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Sex Differences in Coronary Artery Calcification Score and its Use as a Predictor of Progression of Diabetic Nephropathy in Japanese Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Objective: *This study was to investigate the relationship between the progression of Diabetic nephropathy (DN) and Coronary artery calcification score (CACS) in Japanese patients with Type 2 Diabetes mellitus (T2DM) at baseline and over 5 years of follow-up.* ***Methods:*** *A total of 107 patients with T2DM who underwent coronary computed tomography (CT) angiography using multidetector CT and were assessed for DN each year were studied. Patients were divided into two groups based on the median CACS derived from the Agatston score. Kaplan-Meier analyses were performed to examine whether the relationship between CACS and DN progression was different between the sexes.* ***Results:*** *Over a 5-year follow-up, men in the high CACS group demonstrated more DN progression compared with those in the low CACS group. In male patients without diabetic retinopathy (DR), those in the high CACS group also had significantly higher DN progression than those in the low CACS group. Patients with DR in the high and low CACS groups did not have a significantly different rate of DN progression. In women, DN progression was not significantly different between the high and low CACS groups.* ***Conclusions:*** *In men with T2DM, CACS is a good predictor of DN progression. Overall, DN progression was not related to the presence of DR, suggesting that the progression of DN in men may be affected by atherosclerotic factors more than in women.*

Keywords: Diabetic nephropathy, Coronary artery calcification, Sex difference, Diabetic microangiopathy, Macroangiopathy

INTRODUCTION

According to statistics on causes of death of patients with diabetes mellitus in Japan, cardiovascular disease is the third leading cause, following malignant tumors and infection. For patients with diabetic nephropathy (DN), concomitant cardiovascular disease is the major cause of death as well as malignant tumors [1]. In patients with diabetes mellitus, cardiovascular disease is often asymptomatic or mild, and physicians have been advised to aggressively examine whether the patients have cardiovascular disease [2-4]. In addition, DN has been the annual leading cause of initiation of dialysis [5]. While the progression of DN is correlated with cardiovascular disease and diabetic microangiopathy [6,7], limited clinical studies have been reported on the prediction of the progression of DN by assessing cardiovascular disease [8]. Moreover, the incidence of DN, like cardiovascular disease, has also been reported to differ between men and women [9,10]. In the present study, we calculated coronary artery calcification score (CACS) using coronary computed tomography (CT) angiography, which was performed to determine the severity of atherosclerosis in patients with type 2 diabetes mellitus (T2DM). Then, we examined CACS and progression of DN over the course of five years separately for male and female patients to determine how CACS was associated with the severity of atherosclerosis, particularly DN progression.

PATIENTS AND METHODS

This study included 107 Japanese patients (71 males) with T2DM who underwent coronary CT angiography using

multi-detector CT to calculate CACS. Those with a serum creatinine level of 1.0 mg/dl or higher were excluded. The CACS was calculated using Agatston scores [11]. Male and female patients were each divided into the following two groups of the same number of patients by gender respectively: the low-CACS group (< 116 U for men and < 65 U for women) and the high-CACS group (≥ 116 U for men and ≥ 65 U for women). The assessment of DN was based on the staging classifications developed by the Japan Diabetes Society, American Diabetes Association, or European Association for the Study of Diabetes. The data are expressed as the mean ± the standard deviation. Student's t-test and logistic regression analysis were performed to identify the factors associated with the DN progression, and Kaplan-Meier survival analysis was used to evaluate the association between CACS and DN progression in male and female patients separately. In all cases, p values < 0.05 was considered significant. Statistical analysis was performed with the SPSS statistics software (SPSS Inc., Chicago, IL, USA).

Ethical Review

The ethics committee of Tokyo Women's Medical University approved this study on October 30, 2017 (Approval No. 3665). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent or substitute for it was obtained from all patients for being included in the study.

