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RELATIONSHIP BETWEEN SEVERITY OF CORONARY ARTERY STENOSIS AND OF CALCIFICATION AND CKD : COMPARISONS OF CT CORONARY ANGIOGRAPHY WITH EGFR IN PATIENTS WITH CARDIOVASCULAR DISEASE

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Abstract
To investigate the relationship between chronic kidney disease (CKD) and the severity of coronary artery stenosis and of calcification, we compared estimated glomerular filtration rates (eGFR) with coronary stenosis and coronary artery calcification scores (CACS) assessed by CT coronary angiography in 300 patients (146 men, 154 women ; average age, 68.8 y). Among these, 275 assessable patients were classified according to stenosis rates of <25%, 25–49%, 50–74% and ≥75% as normal coronary arteries (n=129) and slight (n=50), moderate (n=39) and severe (n=57) stenosis, respectively. They were also classified by total CACS of 0, 0.1–100, 101–399 and ≥400 as having non-calcification (n=93), slight (n=79), moderate (n=50) and severe calcification (n=53), respectively. The average (± standard deviation) eGFR values of the groups with normal arteries, slight, moderate and severe stenosis were 81.86±20.10, 76.29±19.51, 76.59±19.83 and 66.83 ± 17.75, respectively. Those of the groups with non-calcification, slight, moderate and severe calcification were 80.76±17.53, 79.46±23.06, 72.69±20.65 and 70.84±17.76, respectively. Our findings indicated that CKD might cause coronary stenosis and calcification to be severe.

Key words : CKD, eGFR, coronary calcification, coronary stenosis, CT coronary angiography

Introduction

Hypertension (HT), diabetes mellitus (DM) and dyslipidemia (DL) are traditional coronary risk factors that are closely associated with the progression of coronary artery calcification (CAC) and stenosis. Coronary stenosis is a main cause of the development of cardiovascular disease (CVD) and CAC is an important background of stenosis. Furthermore, atherosclerosis is a main cause of CAC and the degree of CAC correlates with the severity of atherosclerosis[1,2]. Chronic kidney disease (CKD) is a lifestyle-related disease that is similar to metabolic syndrome, and it is an important condition in preventive medicine as it is a considerable risk factor for CVD. High rates of CKD are associated with the development and mortality of myocardial infarction, congestive heart failure and cerebral infarction[3-9]. Thus, CKD should be prevented and treated like conventional coronary risk

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factors to prevent CVD.　Computed tomography (CT) coronary angiography (CTCA) using multidetector-row CT (MDCT) has recently become a popular diagnostic tool for imaging the coronary arteries.　Low invasiveness and excellent quality images are features of CTCA, which along with conventional coronary angiography (CAG) equals the utility of coronary imaging in diagnosing coronary artery disease[10-14].　Furthermore, evaluations of CAC with coronary plane CT using MDCT or electron beamed CT is useful screen for ischemic heart disease[15-19].　The present study investigates the relationship between CKD as a novel risk factor for CVD and the severity of coronary stenosis and CAC.　Here, we compared estimated glomerular filtration rates (eGFR) with coronary stenosis and CAC scores (CACS) assessed by CTCA in patients who were diagnosed or suspected as CVD.

Methods

Patients

We enrolled 300 consecutive patients (male/female, 146/154 ; average age ± standard deviation (SD) of all patients, 68.8±10.8 y ; men, 67.4±11.2 y ; women, 70.2 ±10.1 y) who underwent CTCA using 64-row CT, Aqulion (Toshiba, Tokyo, Japan) between January 4th, 2007 and February 16th, 2010.　All male and female patients were respectively classified by age decade as follows : 20s ($n=0$ and 1), 30s ($n=3$ and 0), 40s ($n=6$ and 4), 50s ($n=25$ and 18), 60s ($n=41$ and 37), 70s ($n=55$ and 64), 80s ($n=15$ and 30) and 90s ($n=1$ and 0).　They comprised 20 patients with old myocardial infarction ; 183 with angina pectoris ; 31 at silent high risk with over three conventional coronary risk factors such as HT, DL, DM, or family history (FH) of CVD and smoking ; 56 with atypical chest pain without detectable ischemic change ; and 10 with other conditions.

