Does a Reduction in the Glomerular Filtration Rate Increase the Overall Severity of Coronary Artery Stenosis?

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Abstract

Objective Chronic kidney disease is a risk factor of coronary events, however, its impact on coronary artery stenosis has not yet been clarified with the use of a large database. We examined the association between a reduced glomerular filtration rate (GFR) and the overall severity of coronary stenosis.

Methods We enrolled 1,150 patients [mean age, 68±12 (SD) years; 66.6% men] who consecutively underwent coronary angiography for suspected stable angina pectoris. The overall severity of stenosis in the coronary arteries was assessed by the Gensini score (GS), and its logarithmic values (log-GS) were used for statistical analyses since the GS does not follow a normal distribution.

Results The log-GS was significantly larger in men than in women (2.5±1.5 vs. 1.9±1.7), while the estimated GFR (eGFR) and comorbidities were comparable between both sexes. A multivariate regression analysis indicated that age, smoking, eGFR, HDL-cholesterol and HbA1c were independent explanatory variables of the log-GS in men, although the eGFR explained only 1.2% of the log-GS variation. In women, the eGFR was not included in the significant explanatory variables shown by the multivariate analysis. However, the sex difference in the regression for the eGFR-log-GS relationship was not statistically significant.

Conclusion A reduced eGFR is a significant, but minor, determinant of the overall severity of coronary artery stenosis in men and potentially women.

Key words: chronic kidney disease, coronary artery disease, Gensini score, BOREAS study

(Intern Med 55: 871-877, 2016)
(DOI: 10.2169/internalmedicine.55.5198)

Introduction

Close associations of chronic kidney disease (CKD) with atherosclerotic cardiovascular events have been demonstrated by a number of recent studies (1-3). However, it is still controversial whether a reduction in the renal function per se is a risk factor contributing to the development of atherosclerosis or a marker of an accumulation of classic risk factors (so-called “coronary artery disease risk equivalent”) (4, 5). The majority of CKD patients have hypertension, impaired glucose tolerance, dyslipidemia and/or obesity, and after adjusting for these classic risk factors in multivariate analyses, CKD has been shown to remain an independent risk factor of cardiovascular events in some, but not all, studies to date (1-6). The reason for the apparent discrepancy in the results of the previous studies remains unclear, though differences in the degree of renal dysfunction severity in the study populations are likely involved. Another factor possibly contributing to the differences in the reported relationships between CKD and cardiovascular events is sex difference in the risk raised by CKD. Diabetes and hypertension have been shown to increase the coronary event rate more in women than in men (7, 8). However, sex difference in the impact of CKD on cardiovascular events has not been closely examined.

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Received for publication February 22, 2015; Accepted for publication June 28, 2015

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The mechanisms by which CKD increases coronary events have not been fully elucidated. Increased vulnerability of coronary plaque by increased lipid deposition and necrosis within the plaque has been suggested by several studies using integrated backscatter intravascular ultrasound (IB-IVUS) imaging and intracoronary angiography (9-13). In contrast, reported results regarding the change in the coronary plaque volume by CKD in earlier studies are inconsistent (14-18). However, the numbers of patients with severe renal dysfunction were not large, and the overall severity of coronary artery disease has not been determined for the comparison of patients with and without CKD in those studies. Hence, we aimed to clarify the impact of a reduced glomerular filtration rate (GFR) on the overall severity of coronary artery disease using a large database. We performed a cross-sectional analysis of 1,150 consecutive patients with suspected stable angina pectoris, including 130 patients with an estimated GFR (eGFR) <45 mL/min/1.73 m². The overall severity of coronary stenosis was determined using a score system originally reported by Gensini (19), and a multiple linear regression analysis was performed to examine whether the eGFR is an independent explanatory factor of coronary stenosis severity. The results of the analysis suggest that a reduction in the eGFR slightly promotes the development of coronary artery stenosis in men and potentially women.

Materials and Methods

The present study was approved by the institutional review board and conducted in accordance with the World Medical Association Declaration of Helsinki. This study was conducted as a project of the BOREAS (Broad-range Organization for REnal, Arterial and cardiac studies by Sapporo Medical University Affiliates) Study.