RESULTS

For male patients at baseline, urinary albumin excretion (UAE) levels were significantly higher in the high-CACS group than in the low-CACS group (283.1 ± 420.1 mg/g・Cr vs. 83.0 ± 228.7 mg/g・Cr, p = 0.016), and the incidence of diabetic retinopathy (DR) was also significantly higher in the high-CACS group than in the low-CACS group (53.1% vs. 21.9%, p=0.010) (Table 1).

No significant differences between the two groups were observed in terms of other baseline values including, age, duration of diabetes mellitus, blood pressure, serum creatinine, estimated glomerular filtration rate (eGFR), uric acid, lipid levels, smoking status, or medications such as statins, angiotensin-converting enzyme inhibitors (ACEIs), or angiotensin receptor blockers (ARBs). Meanwhile, female patients in the high-CACS group were significantly older than those in the low-CACS group (70 ± 6 years vs. 64 ± 7 years, p=0.036). In the high-CACS group compared with the low-CACS group, the eGFR was significantly lower (64.2 ± 10.6 ml/min/1.73m^2 vs. 74.0 ± 11.7 ml/min/1.73m^2, p=0.019), and the serum creatinine (Cre) levels were significantly higher (0.70 ± 0.14 mg/dl vs. 0.63 ± 0.85 mg/dl, p=0.041). No significant differences between the two groups were observed for other factors (Table 1).

Table 1 Characteristics in subjects with Low and High CACS

	Men			Women		
	Low CACS (<116.2U)	**High CACS (≥116.2U)**	**P-value**	**Low CACS (<65.2U)**	**High CACS (≥65.2U)**	**P-value**
Age (years old)	64 ± 7	65 ± 7	0.871	64 ± 7	70 ± 6	0.036*
BMI (kg/m²)	24.1 ± 2.9	24.4 ± 3.1	0.68	25.5 ± 2.9	26.9 ± 3.8	0.26
Duration of DM (years)	9 ± 10	11 ± 10	0.463	8 ± 7	10 ± 8	0.639
Current smokers (%)	44.8	54.8	0.303	0	28.6	0.113
Diabetic retinopathy (%)	21.9	53.1	0.010*	50	42.9	0.5
Systolic BP (mmHg)	138 ± 25	144 ± 22	0.247	141 ± 21	138 ± 12	0.647
Diastolic BP (mmHg)	79 ± 13	81 ± 12	0.585	78 ± 13	73 ± 11	0.252
ACEI or ARB users (%)	14.3	27.8	0.135	50	50	
HbA1c (%)	8.1 ± 2.1	8.5 ± 2.4	0.41	9.1 ± 2.7	8.0 ± 1.7	0.172
AST (U/l)	28 ± 21	26 ± 11	0.549	25 ± 13	27 ± 13	0.654

ALT (U/l)	30 ± 24	25 ± 13	0.288	27 ± 16	28 ± 19	0.788
gGTP (U/l)	52 ± 49	93 ± 42	0.309	56 ± 46	42 ± 47	0.396
Serum Cre (mg/dl)	0.81 ± 0.17	0.81 ± 0.14	0.964	0.63 ± 0.85	0.70 ± 0.14	0.041*
eGFR (ml/min/1.73m²)	78.6 ± 28.2	76.9 ± 16.2	0.761	74.0 ± 11.7	64.2 ± 10.6	0.019*
UAE (mg/gCre)	83.0 ± 228.7	283.1 ± 420.1	0.016*	359.6 ± 891.4	155.1 ± 381.5	0.406
Uric acid (mg/dl)	4.9 ± 1.1	5.2 ± 1.3	0.289	4.7 ± 1.0	5.1 ± 1.2	0.303
Total cholesterol (mg/dl)	205 ± 37	217 ± 97	0.477	236 ± 62	206 ± 27	0.09
LDL cholesterol (mg/dl)	126 ± 36	115 ± 37	0.225	146 ± 52	120 ± 20	0.074
HDL cholesterol (mg/dl)	51 ± 11	57 ± 14	0.052	56 ± 17	58 ± 15	0.787
Triglyceride (mg/dl)	166 ± 84	148 ± 93	0.378	199 ± 78	170 ± 90	0.337
Statin users (%)	20	22.2	0.525	31.3	50	0.236
WBC (μ/l)	6910 ± 2850	6260 ± 1540	0.23	6050 ± 1790	6680 ± 1880	0.34
Mean ± SD						
*p<0.05 Low CACS vs. High CACS						
BP: Blood pressure						
ACEI: Angiotensin-converting enzyme inhibitor						
ARB: Angiotensin II receptor blocker						
eGFR: Estimated glomerular filtration rate						
UAE: Urinary albumin excretion						

