Correlation of coronary plaque characteristics and obstructive stenosis with chronic kidney disease by coronary CT angiography

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Background: Chronic kidney disease (CKD) is an independent risk factor for cardiovascular events. We evaluated the correlation of coronary plaque characteristics and obstructive stenosis with CKD by coronary computed tomographic angiography (CCTA).

Methods: We enrolled 491 subjects who were suspected coronary artery disease (CAD) undergoing CCTA. Estimated glomerular filtration rate (eGFR) was calculated by the modification of diet in renal disease (MDRD) equation. Patients were subdivided into four groups based on their eGFR: normal GFR (n=213, eGFR \geq 90 mL/min/1.73 m²), mild renal insufficiency (n=191, eGFR 60-89 mL/min/1.73 m²), moderate renal insufficiency(n=78, eGFR <60 mL/min/1.73 m², \geq 30 mL/min/1.73 m²), and severe renal insufficiency (n=9, eGFR <30 mL/min/1.73 m², \geq 15 mL/min/1.73 m²).

Results: Spearman correlation regression analysis showed that the prevalence of any plaque, calcified plaque (CP), mixed plaque (MP) were positively correlate with CKD (r=0.173, P<0.001; r=0.127, P=0.005; r=0.171, P<0.001), after adjustment for traditional risk factors the prevalence of any plaque and MP were still positively correlate with CKD (r=0.106, P=002; r=0.178, P<0.001). And the prevalence of any stenosis and severe stenosis were positively correlate with CKD (r=0.13, P<0.001; r=0.149, P<0.001), after adjustment for traditional risk factors the traditional risk factors were still positively correlate with CKD (r=0.134, P=0.001; r=0.174, P<0.001).

Conclusions: CKD is closely related with occurrence of CAD. CKD patients from mild renal insufficiency to severe renal insufficiency are the risk factors for CAD. More serious renal function impairment will indicates higher risk of coronary plaque, MP and obstructive stenosis.

Keywords: Chronic kidney disease (CKD); coronary computed tomographic angiography (CCTA); coronary artery disease (CAD)

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Introduction

Chronic kidney disease (CKD) has been a worldwide public health problem (1-4). Increasing prevalence of CKD is astounding. In the United States about 8 million adults had CKD of at least stage 3 (1), and investigation on adult population of Beijing in China showed that the prevalence of CKD was 13.0% (2). As a result, CKD has been an independent risk factor for adverse cardiovascular disease (CVD) (3-5). Progressive impairment of renal function will independently give rise to increased risks of CVD. CKD patients are more likely to die of CVD than to progress to ESKD (6). Epidemiological studies from China showed the prevalence of ESKD in China is far less than the prevalence of mild or moderate renal insufficiency (2,7,8). Hence, the



Figure 1 Flowchart of the selection of study population. PCI, percutaneous coronary intervention; CABG, coronary artery by-pass graft.

burden of CVD in the population with CKD should be emphasized. It may induce a greater impairment of health than does ESKD.

In the other words, CKD also accelerate the occurrence of coronary artery disease (CAD). Date from epidemiologic studies reported that glomerular filtration rates (GFR) is negatively correlated with CAD (3,5). CAD has long been identified as a leading cause of death among patients with ESRD. Decreased GFR and proteinuria are both found to be independently associated with CAD. Considering the high risk of CVD in the population with CKD, the American College of Cardiology/American Heart Association task force and the National Kidney Foundation in 2003 regarded CKD as a CAD risk equivalent (9).

Recently, the development of computed tomographic has almost solved the problem of cardiac examination. Coronary computed tomographic angiography (CCTA) has been playing a significant role in the noninvasive assessment of coronary plaque and stenosis. It not only leads to higher diagnostic accuracy for CAD, but also reduces the dose of contrast agent and radiation. There was increasing evidence proves that CCTA has high diagnostic accuracy for CAD (10,11). Although several studies have found the negative correlation of CKD with CAD, the coronary plaque characteristics of patients with CKD are still remains unclear. Therefore, this present study aimed to investigate the correlation of coronary plaque characteristics and obstructive stenosis with CKD in Dual source computed tomography (DSCT).