Study subjects

Using a retrospective search of the medical records, we consecutively enrolled patients who underwent coronary angiography for suspected stable coronary artery disease from January 2007 to May 2013 at Sapporo Medical University Hospital and from January 2011 to December 2012 at JR Sapporo Hospital. Exclusion criteria included a history of percutaneous coronary intervention, coronary bypass surgery, end-stage renal disease requiring regular dialysis, and acute kidney injury.

Data collection

Data for the demographic parameters and data for the blood tests on the day before or closest to coronary angiography were collected from the medical records. Information regarding co-morbidities and regular medications was obtained from the records on admission. Coronary angiography was performed electively in all study subjects, and the severity of coronary stenosis was determined using the Gensini Score (GS) by an investigator (J.N.) who was blinded to the clinical and biochemical parameters for each case. The eGFR was calculated using the data for the serum creatinine level, age and sex using equations for Japanese subjects (20).

Statistical analysis

The group mean data are expressed as the means ± SD. Inter-group differences (expressed in percentages) of the demographic parameters were examined by the chi-square test. The relationships between the parameters were examined using simple and multiple linear regression analyses. Differences in the GS between subject groups were tested using the Wilcoxon rank sum test. In univariate and multivariate regression analyses, the GS data were converted to their logarithmic values (log-GS) since the GS values were not normally distributed. Because the GS was 0 in 12.5% of the study subjects, 0.5 was added to the GS for each subject before converting to its logarithmic value.

In the multiple linear regression analysis, we prepared multiple models using all or different combinations of the parameters as independent variables for the calculation of the regression coefficients and Akaike’s Information Criterion (AIC), an index of the quality of a statistical model. Among the candidate models, we selected the best-fit model for the log-GS, a dependent variable, using AIC. To examine the interaction between sex and the eGFR in their effects on the log-GS, an interaction term was included in the explanatory variables in the multiple regression analysis. To avoid multicollinearity, we used a mean-centered interaction term: (eGFR-mean eGFR) × (sex-mean sex). Statistical analyses were carried out using the JMP software program (version 11, SAS Institute, Cary, USA) and statistical significance was considered to exist at p values of less than 0.05.

Results

Clinical characteristics of the study subjects

The demographic parameters, data for blood tests, GS and co-morbidities of the enrolled patients are presented in Table 1. Compared with men, women were significantly older and had a lower diastolic blood pressure (BP), higher total and HDL-cholesterol levels, and lower hemoglobin, serum triglyceride, creatinine and uric acid levels. The proportions of smokers, patients with prior stroke and patients with angina (significant coronary stenosis) were higher in men than in women. However, the eGFR was comparable between men and women (70±24 vs. 67±24 mL/min/1.73 m²). The GS and log-GS were significantly larger in men than in women (28±33 vs. 18±24, 2.5±1.5 vs. 1.9±1.7, respectively).

Statins and calcium channel blockers were more frequently used and antiplatelet agents were less frequently used in women than in men, however, other medications were used comparably in both sexes (Table 2). The propor-
Table 1. Demographic and Clinical Characteristics.