During the five-year follow-up period, DN progressed by one stage or greater in 52.8% of male patients in the high-CACS group, being significantly higher compared with the low-CACS group (22.9%, p = 0.008) (Figure 1A). Moreover, DN progressed more in male patients without DR in the high-CACS group than in the low-CACS group (60.0% vs. 20.0%, p=0.007) (Figure 2A). For male patients with DR, no significant difference in DN progression was observed between the high- and low-CACS groups (47.1% vs. 14.3%, p=0.145) (Figure 2B). In contrast, for female patients, no significant difference in DN progression was observed between the high- and low-CACS groups (25.0% vs. 43.7%, p=0.233) (Figure 1B), regardless of the presence or absence of DR (Figure 2C-D).

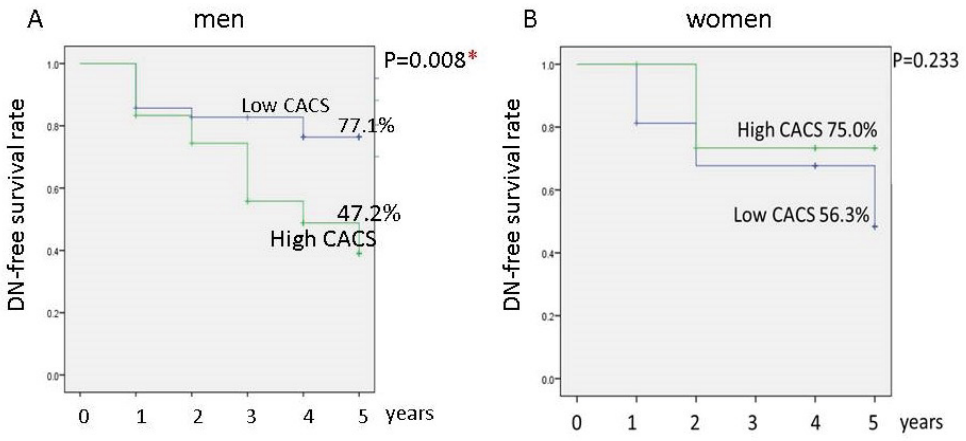

Figure 1 A: Kaplan-Meier curves for progression of diabetic nephropathy (DN) in the low coronary artery calcification score (CACS) and high-CACS groups (men); B: Kaplan-Meier curves for progression of DN in the low-CACS and high-CACS groups (women)