Methods

Study population

We retrospectively studied 646 consecutive subjects who were suspected CAD undergoing CCTA with DSCT from March 2014 to February 2015 in the Department of Imaging Center of Nanfang Hospital. Firstly, 151 subjects were excluded: missing any data of clinical information (n=97), had histories of percutaneous coronary intervention (PCI, n=32) or coronary artery by-pass graft (CABG, n=8), poor quality of image (n=15), patients with eGFR <15 mL/min/1.73 m² and/or performed dialysis or transplantation (n=3). As a result, 491 subjects [345 males and 146 females, age 26-87 years, mean age (59.0±10.6) years] were enrolled in our study. The process was showed in *Figure 1*.

Collection of clinical characteristics

The lifestyle and clinical characteristics of all subjects were obtained by referred to completion of electronic medical record or accomplished an interview. We collected information including age, sex, height (cm), body weight

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(kg), serum creatinine (Scr), blood pressure (BP), smoking status, serum levels of triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), fasting blood glucose, medical history of hypertension (HT), diabetes mellitus (DM) and hyperlipidemia (HPL). Evaluation of renal function was based on the estimated GFR (eGFR). For all participants the eGFR were calculated by the modification of diet in renal disease (MDRD) study Eq. [1] (12):

eGFR (mL/min/1.73 m²) =186× (SCr/88.41)^{-1.154}× (age)^{-0.203} (0.742 if female) [1]

Scr was tested in the first month before undergoing CCTA with extracting fasting venous blood. The stage of CKD based on the K/DOQI (13) clinical practice guidelines for CKD as follows: CKD stage 1, renal function is normal or with increased GFR (eGFR $\geq 90 \text{ mL/min}/1.73 \text{ m}^2$); CKD stage 2, renal function is mildly insufficient (eGFR $<89 \text{ mL/min}/1.73 \text{ m}^2$, $\geq 60 \text{ mL/min}/1.73 \text{ m}^2$); CKD stage 3, renal function is moderately insufficient (eGFR<60 mL/min/ 1.73 m^2 , $\geq 30 \text{ mL/min}/1.73 \text{ m}^2$); CKD stage 4, renal function is severely insufficient (eGFR <30 mL/min/1.73 m^2 , \geq 15 mL/min/1.73 m²); CKD stage 5, kidney failure (eGFR <15 mL/min/1.73 m²). Afterwards, we divided all subjects into four categories: normal eGFR group $(eGFR \ge 90 \text{ mL/min}/1.73 \text{ m}^2)$, mild renal insufficiency group (eGFR <89 mL/min/1.73 m², \geq 60 mL/min/1.73 m²), moderate renal insufficiency group(eGFR <60 mL/min/ 1.73 m^2 , $\geq 30 \text{ mL/min}/1.73 \text{ m}^2$), and severe renal insufficiency group (eGFR <30 mL/min/1.73 m², \geq 15 mL/min/1.73 m²). HT was defined as a self-reported history of HT or treatment of antihypertensive treatment, or blood pressure ≥140/90 mmHg. HPL was defined as self-reported history of HPL or a lipid-lowing treatment, or LDL-C >140 mg/dL or TG >200 mg/dL. DM was defined as a self-reported history of DM or a glucose-lowing treatment. Body mass index (BMI) was calculated by dividing body weight (kg) by the square of height (m).