|                      | All patients | Men    | Women | p value* |
|----------------------|--------------|--------|-------|----------|
| Number               | 1,150        | 766 (66.6%) | 384 (33.4%) | -        |
| Age (years)          | 68 ± 12      | 67 ± 12 | 70 ± 12 | <0.01    |
| BMI (kg/m²)          | 24 ± 4       | 24 ± 4 | 23 ± 4 | 0.054    |
| Systolic BP (mmHg)   | 125 ± 19     | 125 ± 19 | 126 ± 21 | 0.64     |
| Diastolic BP (mmHg)  | 69 ± 12      | 70 ± 12 | 67 ± 12 | <0.01    |
| Heart rate (bpm)     | 70 ± 13      | 69 ± 13 | 70 ± 13 | 0.19     |
| LVEF (%)             | 60 ± 13      | 59 ± 13 | 62 ± 13 | <0.01    |
| Coronary risk factors|              |        |       |          |
| Smoking              | 428 (37.2%)  | 357 (46.6%) | 71 (18.5%) | <0.01    |
| Dyslipidemia         | 568 (49.4%)  | 366 (47.8%) | 202 (52.6%) | 0.11     |
| Hypertension         | 704 (61.2%)  | 462 (60.3%) | 242 (63.0%) | 0.34     |
| Diabetes             | 321 (27.9%)  | 210 (27.4%) | 111 (28.9%) | 0.58     |
| Peripheral artery disease | 98 (8.5%) | 71 (9.3%) | 27 (7.0%) | 0.19     |
| Prior stroke         | 117 (10.2%)  | 97 (12.7%) | 20 (5.2%) | <0.01    |
| Total cholesterol (mg/dL) | 188 ± 39 | 185 ± 39 | 194 ± 38 | <0.01    |
| Triglyceride (mg/dL) | 136 ± 82     | 141 ± 83 | 125 ± 79 | <0.01    |
| LDL-C (mg/dL)        | 111 ± 31     | 110 ± 31 | 114 ± 31 | 0.04     |
| Non-HDL-C (mg/dL)    | 50 ± 15      | 48 ± 15 | 54 ± 15 | -0.01    |
| BUN (mg/dL)          | 18 ± 8       | 18 ± 7  | 17 ± 9  | 0.13     |
| Serum creatinine (mg/dL) | 0.9 ± 0.6 | 1.0 ± 0.5 | 0.8 ± 0.6 | <0.01    |
| eGFR (mL/min/1.73m²) | 69 ± 24      | 70 ± 24 | 67 ± 24 | 0.09     |
| Uric acid (mg/dL)    | 5.9 ± 1.7    | 6.2 ± 1.6 | 5.5 ± 1.8 | <0.01    |
| Calcium (mg/dL)      | 9.2 ± 0.5    | 9.2 ± 0.5 | 9.3 ± 0.5 | <0.01    |
| Phosphorus (mg/dL)   | 3.3 ± 0.6    | 3.2 ± 0.6 | 3.5 ± 0.6 | <0.01    |
| HbA1c (%)            | 5.9 ± 1.2    | 5.9 ± 1.2 | 5.9 ± 1.3 | 0.80     |
| Hemoglobin (g/dL)    | 13 ± 2       | 14 ± 2  | 12 ± 2  | <0.01    |
| Serum albumin (g/dL) | 4.0 ± 0.5    | 4.0 ± 0.5 | 4.0 ± 0.4 | 0.99     |
| Proteinuria          | 171 (16.2%)  | 124 (16.2%) | 47 (12.2%) | 0.06     |
| Gensini score        | 25 ± 31      | 28 ± 33 | 18 ± 24 | <0.01    |
| Coronary artery disease | 599 (52.1%) | 436 (57.0%) | 163 (42.4%) | <0.01    |
| Left main trunk      | 70 (6.1%)    | 60 (7.8%) | 10 (2.6%) | -0.01    |
| LAD                  | 338 (29.4%)  | 249 (32.5%) | 89 (23.2%) | <0.01    |
| Diagonal branch      | 246 (21.4%)  | 179 (23.4%) | 67 (17.4%) | 0.02     |
| LCX                  | 338 (29.4%)  | 240 (31.3%) | 98 (25.5%) | 0.04     |
| RCA                  | 317 (27.6%)  | 230 (30.0%) | 87 (22.7%) | <0.01    |

Vales are mean ± SD or n (%). BMI: body mass index, BP: blood pressure, bpm: beat per minute, LVEF: left ventricular ejection fraction, LDL-C: LDL cholesterol, HDL-C: HDL cholesterol, non-HDL-C: non-HDL cholesterol, LAD: left anterior descending artery, LCX: left circumflex artery, RCA: right coronary artery *Men vs. Women.

tions of patients with diabetes mellitus were similar among men and women (Table 1), and there was no significant difference between sexes in the frequency of any agents used for glycemic control (Table 2).

The eGFR level and GS

The patients were divided into three groups according to the eGFR: eGFR ≥60 mL/min/1.73 m², 30 ≤ eGFR <60 mL/min/1.73 m², and eGFR <30 mL/min/1.73 m². As shown in Figure (panel A), the GS in the group with eGFR <30 mL/min/1.73 m² was significantly larger than those in groups with higher ranges of eGFRs.

