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ORIGINAL ARTICLE

Influence of chronic kidney disease on coronary plaque components in coronary artery disease patients with both diabetes mellitus and hypertension

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Abstract

Chronic kidney disease (CKD) is well known to be associated with an increased incidence of coronary artery disease (CAD). Diabetes mellitus (DM) and hypertension (HTN), both of which are traditional risk factors for CAD, are the two most common causes of CKD. However, the influence of CKD on coronary atherosclerosis in CAD patients who have both DM and HTN remains uncertain. In these patients, we examined the relationship between CKD and coronary plaque using integrated backscatter intravascular ultrasound (IB IVUS). Two hundred two CAD patients with both DM and HTN who underwent percutaneous coronary intervention using IB IVUS were included. The patients were divided into two groups: CKD group ($n=106$) and non-CKD group ($n=96$). Gray-scale and IB IVUS examinations were conducted for the non-culprit segment of a coronary artery. As a result, although there was no significant difference in the percentage of plaque volume, the percentage of lipid volume was significantly higher in the CKD group than in the non-CKD group [median (IQR): 56.7% (45.4–67.0%) vs. 52.0% (38.3–60.2%), $p=0.03$]. In all of the patients, estimated glomerular filtration rate levels were negatively correlated with the percentage of lipid volume ($r=-0.15$, $p=0.03$) and positively correlated with the percentage of fibrosis volume ($r=0.15$, $p=0.04$). A multivariate regression analysis showed that CKD was an independent predictor associated with the increased lipid volume ($\beta=0.15$, $p=0.047$) and decreased fibrosis volume ($\beta=-0.16$, $p=0.03$) in coronary plaques. In conclusion, among CAD patients who had both DM and HTN, CKD was associated with lipid-rich coronary plaques. CKD may contribute to the vulnerability of coronary plaque in these very high-risk patients.

Keywords Chronic kidney disease · Coronary plaque · Intravascular ultrasound · Diabetes mellitus · Hypertension

Introduction

Chronic kidney disease (CKD), the progressive loss of kidney function, is an expanding global public health problem [1]. It is well known that CKD is associated with adverse cardiovascular disease risk [2–4]. The two most common causes of CKD in many developed and developing countries are diabetes mellitus (DM) and hypertension (HTN) [2, 3], both of which are also traditional risk factors for coronary artery disease (CAD). A large-scale epidemiological study reported that patients with both DM and CKD had higher cardiovascular mortality than those with DM but without CKD [5]. It has also been reported that a low GFR independently predicts an increased risk for CAD in older patients with HTN [6]. Thus, CKD is associated with an increased risk of cardiovascular events in patients with DM or HTN.

Gray-scale intravascular ultrasound (IVUS) provides a more comprehensive assessment of atherosclerotic coronary plaques than coronary angiography in humans [7]. However, conventional IVUS cannot be used to accurately identify different components of coronary plaque. Recently, integrated backscatter IVUS (IB IVUS) has been developed to evaluate the tissue characteristics of coronary plaques in humans

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[8]. It has been reported that coronary plaque compositions as evaluated by IB IVUS are well correlated with histological findings of coronary atherosclerosis [8]. In fact, an increased lipid composition in coronary plaques as assessed by IB IVUS has been reported to be an independent predictor of future cardiac events in patients with CAD [9, 10]. A recent study using IB IVUS reported that lower estimated glomerular filtration rate (eGFR) levels were associated with greater lipid and lower fibrous components [11]. In CAD patients with DM, another study using virtual histology IVUS showed that patients with a lower level of eGFR had a greater necrotic core volume than those with a higher level of eGFR [12]. However, in CAD patients with both DM and HTN, who are at very high risk of future cardiac events, the impact of CKD on coronary atherosclerosis as evaluated by IB IVUS remains unclear. The purpose of the present study was to examine the relationship between CKD and coronary plaque using IB IVUS in CAD patients with both DM and HTN.

Materials and methods

Patients and study design

For this retrospective single-center study, a total of 1822 patients with stable CAD who underwent percutaneous coronary intervention (PCI) at Fukuoka University Hospital from October 2010 to January 2018 were screened. Of these, patients without DM or HTN, or who did not undergo PCI using IB IVUS, were excluded. The remaining patients were excluded from this study according to the following exclusion criteria: (1) patients with unanalyzable IVUS images of the non-culprit segment [7] (Fig. 1); (2) patients who underwent PCI for coronary bypass graft diseases; (3) familial hypercholesterolemia; (4) contraindication to antiplatelet agents; (5) severe infection; and (6) recent surgery or trauma. Ultimately, 202 CAD patients who underwent IB IVUS-guided PCI were included in the present study.

Patients were diagnosed as DM if they satisfied any of the diagnostic criteria defined by the Japan Diabetes Society [fasting blood sugar (FBS) level ≥ 126 mg/dl, 2-h 75 g oral glucose tolerance test glucose level ≥ 200 mg/dl or random plasma levels of blood sugar ≥ 200 mg/dl], or if they continued to take hypoglycemic drugs with a clear diagnosis of DM, as reported previously [13]. If patients had a current systolic blood pressure/diastolic blood pressure ≥ 140/90 mmHg or were receiving antihypertensive agents, they were considered to have HTN [14]. eGFR was calculated using the Modification of Diet in Renal Disease formula, and CKD was defined as eGFR < 60 ml/min/1.73 m^2 [15]. According to the Japanese guidelines for the secondary prevention of myocardial infarction, all of the patients received standard antiplatelet therapy before PCI