CCTA scan protocol

The study was approved by the ethical committee, and obtained patient himself or her family's agreement and signed the medical informed consent document. All patients were performed with CCTA using ECG-gated DSCT (Somatom Definition, Siemens Healthcare, Forchheim, Germany). Before examination, blood pressure and heart rate were measured, breath training was did, 20 G trocar was leaved in patient's median cubital vein, 1-2 snap Nitroglycerin was injected in patient sublingual mucosal. At the beginning, coronary calcium scoring (CCS) scan was performed; scan range was from tracheal juga to the diaphragm. Then, 75-85 mL of contrast medium (Iopamiron 370, Bayer Schering Pharma AG, Berlin, Germany), according to the patient's weight, was injected through a dual channel high pressure syringe at a rate of 5.0<5.5 mL/s into cubital vein, followed by 30 mL of saline solution chaser, using a bolus tracking technique at the slice of aortic root to determine the trigger time. When the density reached a predefined threshold of 90 Hounsfield units (HU), the scan automatically started with a 6 seconds scan delay during one breath-hold with simultaneous recording of the ECG-tracing. Heart rate and ECG were monitored during CCTA. The image parameters were a slice collimation of 32 mm \times 0.6 mm, slice acquisition 64 mm \times 0.6 mm by means of a Z-axis flying focal spot, 120 KV, 350 mAs, 0.33 s rotation time. All patients were performed with retrospective ECG gated scan.

Image reconstruction

Original date (standard DICOM 3.0 image) was transmitted to the Syngo post-processing workstation of Siemens, layer thickness of 0.75 mm, interval of 1 mm. Two independent blinded radiologists analysed the coronary lesion with Circulation software, and measured the CCS with CaScoring software. Before analysis, we would select one of the best phase for reconstruction by means of volume rending (VR), curved planar reformation (CPR), maximum intensive projection (MIP), multiple planar reconstruction techniques (MPR) and virtual digital subtraction angiography (DSA). As soon as reconstruction was accomplished, all images would be sent to picture achieving and communication system (PACS) of Nanfang Hospital for diagnosis.

Image analysis

All images would be analyzed by two independent blinded radiologists in PACS. If views inconsistent, carefully discussion would be processed for the uniform views. Coronary image quality were divided into 4 levels according to the 4-point scale as follow: 1, excellent, no motion artifacts, clear delineation of vascular contours; 2, good, minor artifacts, mild blurring of vascular contours; 3, adequate, moderate artifacts, moderate blurring without structure discontinuity of vessel; 4, not evaluative, doubling



Figure 2 An example of a 51-year-old man with mild renal insufficiency (eGFR =80.5 mL/min/1.73 m²) who appears a non-calcified plaque in the middle segment of right coronary artery (A). An example of a 72-year-old woman with moderate renal insufficiency who appears a MP in the proximal segment of left anterior descending (B) and a calcified plaque in the proximal segment of left circumflex (C).

or discontinuity in the course of the segment preventing evaluation or vessel structures not differentiable (14). Score 1-3 were considered for diagnostic, score 4 was excluded. Based on the recommendations of the American Heart Association study, coronary arteries were divided into 15 segments and 4 main branches (15). CCS was calculated by the Agatston score (16), calcification was defined as a threshold of 130 HU of attenuation value and 1 mm² of Region of Interest Controls (ROI) area. CCS =[calcified plaque (CP) area] × (highest CT value coefficient), coefficient of HU: 1=133-199 HU; 2=200-299 HU; 3=300-399 HU; 4≥400 HU. Plaque was clarified into 3 types: CP, mixed plaque (MP), non-calcified plaque (NCP). Calcified plaque was defined as a plague with higher CT value than vessel, non-calcified plaque was defined as a plaque with lower CT value than vessel, MP was defined as a plaque consist of calcium and soft tissue ingredient. Obstructive stenosis was described as follows: no stenosis or existence of irregular vascular contours (stenosis percentage <30%), mild stenosis (stenosis percentage $\geq 30\%$, <50%), moderate stenosis (stenosis percentage $\geq 50\%$, <75%), severe stenosis or blocking (stenosis percentage $\geq 75\%$). Multi-vessels disease was defined as two or more vessels prevalence of any plaque or stenosis (Figure 2).