Regression analyses for the log-GS

To identify the clinical parameters that significantly associate with coronary stenosis, relationships between the log-GS and the clinical parameters were examined by univariate and multivariate regression analyses. In the univariate analysis of all study subjects (Table 3), the log-GS correlated with age, coronary risk factors, peripheral artery disease, prior stroke, serum albumin level, renal function indices (BUN, serum creatinine, eGFR), serum calcium level, HbA1c and hemoglobin. The correlation coefficient for the eGFR-log-GS relationship was very small (Table 3 and panel B in Figure), although the correlation was statistically significant (r=-0.14, p<0.01). The results of the univariate analyses were similar in separate analyses of men alone and women alone, although total cholesterol and smoking were not significantly correlated with the log-GS in men and women, respectively.

In the multiple linear regression analysis, we prepared several models using all or different combinations of the independent variables for calculation of both the regression coefficients and AIC, and the best model is shown in Table 4; this model showed that sex, smoking, age, systolic BP, HbA1c and serum albumin level were independently associated with the log-GS, whereas the association between the eGFR and log-GS was marginally significant (p=0.05).

A parameter for the detection of sex difference in the regression model for the eGFR-log-GS relationship [(eGFR-mean eGFR) × (sex-mean sex)] was not statistically significant. To exclude sex-related confounding effects, we per-
formed a multivariate regression analysis for the log-GS separately in men and women (Table 5). In both men and women, age and HbA1c were commonly selected as independent explanatory factors of the log-GS. However, the eGFR and smoking were significantly correlated with the log-GS in men but not in women, while systolic BP and serum albumin level were correlated with the log-GS only in women.

### Table 2. Medications.

|                         | All patients | Men     | Women   | p value * |
|-------------------------|--------------|---------|---------|-----------|
| Total subjects          | n = 1,150    | n = 766 | n = 384 |           |
| CCB                     | 462 (40.2%)  | 287 (37.5%) | 175 (45.6%) | <0.01 |
| ACEI                    | 47 (4.1%)    | 34 (4.4%)  | 13 (3.4%) | 0.39     |
| ARB                     | 430 (37.4%)  | 294 (38.4%) | 136 (35.4%) | 0.36    |
| Statin                  | 335 (29.1%)  | 207 (27.0%) | 128 (33.3%) | 0.02    |
| Diuretics               | 269 (23.4%)  | 171 (22.3%) | 98 (25.5%)  | 0.21    |
| β-blocker               | 261 (22.7%)  | 179 (23.4%) | 82 (21.4%)  | 0.46    |
| Antiplatelet agent      | 479 (41.7%)  | 351 (45.8%) | 128 (33.3%) | <0.01  |

*Male vs. Female

**Information regarding medications was unavailable in 2 of 321 diabetic patients (one male and one female). Each patients was treated with a single or multiple medications for glycemic control.

CCB: calcium channel blocker, ACEI: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, DPP-4 inhibitor: dipeptidyl peptidase-4 inhibitor

Table 3. Univariate Regression Analysis for Log GS.

|                         | r  | p value |
|-------------------------|----|---------|
| Age (years)             | 0.279 | <0.01 |
| BMI (kg/m²)             | 0.036 | 0.22 |
| Systolic BP (mmHg)      | 0.137 | <0.01 |
| Diastolic BP (mmHg)     | 0.031 | 0.29 |
| Heart rate (bpm)        | -0.026 | 0.38 |
| LV-EF (%)               | -0.062 | 0.047 |

Coronary risk factors

| Smoking                  | 0.157 | <0.01 |
| Dyslipidemia             | 0.243 | <0.01 |
| Hypertension             | 0.252 | <0.01 |
| Diabetes                 | 0.250 | <0.01 |
| Peripheral artery disease| 0.189 | <0.01 |
| Prior stroke             | 0.152 | <0.01 |
| Total cholesterol (mg/dL)| -0.087 | <0.01 |
| Triglyceride (mg/dL)     | 0.058 | 0.054 |
| LDL-C (mg/dL)            | -0.017 | 0.59 |
| HDL-C (mg/dL)            | -0.165 | <0.01 |
| Non-HDL-C (mg/dL)        | -0.029 | 0.36 |
| BUN (mg/dl)              | 0.168 | <0.01 |
| Serum creatinine (mg/dL) | 0.147 | <0.01 |
| eGFR (mL/min/1.73m²)     | -0.142 | <0.01 |
| Uric acid (mg/dL)        | 0.003 | 0.93 |
| Calcium (mg/dL)          | -0.094 | <0.01 |
| Phosphorus (mg/dL)       | -0.057 | 0.10 |
| HbA1c (%)                | 0.155 | <0.01 |
| Hemoglobin (g/dL)        | -0.110 | <0.01 |
| Serum albumin (g/dL)     | -0.165 | <0.01 |