Assessment of coronary stenosis using CTCA

Coronary stenosis was assessed from CTCA images using a Workstation and the analyzing coronary artery software, ZIOSOFT M900 (Amin, Tokyo, Japan), volume rendering and curved multiplanar reformation (curved-MPR).　Images were visually assessed for coronary stenosis at our hospital by the consensus of two physicians and one radiologist.　All patients were classified into groups according to rates of stenosis in the major coronary arteries that were amenable to percutaneous coronary intervention (PCI) as follows.　Normal coronary arteries, slight, moderate and severe stenosis were classified as <25%, 25-49%, 50-74% and ≥75% stenosis, respectively (Fig. 1).　Patients who had already undergone PCI before CTCA were considered as having severe stenosis regardless of the CTCA findings.　Normal coronary arteries and slight, moderate and severe stenosis were scored by CT as 1, 2, 3 and 4, respectively.　These CT scores were summed for each group according to renal function.　We respectively compared the average values of eGFR and the ratios of patients with CKD in each stenosis group.

Assessment of CACS

Cardiac plane CT was performed during one maximal breath with consecutive scans under the following conditions : slice width, 3 mm ; slice intervals, 3 mm ; scan range between the base and the apex of heart, 90 mm. We calculated CACS from CT images using a workstation with the CACS analysis software, ZIOSOFT M900, according to Agatston's method[15] as follows.　We established regions of interest (ROI) for CAC in each scanned slice and considered a CT number of ≥130 Hounsfield units (HU) and an area of ≥0.51 mm^2 (2 pixels) as significant calcification.　Furthermore, all ROI with significant calcifications were scored as numbers according to maximal CT ranges of 130-199, 200-299, 300-399 and ≥400 HU as 1, 2, 3 and 4, respectively.　The CACS for the ROI were calculated by multiplying the calcification area by the score.　The total CACS in patients were calculated by summing all CACS of the calcification areas.　Total CACS for the patients with PCI were assessed without calculating the CACS for coronary stent areas.　All assessable patients were classified into groups according to total CACS as follows.　Absent, slight, moderate and severe calcification were classified as total CACS of 0, 0.1- 100, 101-399 and ≥400, respectively.　Moreover, absent, slight, moderate and severe calcification were graded as 1, 2, 3 and 4, respectively.　These CAC grades were used included in multiple regression analysis of CAC and
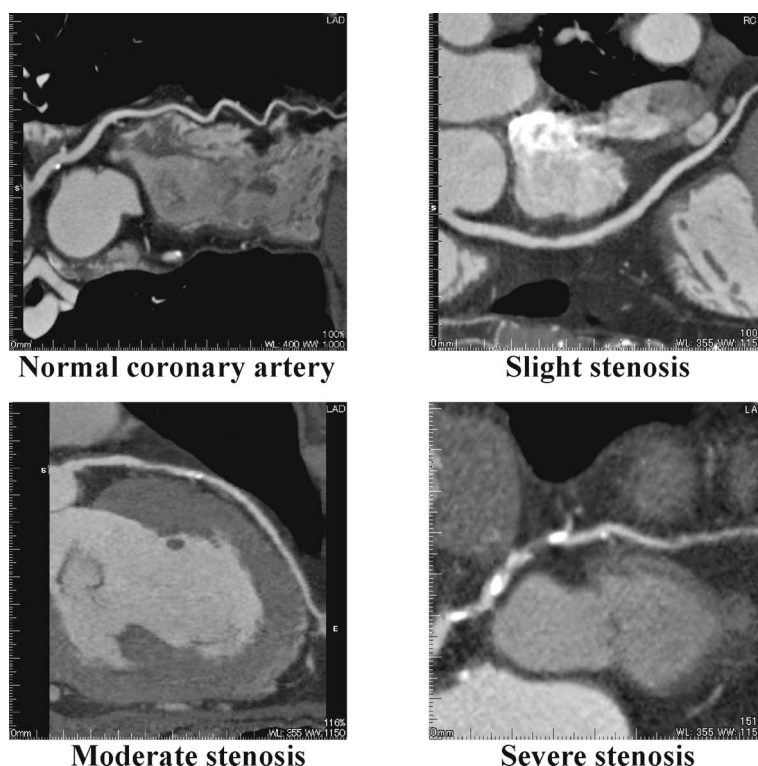
Fig. 1. Curved-MPR images of coronary arteries with coronary stenosis visually evaluated with CTCA using MDCT. Stenosis rates of <25%, 25-49%, 50-74% and ≥75% are classified as normal coronary artery and slight, moderate and severe stenosis, respectively.

coronary risk factors.