Statistic analysis

Continuous variables of clinical characteristic were presented

as mean and standard deviations (mean±SD). Regular smoking, prevalence of HT, HPL, DM were categorized as ves/no. Categorical variables of clinical characteristic were presented as percentage which was the frequency of positive events. Comparison of continuous variables was performed with one-way ANOVA and least-significant difference (LSD) was used for multiple comparisons. Comparison of categorical variables was performed with chi-square test. Firstly, Spearman's correlation was applied to evaluate the correlation of coronary lesion with CKD. Then, partial correlation was used for adjustment for following covariates: age, sex, regular smoking, BMI, prevalence of HT, HPL, and DM. All P values were 2-sided, P values <0.05 was considered to identify statistically significant differences. All analysis was carried out using SPSS, version 20.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline clinical characteristics

All images were of sufficient quality for analysis. After examination of CCTA, all the subjects have not appeared the exacerbation of renal function during our followup for three to 6 month. A total of 491 subjects were divided into four groups: normal eGFR group (n=213), mild renal insufficiency group (n=191) moderate renal insufficiency group (n=78), severe renal insufficiency

 Table 1 Baseline clinical characteristics of all subjects

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Characters	All	Normal	Mild	Moderate	Severe	Р	
Age (years)	59.0±10.6	56.9±10.2	59.4±10.4	63.6±10.9	62.7±10.5	<0.001	
eGFR (mL/min/1.73 m ²)	86.1±29.3	112±9.7	75.7±10.2	47.9±8.6	22.3±5.0	<0.001	
BMI (kg/m ²)	23.9±3.4	23.4±3.1	24.2±3.3	24.7±4.2	24.0±2.3	0.014	
Sex (male, %)	345 (70.3)	111 (52.1)	159 (83.2)	69 (88.5)	6 (66.7)	<0.001	
HT (yes, %)	238 (48.5)	86 (40.4)	89 (46.6)	56 (71.8)	7 (77.8)	<0.001	
DM (yes, %)	147 (29.9)	42 (19.7)	76 (39.8)	25 (31.6)	4 (44.4)	<0.001	
HPL (yes, %)	200 (40.7)	87 (40.8)	77 (40.3)	31 (39.7)	5 (55.6)	0.834	
Regular smoking (yes, %)	215 (43.9)	86 (40.3)	88 (41.4)	36 (46.2)	5 (55.6)	0.553	

Data are expressed as mean±SD or n (%). P value indicates the difference among different group of CKD, P<0.05 was considered to identify statistically significant differences. eGFR, estimated glomerular filtration rate; BMI, body mass index; HT, hypertension; DM, diabetes mellitus; HPL, hyperlipidemia.

group (n=9). The baseline clinical characteristics were showed in *Table 1*: among all subjects the mean eGFR was 86.1±29.3, normal renal insufficiency group was 112±19.7, mild renal insufficiency group was 75.7±10.2, moderate renal insufficiency group was 47.9±8.6, and severe renal insufficiency group was 22.3±5, difference among groups was statistically significant (P<0.0001). Compared with normal eGFR group, mild renal insufficiency, moderate renal insufficiency group and severe renal insufficiency group had a higher prevalence of advanced age, BMI, male, HT, and DM, differences among groups all were statistically significant (P<0.05). However, differences among groups of prevalence of HPL and regular smoking were no statistically significant (P=0.834, P=0.553).

Coronary artery disease (CAD)

The results were showed in Table 2.

Coronary plaque characteristics

Coronary plaque was found in 374 of 491 subjects (76.2%). Prevalence of any plaque, calcified plaque and MP were positively correlate with CKD (r=0.173, P<0.0001; r=0.127, P=0.005; r=0.171, P<0.0001). Prevalence of non-calcified plaque had no correlation with CKD (r=-0.035, P=0.436). After adjustment for traditional risk factors, prevalence of any plaque and MP were still positively correlate with CKD (r=0.106, P=002; r=0.178, P<0.0001). Nevertheless, prevalence of calcified plaque being no correlation with CKD.

Obstructive stenosis

Stenosis was found in 308 of 491 subjects (62.7%).