BMI: body mass index, BP: blood pressure, bpm: beat per minute, LV-EF: left ventricular ejection fraction, LDL-C: LDL cholesterol, HDL-C: HDL cholesterol, non-HDL-C: non-HDL cholesterol

Figure. Relationships between the Gensini scores and the eGFR. A: Comparison of the Gensini scores in the group with eGFR ≥ 60 mL/min/1.73m², the group with 30 ≤ eGFR < 60 mL/min/1.73m² and the group with eGFR < 30 mL/min/1.73m². *p<0.05. GS: Gensini score. B: Scatterplot and a regression line for the relationship between the eGFR and log-GS.

Discussion

The results of previous studies regarding the change in...
the coronary plaque volume by CKD are inconsistent (14-18), and the effect of CKD on the development of coronary stenosis has not yet been elucidated. In the present study, the multiple regression analysis using data from both men and women indicated that the association between the eGFR and the log-GS was marginally significant (Table 4). Because female sex is a well-known protective factor against both age-dependent GFR decline (21) and coronary stenosis (22, 23), we repeated the multiple regression analysis separately in men and women and found that the eGFR was a significant explanatory factor of the log-GS in men, but not women (Table 5). However, a significant interaction between the eGFR and sex was not detected for the eGFR-log-GS relationship in an analysis using data for all of the study subjects \([p=0.41 \text{ for } (\text{eGFR-mean eGFR}) \times (\text{sex-mean sex}), \text{Table 4}]\). On the other hand, the number of patients with relatively large log-GS values was smaller in women than in men (log-GS values were 1.9±1.7 in women and 2.5±1.5 in men). Taken together, the present findings indicate that the eGFR is an independent explanatory factor of the log-GS in men, and potentially women, although the impact of the eGFR in women was not clearly shown due to a relatively small number of cases with large GS.

Although the contribution of reduced eGFR to increase the log-GS was statistically significant in men, the impact of eGFR appears to be relatively small. In a post hoc analysis,
we calculated the coefficient of determination ($R^2$) of a model in which the eGFR alone was retracted from the explanatory variables in the model shown in Table 5. The difference in the $R^2$ values between the models with and without eGFR (0.1945 and 0.1824, respectively) was 0.012, indicating that eGFR explains only 1.2% of the log-GS variations. In other words, 18% of the log-GS variations can be explained by other risk factors. Hence, the impact of eGFR reduction on coronary stenosis is relatively minor and thus unlikely to explain the substantial increase in cardiovascular events by CKD.

Kim et al. (24) recently analyzed the data of 1,192 patients who underwent coronary angiography and reported that the eGFR was an independent predictor of the GS, as were diabetes, hypertension, LDL-cholesterol and hemoglobin. Surprisingly, age, sex and smoking status were not included in the parameters that were significantly associated with the GS in their multivariate analysis. Because they did not report the results for the parameters associated with the GS in each sex group, it is not clear whether the association between the eGFR and GS was similar or different between men and women. However, it is notable that the mean age of the study subjects was older, the ratios of subjects with diabetes, hypertension and who smoked were higher and the mean GS was smaller in the present study than in the study by Kim et al. (24). In addition, they used the GS itself for the regression analyses, however, we used the log-GS since the GS does not follow a normal distribution. The differences in the patient backgrounds and statistical analyses are plausible explanations for inconsistent results between our study and the study by Kim et al. (24). Nevertheless, both studies suggest that the relative contribution of renal dysfunction to the severity of coronary stenosis depends on the presence of other risk factors.

