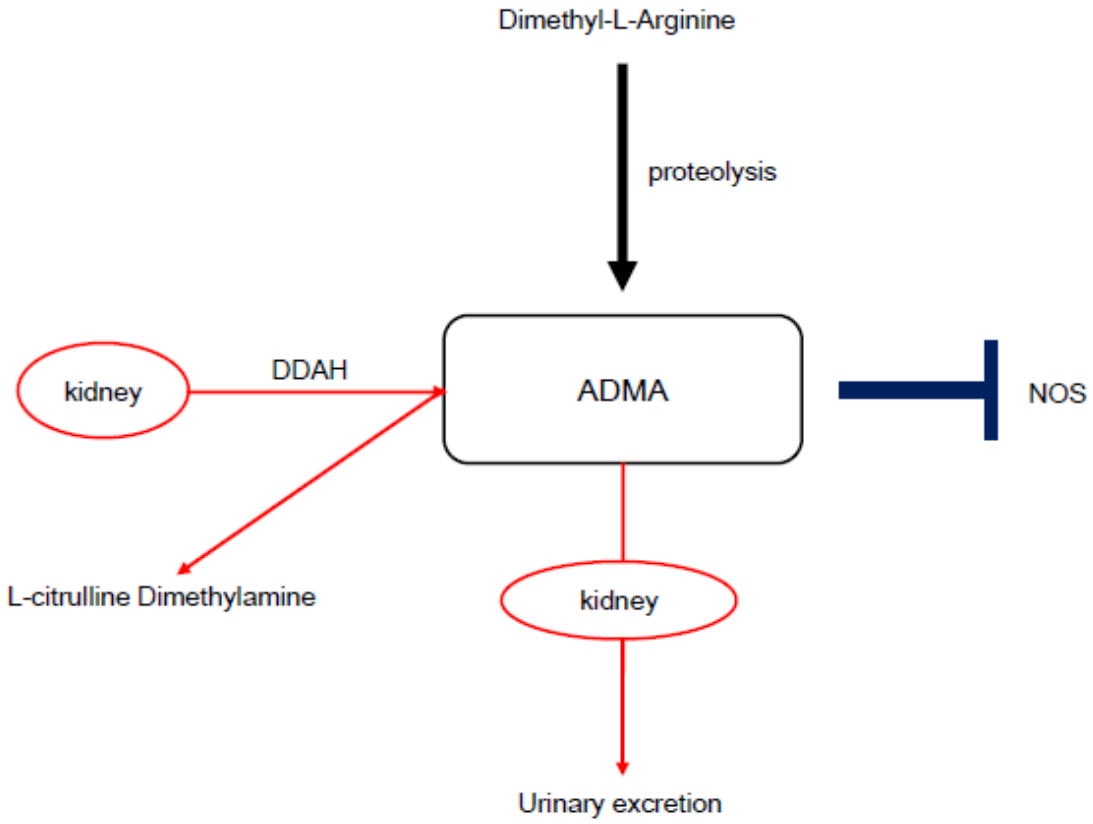

Figure 2. Overview of metabolic pathways for asymmetric dimethylarginine (ADMA).

DDAH, dimethylarginine dimethylaminohydrolase; NOS, nitric oxide synthesis

4. Strengths and limitations

Study participants were recruited from a rural community of a single ethnic background. Accordingly, the findings of study are not seemed to be influenced by potential confounding variables, for example ethnicity, residential area, or environmental factors. Secondly, I adjusted for various confounders with multiple statistical analyses. Potential confounders were selected based on previous studies and included sex, age, BMI, blood pressure, total and HDL cholesterol, and smoking and drinking habit. Lastly, even though a few researches have been conducted for Asian people, I performed exclusively on the elderly Koreans. Thus, I could assess whether eGFR reduction was related to elevated ADMA concentration in Korean elderly population.

I also have some limitations. First, the findings could suggest only an association between eGFR and ADMA concentrations because of its cross-sectional design. Since I could not find a causal relationship, the definitive mechanisms between kidney function and ADMA were not explained. Second, people who live a single rural community were only enrolled in this study. Hence, the results would be hard to be generalized to other population. Third, I could not measure GFR directly. I only used eGFR for measuring kidney function. Although many studies measured renal function using eGFR, the measurement is an estimated equation. Therefore, using estimated GFR could be not exact to measure kidney function and lead to incorrect conclusion. Lastly, I could not explain sex-dependent results. Even though a few papers studies the association between kidney function and endothelial or cardiovascular disease, the authors indicated only the potential

explanation, not definitive reason about sex-bias results. Hence, finding clear mechanisms for sex-dependent results should be more studied.

Ⅴ. CONCLUSION

In conclusion, lower eGFR was associated with higher ADMA concentration in a dose-response manner among the general elderly population. This finding implies that older adults with minimally to moderately reduced GFR might have endothelial dysfunction and increased risk of cardiovascular disease. Further studies are required to verify the causal relationship of eGFR and plasma ADMA concentration.