Prevalence of any stenosis and severe stenosis were positively correlate with CKD (r=0.13, P<0.001; r=0.149, P<0.001). After adjustment for traditional cardiovascular risk factors, prevalence of any stenosis and severe stenosis were still positively correlate with CKD (r=0.134, P=0.003; r=0.174, P<0.001)

Prevalence of multi-vessels disease and CCS

Multi-vessels disease was found 230 of 491 subjects (46.8%). Prevalence of multi-vessels lesion was positively correlate with CKD (r=0.167, P<0.001). After adjustment for traditional cardiovascular risk factors, prevalence of multi-vessels lesion was still positively correlate with CKD (r=0.167, P<0.001). CCS of all subjects was 117.8±394.3, normal eGFR group was 72±195.6, mild renal insufficiency group was 132.2±534.2, moderate insufficiency group was 187.6±404.9, severe renal insufficiency group was 191.4±217.4. CCS was positively correlate with the CKD (r=0.219, P<0.001). After adjustment for traditional cardiovascular risk factors, CCS were still positively correlate with CKD (r=0.103, P=0.02).

Discussion

CKD is characterized by a progressive decline in GFR over many years resulting in permanent kidney failure requiring dialysis or transplantation. Although the mechanisms linking renal insufficiency to high CAD risk have not been completely understood and further study should be did, publics had an indisputable implications of the adverse result for health. Previous studies reported that both traditional risk factors (advanced age, male sex,

Table 2 Coronary artery disease of a	ll subjects								
Variables	All	Normal	Mild	Moderate	Severe	-	۵.	Partial-r	٩
Prevalence of any plaque (yes, %)	374 (76.2)	147(69.0)	149 (78.0)	69 (88.5)	9 (100)	0.173	<0.0001	0.106	0.02
Prevalence of CP (yes, %)	222 (45.2)	83 (39.0)	90 (47.1)	43 (55.1)	6 (66.7)	0.127	0.005	0.057	0.21
Prevalence of MP (yes, %)	153 (31.2)	50 (23.5)	63 (330.)	36 (46.2)	4 (44.4)	0.171	<0.0001	0.178	<0.001
Prevalence of NCP (yes, %)	169 (34.4)	80 (37.6)	57 (29.8)	29 (37.2)	3 (33.3)	-0.035	0.436	-0.071	0.121
Prevalence of any ST (yes, %)	308 (62.7)	123 (57.7)	117 (61.3)	60 (76.9)	8 (88.9)	0.13	0.004	0.134	0.003
Prevalence of SST (yes, %)	67 (13.6)	19 (8.9)	27 (14.1)	18 (23.1)	3 (33.3)	0.149	<0.0001	0.174	<0.001
Prevalence of M-V (yes, %)	230 (46.8)	86 (40.4)	85 (44.5)	52 (66.7)	7 (77.8)	0.167	<0.0001	0.162	<0.001
CCS	117.8±394.3	72±195.6	132.2±534.2	187.6±404.9	191.4±217.4	0.219	<0.0001	0.103	0.02
Data are expressed as n (%) or me correlation CP calcified plaque. N	ean ± SD. r valu MP mixed placi	ue indicates tl	he correlation	of CAD with C	SKD, r>0 indicat is: SST severe	tes the positives at the stenders of the stenders of the stendard of the stend	ve correlation, V. multi-vessel	r<0 indicates	the negative
calcification score.									

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DM, HT, HPL, smoking, obesity, sedentary lifestyle, and family history of CVD and so on) and nontraditional risk factors (endothelial dysfunction, CKD-MBD abnormalities, increased oxidative stress, and inflammation and so on) commonly contributed to the formation of coronary plaques and heavy burden of CVD to the patients with renal insufficiency. Traditional cardiovascular risk factors were reliable predictor for cardiovascular event, especially for CAD (17-21). The present study focused attentions on the traditional cardiovascular risk factors, the results showed that population with renal insufficiency had a higher prevalence of advanced age, advanced BMI, male, HT, and DM. Though, prevalence of HPL and regular smoking had no differences among different groups in the present study, analysis of risk factor of CKD in previous studies reported that total cholesterol level in patients with CKD was higher than patients with no CKD (5,17). Hence, the results indicate that patients with CKD easily exposed to traditional cardiovascular risk factors. As a disappointed consequence, it will give rise to higher incidence of CVD.