Although we could not detect a significant difference between men and women regarding the effect of eGFR reduction on the severity of coronary stenosis (Table 4), the possibility of a sex difference cannot be completely excluded. One possibility is an earlier onset of atherosclerosis in men and another is the involvement of testosterone deficiency in the facilitation of coronary plaque growth. Atherosclerotic lesions develop earlier in men compared with women, which is partly explained by the anti-atherosclerotic effects of estrogen in women (22). A certain level of pre-existing endothelial dysfunction or atherosclerosis might be necessary for pro-atherosclerotic effects of renal dysfunction. A more intriguing hypothesis is the withdrawal of the anti-atherosclerotic action of testosterone in patients with renal dysfunction. The plasma level of testosterone is reduced by decreased clearance of prolactin and the inhibition of lutetinizing hormone signaling in Leydig cells in patients with renal insufficiency (25-27). Testosterone has immunomodulatory actions that inhibit inflammation and atheroma formation (27), and testosterone has been demonstrated to inhibit the atheromatous plaque size in experimental animal models (28). Thus, the promotion of coronary stenosis via testosterone deficiency by renal dysfunction is an interesting and important hypothesis to be tested because it potentially leads to testosterone supplement therapy in male CKD patients.

There are several limitations associated with the present study. First, since this was a cross-sectional study, the effect of longitudinal change in the eGFR on coronary plaque growth could not be quantified. Second, we cannot exclude the possibility that the weak association between a reduced eGFR and increased coronary stenosis is a result of a common cause that was not included as one of the explanatory variables in the present regression analyses. Third, we could not examine the relationship between the level of proteinuria and severity of coronary stenosis because data for the urinary protein-to-creatinine ratios were unavailable for most of the study subjects. Hence, the impact of CKD on the severity of coronary stenosis has not been fully characterized in this study. Finally, the natural history of coronary artery atherosclerosis cannot be characterized by the GS alone, and a marginal effect of eGFR reduction on log-GS does not exclude the possibility that remodeling of the coronary artery is substantially influenced by a reduction in the GFR. In fact, recent studies have shown that CKD increases the diameter and stiffness of the carotid artery, although its effects on the plaque volume and intima-media thickness were inconclusive (29-33).

In conclusion, the present cross-sectional analysis suggests that a reduced eGFR is independently associated with an increased severity of coronary artery stenosis in men, and potentially women, although its contribution to stenosis is minor compared with the contribution of other established risk factors.

Author’s disclosure of potential Conflicts of Interest (COI).
Yoshito Ohnuma: Employment, Hokkaido Railway Company.
Tohru Hasegawa: Employment, Hokkaido Railway Company.
Akihito Tsuchida: Employment, Hokkaido Railway Company.

Financial Support
This study was supported by Grants-in-Aid for Education and Research from Sapporo Medical University 2013 and 2014.