Calculation of eGFR and patient classification according to renal function

The standard for evaluating GFR is inulin clearance, which is very difficult to measure. Therefore, eGFR (ml/min/1.73 m^2 ; units are omitted from subsequent values, which are shown as numbers) is used as a substitute for GFR in routine clinical practice. It is a standard modality for diagnosing CKD that depends on age, serum creatinine and sex[20,21]. We calculated eGFR values for assessable patients using the portable computer, J Pocket Clearance 2008 (Kureha, Tokyo, Japan) which measures Japanese eGFR[21]. We also measured serum creatinine using an enzymatic method and the automated analytical instrument, 80FRNEO2 (Toshiba, Tokyo, Japan) before performing CTCA. We classified CKD stages in assess-able patients according to eGFR values of ≥90, 60-90 and <60 as normal renal function equivalent to CKD stage 1 or high risk, slight renal dysfunction equivalent to CKD stage 2 and CKD equivalent to CKD stage 3-5, respectively. We compared the average CT scores and the total CACS in each of the renal function groups.

Definition of coronary risk factors in this study

We defined the traditional coronary risk factors in this study such as increase age (IA), HT, DM, DL (hyper-low density lipoproteinemia [LDL] or hypo-high density lipoproteinemia [HDL]), smoking and FH of CVD, because considerable evidence has established that these factors associated with CVD[22-29]. Diagnosing standards as positive IA, HT, DL and DM were respectively male age ≥45 y, female age ≥55 y, systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, LDL ≥140 mg/dl,

HDL <40 mg/dl, HbA1c ≥5.8% and patients with who had previously received treatment for these risks before CTCA regardless of measured values.　Information about these conventional risk factors and CKD (eGFR <60) was obtained from all assessable patients by anamneses, consultation findings, chest X-rays, ECG, blood biochemical test and ultracardiography findings before CTCA.　We investigated the degrees to which the seven risk factors contributed to the severity of stenosis and of calcification.

Statistical analysis

Data were analyzed using Stat View 5.0 or Windows Excel 2003 software.　Average differences between two groups were compared using a t-test when the analysis of variance (ANOVA) indicated significant differences in all populations.　Significant differences in ratios between two groups were compared using Ryan's method after significance in all populations was determined using the χ^2 test with a contingency table.　We investigated the relationship between each risk factor and the severity of coronary stenosis and of CAC using multiple regression analysis as follows.　We analyzed the independent dummy variables comprising the seven risk factors assessed as positive or negative, and 1 or 0, and dependent variables as CT scores and CAC grades.　A value of $p<0.05$ indicated significant difference.

Results

1.　Classifications of 275 assessable patients

Among 300 patients, coronary stenosis could not be evaluated in 15 due to significant calcification, motion artifacts and insufficient coronary artery enhancement, and 10 had peripheral artery stenosis or lateral branch stenosis that would not be amenable to PCI.　These 25 patients were considered as not assessable.　Table 1 shows 275 assessable patients were respectively classified by stenosis rate, the numbers of patients positive for each risk factor, renal function and total CACS.　275 assessable patients comprised 129 with normal coronary arteries, 50 with slight, 39 with moderate and 57 with severe stenosis, including 41 who had undergone PCI.　We also respectively classified the 275 patients were by the numbers of patients positive for each risk factor as : IA ($n=$ 258), HT ($n=222$), Smoking ($n=35$), FH ($n=62$), DL ($n=$ 172), DM ($n=61$) and CKD ($n=49$).　Moreover, the assessable patients comprised 59 with normal renal function, 167 with slight renal dysfunction and 49 with CKD.　They also comprised 93 without calcification, and

Table 1.　Classifications of 275 assessable patients.