Previous studies demonstrated that moderate renal dysfunction may accelerate the formation of coronary plague and increase the frequency of plaque disruption. Moreover, the morphology of atherosclerotic plaque differs between patients with and without CKD (22-25). Our study recruited subjects with normal eGFR to severe renal insufficiency to discuss the correlation with the coronary plaque characteristics and obstructive stenosis. To the best of our knowledge, few studies recruited different degree of renal insufficiency to investigate the correlation mentioned above, especially patients with an eGFR <30 mL/min/1.73 m². We demonstrated that the correlation of prevalence of any coronary plaque, MP, any stenosis, severe stenosis, and multi-vessels disease were significant positively correlate with different degree of renal insufficiency. In addition, after adjustment for traditional cardiovascular risk factors, the relationship still exists. It means that the exacerbation of renal function will accompany with higher risk of prevalence of coronary plaques and obstructive stenosis. Even mild renal insufficiency will be a risk factor of CAD. The existence of vulnerable plaques aggrandizes the risk of suffering acute coronary syndrome (ACS). Although CCTA can't reliably distinct the vulnerable plaques, it can accurately distinct the composition of coronary plaque. The study did by Pundziute et al. showed that the vulnerable plaques usual be mixed-plaque (26). In the present study, higher prevalence of MP indicates us that

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heavier impairment of renal function may motivate higher risk of ACS. Although the correlation of prevalence of calcified plaque with renal insufficiency had no statistically significance, the CACS was positively correlate with the renal insufficiency after adjustment for traditional risk factors. It is well known that vascular calcification is a dependable predictor for adverse cardiovascular events. Quantification of coronary arterial calcification (CAC) provides prognostic information beyond identification of traditional CV risk factors (27,28). Higher CCS was associated with higher prevalence, more diffuse and greater extent of CAD in patients with renal insufficiency (29).

In our present study, less than 1/5 subjects with moderate or severe renal insufficiency, but of them less than 1/3 suffered from coronary severe stenosis. Moreover, more than 1/2 of CKD patients with mild or no CAD. Hence, CCTA could be one of the useful methods for screening of CKD patients who were suspected CAD. It is important to noninvasively identify such low-risk patients for CAD in the high-risk group to spare them further invasive examinations. These results provided further supporting evidence for the relationship between elevated cardiovascular risk and different degree of CKD by CCTA. We suppose that one of the mechanisms by which CKD is associated with a high risk of CVD would be through the different coronary plaques. Accordingly, a reasonable treatment to reduce the risk in these patients would prevent the formation of plaques or stabilize them aggressively. Early detection and treatment of renal insufficiency may reduce the societal burden of CAD, as well as CVD. As a long-term results, it is significant for reduce cardiovascular morbidity and mortality. Although risk factor modification in CKD patients can substantially decrease cardiovascular morbidity and mortality based on the data presented, the presence of CKD should prompt aggressive measures to reach goals for blood pressure and cholesterol recommended for the highest cardiovascular risk group.

Our study had following limitation. Firstly, the patient population of this present study was a relatively small sample, especially the patients with severe renal insufficiency (n=9), because of the risk of contrast induced nephropathy. All the subjects recruited who were suspected CAD undergoing CCTA in a solo health community. As a result, it cannot represent the general population and most of the patients could accompany with coronary heart disease risk factors. Therefore, selection bias could influence the results, and information about causation could not be

provided. Secondly, we measured the serum creatinine only one time and we measured the GFR with MDRD equation. The effect of variation of serum creatinine cannot be excluded. MADR equation is not the most accurate measurement of GFR, the result of MADR equation is an estimate GFR, and hence, the measurement error would influence the results. Thirdly, we did not have information regarding proteinuria and albuminuria because we did not collect urine samples. Although CCTA is a well-established imaging technique for detection of coronary plaques, the functional relevance of the plaques remains unsubstantiated. Finally, we have not investigated patient outcomes because of the relatively short follow-up time.

Conclusions

All in all, more serious renal insufficiency will indicate higher risk of coronary plaque, MPs, obstructive stenosis, multi-vessels disease and CCS. CKD patients from mild renal insufficiency to severe renal insufficiency are the risk factors for CAD. CKD is closely related with the occurrence of CAD.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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