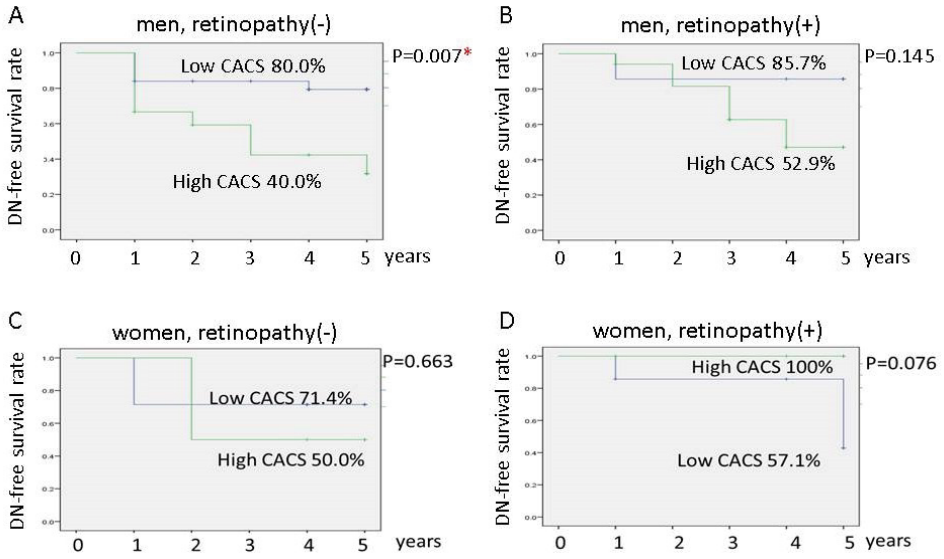

Figure 2 A-B: Kaplan-Meier curves for progression of diabetic nephropathy (DN) in the low coronary artery calcification score (CACS) and high-CACS groups in male patients with and without retinopathy; C-D: Kaplan-Meier curves for progression of DN in the low-CACS and high-CACS groups in female patients with and without retinopathy

Overall, ACEI/ARB use, UAE, and CACSs were significant factors that affected the progression of DN before adjustment (p=0.004, p=0.002, and p=0.049, respectively), and ACEI/ARB use and UAE were also significant factors after adjustment (p=0.043 and p=0.007, respectively) (Table 2).

Table 2 Predictive factors in progression of DN

Univariate analysis			
	Odds ratio	**95% C.I.**	**P value**
ACEI/ABR user vs nonuser	3.6	1.50-8.68	0.004*
UAE (mg/gCre)	1.01	1.00-1.01	0.002*
High CACS vs Low CACS	2.55	1.01-6.49	0.049*
Multivariate analysis			
	Odds ratio	**95% C.I.**	**P value**
ACEI/ABR user vs nonuser	2.73	1.04-7.21	0.043*
UAE (mg/gCre)	1.01	1.00-1.01	0.007*
High CACS vs Low CACS	1.99	0.70-5.73	0.2

In male patients, ACEI/ARB use, UAE, and CACSs were significant factors that affected the progression of DN before adjustment (p = 0.003, p = 0.005, and p = 0.011, respectively). After adjustment, significant differences were observed in ACEI/ARB use (p = 0.04) (Table 3). On the other hand, UAE and CACSs showed no significant difference after adjustments (p = 0.058 and p = 0.13, respectively).

Table 3 Predictive factors in progression of DN of men

Univariate analysis			
	Odds ratio	**95% C.I.**	**P value**
ACEI/ABR user vs nonuser	6.88	1.91-24.80	0.003*
UAE (mg/gCre)	1.01	1.00-1.01	0.005*
High CACS vs Low CACS	3.77	1.36-10.51	0.011*
Multivariate analysis			
	Odds ratio	**95% C.I.**	**P value**
ACEI/ABR user vs nonuser	4.42	1.08-18.01	0.04*
UAE (mg/gCre)	1	1.00-1.004	0.058
High CACS vs Low CACS	2.47	0.77-7.98	0.13

In female patients, γ-glutamyl transpeptidase (γGTP), serum Cre, and eGFR were significant factors that affected the progression of DN before adjustment (p=0.04, p=0.026, and p=0.026, respectively) (Table 4). After adjustment, no factors showed significantly different (p=0.10, p=0.357, and p=0.67, respectively) (Table 4).

Table 4 Predictive factors in progression of DN of women

Univariate analysis			
	Odds ratio	**95% C.I.**	**P value**
γGTP (U/l)	1.02	1.00-1.05	0.040*
Serum Cre (mg/dl)	0	0-0.22	0.026*
eGFR (ml/min/1.73m^2)	1.1	1.02-1.19	0.026*
Multivariate analysis			
	Odds ratio	**95% C.I.**	**P value**
γGTP (U/l)	1.02	0.99-1.04	0.1
Serum Cre (mg/dl)	0	0-89	0.357
eGFR (ml/min/1.73m^2)	0.93	0.68-1.29	0.67

DISCUSSION

In this study, we assessed the association between the progression of DN, fluctuations in CACS, and the effects of sex differences over a five-year period. For male patients, DN was significantly advanced in the high-CACS group, compared with the low-CACS group. However, this tendency was not observed in female patients.