275 assessable patients						
•Coronary stenosis						
Normal coronary ($n=129$)		Slight stenosis ($n=50$)		Moderate stenosis ($n=39$)		Severe stenosis* ($n=57$)
•Numbers of patients positive for each risk factor						
IA ($n=258$)	HT ($n=222$)	Smoking ($n=35$)	FH ($n=62$)	HL ($n=172$)	DM ($n=61$)	CKD ($n=49$)
•Renal function						
Normal function ($n=59$)		Slight dysfunction ($n=167$)		CKD ($n=49$)		
•Total CACS**						
Non calcification ($n=93$)		Slight calcification ($n=79$)		Moderate calcification ($n=50$)		Severe calcification ($n=53$)

Among 300 patients, 25 patients were considered as not assessable.　275 assessable patients were respectively classified by stenosis rate, the numbers of patients positive for each risk factor, renal function and total CACS.　* : Including 41 patients who had undergone PCI.　** : Total CACS for the patients with PCI were assessed without calculating the CACS for coronary stent areas.

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79, 50 and 53 with slight, moderate and severe calcification, respectively.

2. Comparisons of renal function with coronary stenosis

The average ± SD of the eGFR values of the groups with normal coronary arteries, and with slight, moderate and severe stenosis were 81.86 ± 20.10, 76.29 ± 19.51, 76.59 ± 19.83 and 66.83 ± 17.75, respectively (Fig. 2). The value with PCI was 66.10 ± 18.86. The SD values were large, indicating wide variation in the eGFR values for each of the stenosis groups. Nevertheless, increasing stenosis rates were associated with decreasing average eGFR values. Significant differences were found between the group with severe stenosis and those with

moderate and slight stenosis, and normal coronary arteries. (ANOVA ; $p=0.01$, 0.007 and <0.0001, respectively). Figure 3 compares ratios of patients with CKD in each stenosis group. The ratios of CKD of the groups with normal coronary arteries, and with slight, moderate and severe stenosis were 9.3% (12/129), 24.0% (12/50), 17.9% (7/39) and 31.6% (18/57), respectively. Significant differences were found between the groups with normal coronary arteries and slight as well as severe stenosis (Ryan's method ; $p<0.05$). Figure 4 shows that the average ± SD of CT scores of the groups with normal and slight renal dysfunction and CKD were 1.81 ± 1.05, 2.02 ± 1.19 and 2.63 ± 1.21, respectively. Significant differences were found between the group with CKD and those with normal and slight dysfunction (ANO-
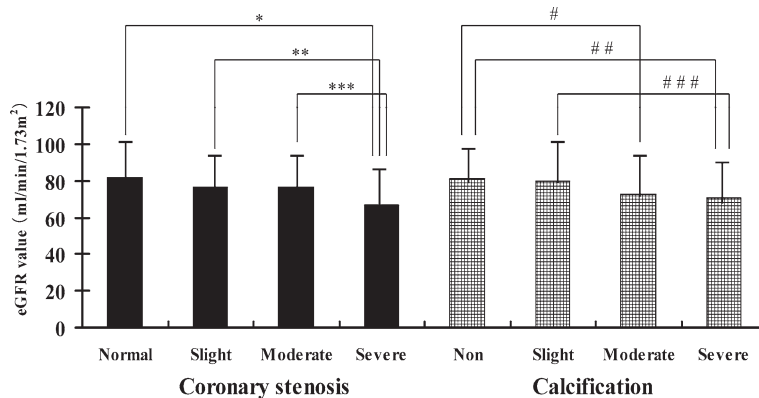

Fig. 2. Values for eGFR according to coronary stenosis and calcification. Significant differences were found between the stenosis groups by ANOVA as follows : *$p<0.0001$; **$p=0.007$; ***$p=0.01$. Decreasing renal function was associated with increasing degree of CAC. ANOVA found significant differences between calcification groups (#$p=0.01$; ##$p=0.001$; ###$p=0.02$).
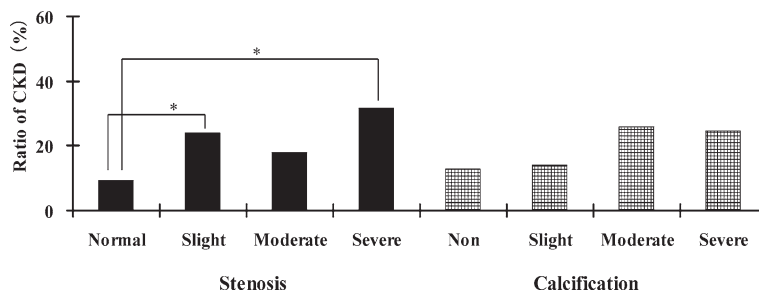

Fig. 3. Ratio of CKD according to coronary stenosis and calcification. Ryan's method identified significant differences between groups with normal coronary arteries and with slight and severe stenosis (*$p<0.05$), but not among groups with calcification.