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Table S1. Association between eGFR and ADMA concentrations in participants with or without hypertension

Variables	Model 1		Model 2		Model 3	
	β (㎛ol/L)	p-value	β (㎛ol/L)	p-value	β (㎛ol/L)	p-value
with hypertension (n=386)						
eGFR (mL/min/1.73m²)	-0.0007	0.096	-0.0007	0.114	-0.0019	0.005
Total cholesterol (mg/dL)			0.0001	0.450	0.0001	0.513
HDL cholesterol (mg/dL)			-0.0001	0.876	0.0001	0.850
Diabetes			-0.0109	0.588	-0.0174	0.391
Current smokers (for non-smokers)			0.0154	0.118	0.0121	0.295
Current drinkers (for non-drinkers)			-0.0195	0.205	-0.0222	0.165
Sex					-0.0208	0.224
Age (yr)					-0.0018	0.118
BMI (kg/m²)					0.0049	0.035
without hypertension (n=219)						
eGFR (mL/min/1.73m²)	-0.0004	0.507	-0.0002	0.689	-0.0014	0.117
Total cholesterol (mg/dL)			-0.0004	0.116	-0.0006	0.023
HDL cholesterol (mg/dL)			-0.0002	0.809	0.0003	0.600
Diabetes			0.0028	0.915	-0.0019	0.942
Current smokers (for non-smokers)			0.0165	0.122	0.0341	0.008
Current drinkers (for non-drinkers)			-0.0265	0.179	-0.0251	0.202
Sex					0.0295	0.152
Age (yr)					-0.0003	0.843
BMI (kg/m²)					0.0081	0.006

eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; BMI, body mass index.

Model 1: unadjusted

Model 2: adjusted for total and HDL cholesterol, diabetes, smoking status, and drinking status.

Model 3: adjusted for sex, age, BMI, total and HDL cholesterol, diabetes, smoking status, and drinking status.

ABSTRACT (KOREAN)

농촌 지역의 일반 노인에서의 사구체 여과율과 혈장 ADMA 농도와의 관련성

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배경 및 목적

노화에 의한 신장 기능의 저하로 인해 사구체 여과율의 감소는 노년층의 일반적인 장애로 알려져 있다. 또한, 혈장 ADMA 농도의 증가는 심혈관계 질환의 위험 인자 중 하나이며, 노화에 따라 증가한다는 연구가 보고된 바 있다. 하지만 신장 기능과 ADMA 농도와의 관련성에 대한 연구는 대부분 신장 기능 장애 환자에 대한 환자-대조군 연구로 진행되고 있으며, 일반적인 노인에 대한 연구는 진행되고 있지 않는 실정이다. 이러한 점에서 이 연구는 환자뿐만 아니라 일반적인 노인을 대상으로 사구체 여과율과 혈장 ADMA 농도와의 관련성을 보는 것을 목적으로 한다.

연구 방법

이 단면 연구는 Korean Social Life, Health, and Aging Project (KSHAP)에 등록되어 있는 651 명의 강화도 거주노인 (269 명의 남자와 382 명의 여자)을 대상으로

진행하였다 (평균 나이, 71.6 세). 사구체 여과율 감소 집단을 세계 신장기능 기준에 따라서 정상 또는 약간 감소 (≥60 mL/min/1.73m^2), 중등도 감소 (30-<60 mL/min/1.73m^2), 심한 감소 (<30 mL/min/1.73m^2)로 나누었다. 혈장 ADMA 농도의 경우 75 퍼센타일을 기준으로 보다 큰 경우를 증가된 ADMA 상태라고 구분하여, 사구체 여과율 감소 집단에 따른 증가된 ADMA 상태와의 관계를 로지스틱 회귀분석을 통해 보았다. 또한, 사구제 여과율이 30 미만인 심한 감소 군을 제외하여(남자 255 명, 여자 350 명) 일반 노인을 대상으로 사구체 여과율과 혈장 ADMA 농도와의 관계를 선형 회귀 분석을 통해 보았다.

연구 결과

혈장 ADMA 의 평균 농도는 사구체 여과율이 정상 또는 약간 감소인 군에 비해 심한 감소인 군에서 통계적으로 유의하게 높았다 (0.715 ㎛ ol/L, P=0.002). 사구체 여과율이 심하게 감소된 군을 제외하고 사구체 여과율과 ADMA 농도와의 관련성을 본 결과, 사구체 여과율이 증가함에 따라 ADMA 농도가 통계적으로 유의하게 감소하는 경향을 보였다 (β=-0.0016, p<0.01). 또한, 사구체 여과율이 정상 또는 약간 감소하는 군에 비해 심한 감소인 군에서 증가된 ADMA 상태를 가질 오즈비가 2.4 (95% 신뢰구간, 1.2-4.7)이었고 잠재적 혼란변수를 모두 보정한 후는 오즈비가 3.7 (1.5-9.1)로 사구체 여과율이 심한 감소를 보이는 군에서 높은 ADMA 를 가질 위험이 증가하는 것을 확인할 수 있었다.

연구 결론

결론적으로, 사구체 여과율이 심하게 감소된 신기능 저하 환자뿐만 아니라 일반적인 건강한 노인에서도 사구체 여과율과 혈장 ADMA 농도간에 음의 관련성이 관찰되었다.