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References
1. Schifrin EL, Lipman ML, Mann JF. Chronic kidney disease: effects on the cardiovascular system. Circulation 116: 85-97, 2007.
2. Matsushita K, van der Velde M, Astor BC, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause
and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet 375: 2073-2081, 2010.
3. Fox CS, Matsushita K, Woodward M, et al. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. Lancet 380: 1662-1673, 2012.
4. Natali A, Boldrini B, Baldi S, et al. Impact of mild to moderate reductions of glomerular filtration rate on coronary artery disease severity. Nutr Metab Cardiovasc Dis 24: 681-688, 2014.
5. Arbel Y, Halkin A, Finkelstein A, et al. Impact of estimated glomerular filtration rate on vascular disease extent and adverse cardiovascular events in patients without chronic kidney disease. Can J Cardiol 29: 1374-1381, 2013.
6. Yahalom G, Kivity S, Segev S, et al. Estimated glomerular filtration rate in a population with normal to mildly reduced renal function as predictor of cardiovascular disease. Eur J Prev Cardiol 21: 941-948, 2013.
7. Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. BMJ 332: 73-78, 2006.
8. Anand SS, Islam S, Rosengren A, et al. Risk factors for myocardial infarction in women and men: insights from the INTERHEART study. Eur Heart J 29: 932-940, 2008.
9. Miyagi M, Ishii H, Murakami R, et al. Impact of renal function on coronary plaque composition. Nephrol Dial Transplant 25: 175-181, 2010.
10. Kono K, Fujii H, Miyoshi N, et al. Coronary plaque morphology using virtual histology-intravascular ultrasound analysis in hemodialysis patients. Ther Apher Dial 15: 44-50, 2011.
11. Wada M, Ueda Y, Higo T, et al. Chronic kidney disease and coronary artery disease in hemodialysis patients. Ther Apher Dial 15: 44-50, 2011.
12. Baber U, Stone GW, Weisz G, et al. Coronary plaque composition, morphology, and outcomes in patients with and without chronic kidney disease presenting with acute coronary syndromes. JACC Cardiovasc Imaging 5: S53-S61, 2012.
13. Hayano S, Ichimiya S, Ishii H, et al. Relation between estimated glomerular filtration rate and composition of coronary arterial atherosclerotic plaques. Am J Cardiol 109: 1131-1136, 2012.
14. Gruberg L, Rai P, Mintz GS, et al. Impact of renal function on coronary plaque morphology and morphology in patients with chronic renal insufficiency as determined by intravascular ultrasound volumetric analysis. Am J Cardiol 96: 892-896, 2005.
15. Nicholls SJ, Tuzcu EM, Hsu A, et al. Comparison of coronary atherosclerotic volume in patients with glomerular filtration rates <60 ml/min/1.73 m²: a meta-analysis of intravascular ultrasound studies. Am J Cardiol 99: 813-816, 2007.
16. Cho I, Min HS, Chun EJ, et al. Coronary atherosclerosis detected by coronary CT angiography in asymptomatic subjects with early chronic kidney disease. Atherosclerosis 208: 406-411, 2010.
17. Kawai H, Sarai M, Motoyama S, et al. Coronary plaque characteristics in patients with mild chronic kidney disease. Analysis by 320-row area detector computed tomography. Circ J 76: 1436-1441, 2012.
18. Joosen IA, Schipf H, Versteelen MO, et al. Relation between mild to moderate chronic kidney disease and coronary artery disease determined with coronary CT angiography. PLoS One 7: e47267, 2012.
19. Gensini GG. A more meaningful scoring system for determining the severity of coronary heart disease. Am J Cardiol 51: 606, 1983.
20. Matsuo S, Imai E, Horio M, et al. Collaborators developing the Japanese equation for estimated GFR. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis 53: 982-992, 2009.
21. Baylis C. Sexual dimorphism in the aging kidney: differences in the nitric oxide system. Nat Rev Nephrol 5: 384-396, 2009.
22. Villalblanca AC, Jayachandran M, Banka C. Atherosclerosis and sex hormones: current concepts. Clin Sci (Lond) 119: 493-513, 2010.
23. Lim S, Shin H, Lee Y, et al. Effect of metabolic syndrome on coronary artery stenosis and plaque characteristics as assessed with 64-detector row cardiac CT. Radiology 261: 437-445, 2011.
24. Kim JY, Hwang IH, Lee KN, et al. Decreased renal function is an independent predictor of severity of coronary artery disease: an application of Gensini score. J Korean Med Sci 28: 1615-1621, 2013.
25. Dunkel L, Raivio T, Laine J, et al. Circulating luteinizing hormone receptor inhibitor(s) in boys with chronic renal failure. Kidney Int 51: 777-784, 1997.
26. Carrero JJ, Stenvinkel P. The vulnerable man: impact of testosterone deficiency on the uraemic phenotype. Nephrol Dial Transplant 27: 4030-4041, 2012.
27. Yilmaz MI, Sonmez A, Qureshi AR, et al. Endogenous testosterone, endothelial dysfunction, and cardiovascular events in men with nondialysis chronic kidney disease. Clin J Am Soc Nephrol 6: 1617-1625, 2011.
28. Carrero JJ, Bárány P, Yilmaz MI, et al. Testosterone deficiency is a cause of anaemia and reduced responsiveness to erythropoiesis-stimulating agents in men with chronic kidney disease. Nephrol Dial Transplant 27: 709-715, 2012.
29. Kawagishi T, Nishizawa Y, Konishi T, et al. High-resolution B-mode ultrasonography in evaluation of atherosclerosis in uremia. Kidney Int 48: 820-826, 1995.
30. Preston E, Ellis MR, Kulinskaya E, et al. Association between castrate and reduced responsiveness to erythropoiesis-stimulating agents in men with chronic kidney disease. Am J Kidney Dis 51: 519-528, 2008.
31. Preston E, Ellis MR, Kulinskaya E, et al. Association between castrate and decreased responsiveness to erythropoiesis-stimulating agents in men with chronic kidney disease. Clin J Am Soc Nephrol 4: 291-298, 2009.
32. Rigatto C, Levin A, House AA, et al. Atheroma progression in chronic kidney disease. J Am Soc Nephrol 22: 967-974, 2011.

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