VA ; $p=0.0003$, 0.002, respectively). Coronary artery stenosis had obviously progressed in the patients with CKD.

3. Comparisons of renal function with coronary calcification

Figure 2 compares the average ± SD of the eGFR values of the groups according to CAC. Those of the groups without calcification and with slight, moderate and severe calcification were 80.76±17.53, 79.46±23.06, 72.69±20.65 and 70.84±17.76, respectively. Decreasing renal function was associated with increasing CAC. Significant differences were found between the groups with non-calcification and moderate or severe calcification, and between those with slight and severe calcification (ANOVA ; $p=0.01$, 0.001, 0.02, respectively). Figure 3 compares the ratios of patients with CKD in each CAC group. The ratios of CKD among the groups without calcification and with slight, moderate and severe calcification were 12.9% (12/93), 13.9% (11/79), 26.0% (13/50) and 24.5% (13/53), respectively. Ryan's method did not identify any significant differences in any population. The average ± SD of the total CACS of the groups with normal and slight dysfunction, and CKD

were 127.2±288.9, 297.7±687.9 and 396.4±735.2, respectively (Fig. 5). An increasing degree of renal dysfunction was associated with increasing average total CACS. However, the large SD values indicated a wide variation in the total CACS for each renal function group, so significant differences were not identified in any of the populations by ANOVA.

4. Multiple regression analysis of relationships between coronary risk factors and the severity of coronary stenosis and of calcification

Table 2 shows a multiple regression analysis of the contributions of the seven coronary risk factors to CT score and CAC grade. The partial regression coefficients and p-values indicated that CKD made the greatest contribution to increasing CT scores, which reflect the degree of coronary artery stenosis. Each of IA, HT, DL and DM also significantly affected these CT scores. On the other hand, the findings indicated that IA and HT were important factors in increasing CAC grades that reflect the degree of CAC. Both CKD and smoking were also significantly associated with CAC grade. However, the multiple correlations between coronary risks and CT score and CAC grade were 0.39 and 0.33, respectively.
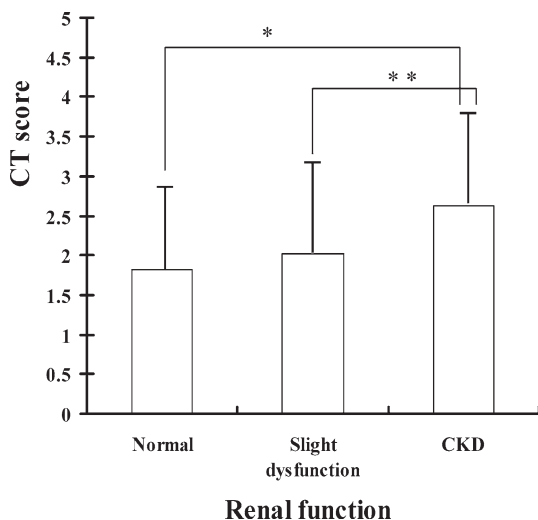

Fig. 4. Average CT score values according to renal function. ANOVA revealed significant differences among renal function groups (*$p=0.0003$ and **$p=0.002$)
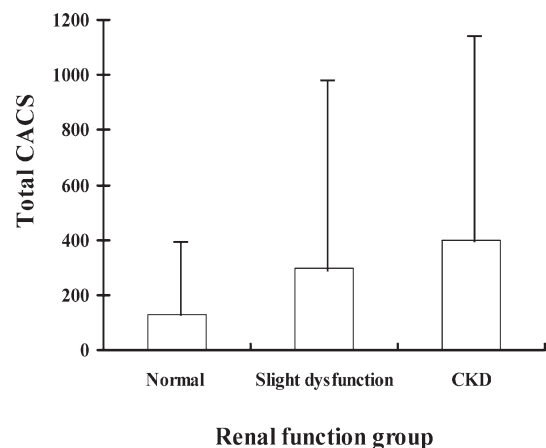

Fig. 5. Total CACS based on renal function. Increasing degree of renal dysfunction was associated with increasing average total CACS. ANOVA found no significant differences in total CACS according to renal function in any population.