There have been sporadic reports that suggest the association between coronary artery calcification and renal impairment [12,13]. There have also been several reports on sex differences in the progression of chronic kidney disease or cardiovascular disease. Overall, several of these reports indicate that renal lesions progress more rapidly in men [8,14]. This may be because more men have pathogenic factors involved in the DN progression, such as hypertension, dyslipidemia, and smoking. In contrast, it has been reported that female hormones have a direct anti-atherosclerotic action that can affect the production of nitric oxide and influence the renin-angiotensin system in a way to protect the kidneys [15,16]. In fact, there is a report describing that estrogen administration alleviates acetylcholine-induced coronary vasospasm [17]. This explains the increased incidence of cardiovascular events in postmenopausal women in their 70`s and 80`s. In Germany, a study on 28,000 patients with type 1 diabetes mellitus reported that the incidence of microalbuminuria was higher in male patients and that their eGFR also decreased faster when compared to women [9]. In the present study, because high CACS and progression of renal lesions were significantly associated with male sex, atherosclerotic lesions may be a more prominent factor for the development of DN in male patients than in female patients. Furthermore, the progression of DN was found in male patients in high CACS without DR. Although there is no clear explanation for the association between the progression of DN and the absence of diabetic retinopathy in male patients, we can infer from our results that atherosclerosis as macroangiopathy assessed by CACS, rather than microangiopathy, likely contributed to the progression of DN.

While the common factors among men and women for the progression of chronic kidney disease are hypertension and smoking, albuminuria is considered to be a predictive factor for progression in men only [18]. In this study, multivariate analysis revealed that urinary albumin levels were identified as a significant factor for the progression of DN in whole participants and ACEI/ARB use was also identified as a significant factor for progression of DN. However, these results were based on the findings obtained from patients positive for urinary albumin who used ACEI or ARB. This may suggest that even use of these drugs could not prevent the progression of DN. In male patients, although multivariate analysis did not identify CACS as a significant factor for the progression of DN, a five-year follow-up revealed that high CACS was a significant factor for the DN progression. This study revealed that positivity for urinary albumin was a clinical factor for the progression of DN in whole patients and also suggested that high CACS in male patients could predict DN progression in five years. In contrast, no significant differences were observed among female patients presumably because of the following reasons: Their mean age was 68 years, meaning that they were at an age when nephropathy progresses more slowly compared with male patients, and the female patients had milder atherosclerotic lesions since basal CACS was lower in female than male. The 5-year follow-up period may not be an enough time to observe the progression of DN.

The CACS used in the present study is considered to be an important tool for assessment of coronary artery disease,

and this has been frequently addressed in the literature. Although the CACS is a globally accepted tool for assessing atherosclerosis, there have been only a few reports on its use for assessing renal lesions. Our study is novel since it investigates the association between CACS and renal lesions.

This study has several limitations. First, because contrast media cannot be used for patients with advanced renal impairment, this study included only those with prior to stage III nephropathy. Second, our sample size was relatively small, and this study was not a prospective study. Third, only treatment methods for diabetes mellitus and hypertension before follow-up periods were analyzed. Fourth, because collecting data on diet therapy and other approaches were difficult, such approaches could not be considered. In the future, prospective studies with a larger sample size are warranted.

CONCLUSION

Taken together, the severity of atherosclerotic lesions measured by CACS can be a predictive factor for progression of DN in men, but this is not applicable to women. Our study suggests that strict multifactorial interventions are necessary for patients with a high risk of DN progression based on our assessments.

DECLARATIONS

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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