Table 2. Multivariate analysis of association between seven coronary risk factors and CT scores and CAC grades.

vs. CT score				vs. CAC grade		
	Partial regression coefficient	Standard error of mean	p-value		Partial regression coefficient	Standard error of mean	p-value
Intercept	0.6393	0.3121	0.0415	Intercept	0.8912	0.2969	0.6029
Increase age	0.6603	0.2840	0.0208	Increase age	0.7519	0.2702	0.0058
Hypertension	0.4613	0.1759	0.0092	Hypertension	0.5455	0.1673	0.0013
Smoking	0.3383	0.2073	0.1039	Smoking	0.4768	0.1972	0.0163
Family history	0.0484	0.1643	0.7684	Family history	0.2310	0.1562	0.1405
Dyslipidemia	0.3461	0.1442	0.0171	Dyslipidemia	−0.0496	0.1372	0.7179
Diabetes mellitus	0.3649	0.1683	0.0311	Diabetes mellitus	0.1988	0.1601	0.2154
CKD	0.6120	0.1781	0.0007	CKD	0.3845	0.1694	0.0241
Multiple correlation coefficient was 0.39.				Multiple correlation coefficient was 0.33.			

Partial regression coefficients and p–values indicated that CKD contributes the most to increasing CT score values, which reflect the degree of coronary artery stenosis.
On the other hand, age and hypertension were important factors that participated in increasing CAC grades, which reflect the degree of CAC.

Discussion

Multiple regression analysis of the risk factor contribution to increasing stenosis rates indicated that CKD in particular, as well as IA, HT, DL and DM, are associated with severe coronary stenosis. As stenosis rates increased, the average eGFR values were significantly low, and the ratios of CKD attended to be high. These findings indicated that CKD represents a significant risk factor for CVD in terms of the severe stenosis, and that active intervention for CKD is indispensable for prevention. Several reports have indicated that treating conventional HT, DM and DL inhibits CKD progression and possibly decreases in GFR[30-34]. The fact that risk factors for CKD and for CVD, namely, IA, HT, DM, DL and smoking, closely overlap supports our findings. Not only is CKD an independent risk factor for CVD, it is also related to each of the traditional coronary risks ; that is, CKD and CVD are closely linked. Thus, the measures for treating CKD are identical to those of aggressive treatment for conventional coronary risks. Moreover, proteinuria, anemia, CKD–related mineral and bone disorder (CKD–MBD), inflammation and nutrition may be also considered as risk factors for CVD in patients with CKD. Microalbuminuria might be associated with a

high risk of developing early CVD[4,9,35-37]. We consider that the reason why CKD has a remarkable effect on the severity of coronary stenosis is as follows. Firstly, atherosclerosis is not only related to conventional risk factors, but also to other factors such as proteinuria, anemia, CKD–MBD, inflammation and nutrition in CKD. Our comparisons of renal function with calcification showed low eGFR values and high ratios of patients with CKD as total CACS increased. These findings indicated that CAC severity is associated with CKD. Multivariate analysis determined that increasing CAC, IA and HT are factors that predominantly contribute to severity of CAC. This analysis also suggested that the contribution of CKD might be significant, but to a lesser extent than those of IA and HT. Several studies have found many patients with severe coronary arteriosclerosis among those with CKD accompanied by renal arteriosclerosis such as stage 5 or on dialysis[38,39]. In addition, CAC also becomes more frequent and severe over time[40]. The severity of CAC might be under a powerful influence of IA. Consequently, we consider that increasing CKD severity over time has deeper effects on CAC. None of our enrolled patients had undergone or were receiving dialysis. This might explain why the contribution of CKD to increasing CAC grade was lower than that of ei-

（34）Coronary stenosis and coronary calcification versus CKD

ther IA or HT. Thus, our findings indicate that CKD is associated with the severity of coronary stenosis and of coronary calcification. To prevent the development of CVD requires curative approaches to CKD.

Conclusions

To investigate the relationship between CKD as a new risk factor for CVD and the severity of coronary stenosis and of coronary calcification, we compared eGFR with coronary stenosis and CACS assessed using 64-row CT in 275 assessable patients who were diagnosed or suspected as CVD. Our findings indicated that CKD causes the severity of coronary stenosis and CAC.

Acknowledgements

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