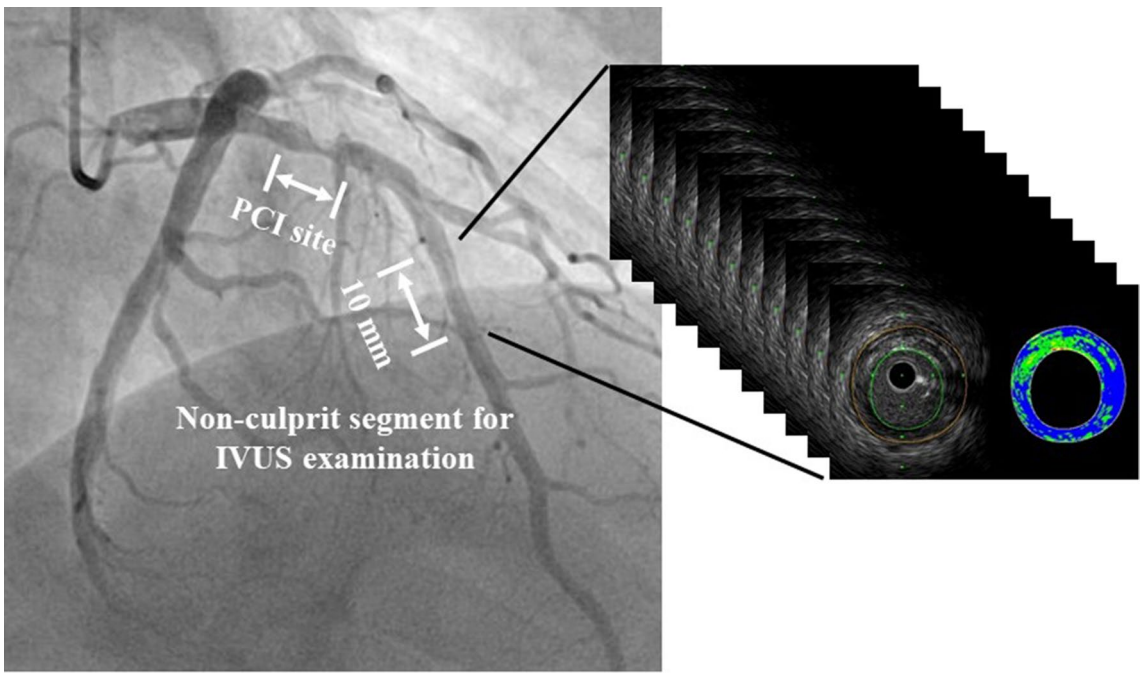

Fig. 1 Representative coronary angiography and IVUS images of the target vessel in gray-scale and IB IVUS analyzes. The length of the target segment for the IVUS analysis was 10 mm. The segment had to be located > 5 mm proximal or distal from the PCI site. *IVUS* intravascular ultrasound, *IB* integrated backscatter, *PCI* percutaneous coronary intervention

[16]. Fasting blood samples for the measurement of clinical laboratory data were collected before the PCI and IVUS procedures.

This study was approved by the ethics committee of Fukuoka University Hospital (EC/IRB: 15-7-14) and conducted according to the Declaration of Helsinki regarding investigations in humans.

IVUS procedure and analysis

Immediately after PCI of the culprit lesion, IVUS examination was conducted for the non-culprit segment (<50% stenosis as evaluated by coronary angiography) of a coronary artery by an imaging catheter and a console (View IT and VISIWAVE, Terumo, Tokyo, Japan). After the intracoronary administration of an optimal dose of nitroglycerin, the IVUS catheter was advanced to the distal side of the PCI site, and pulled back automatically at 0.5 mm/s. As reported previously [17, 18], the most-diseased 10-mm segment (containing the cross-section with the greatest plaque burden) was selected as the target segment for IVUS analysis. The segments had to be located more than 5 mm proximal or distal to the PCI site (Fig. 1).

For IVUS analysis in this study, a quantitative IVUS analysis system (VISIATLAS, Terumo, Tokyo, Japan) was used. This IVUS analysis system can measure both the volume and components of coronary plaque. It has been reported that the IVUS analysis system is suitable for the accurate measurement of coronary atherosclerosis [19]. External elastic membrane (EEM) cross-sectional area (CSA) and lumen CSA were manually traced, and atheroma CSA (EEM CSA minus lumen CSA) was automatically calculated. These measurements were performed at 1-mm axis intervals for a length of 10 mm [17, 18] (Fig. 1). With the IB IVUS analysis system, the volumes of vessel (Σ EEM CSA) and lumen (Σ lumen CSA) were calculated, and total atheroma volume (TAV) was calculated as vessel volume minus lumen volume at the selected segment. Percent atheroma volume (PAV), the plaque burden at the selected segment, was calculated as 100 × TAV/vessel volume. The plaque components were classified into four categories using the software for IB IVUS: lipid, fibrosis, dense fibrosis, and calcification, as described previously [8]. The software for IB IVUS automatically calculated the area and volume of each plaque component, and these IB IVUS parameters were presented as percentages.

According to the clinical expert consensus documents for IVUS analysis [7], an experienced physician who was unaware of the patients' backgrounds conducted the IVUS analysis in this study. In addition, another researcher who had experience with precise IVUS analysis and was blinded to the data of this study confirmed that all of the IVUS parameters were accurately measured.

Clinical laboratory examinations

For measurement of the clinical data in this study, fasting blood samples were collected just before IB IVUS-guided PCI. Low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), creatinine, FBS and hemoglobin A1C (HbA_{1c}) levels were measured at the Fukuoka University Hospital Laboratory Unit. eGFR was calculated as follows: $194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287}$ for males and $194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287} \times 0.739$ for females. Echocardiographic examinations were conducted according to standards recommended by the American Society of Echocardiography [20], and left ventricular ejection fraction (LVEF) was calculated using the modified Simpson's method.

Statistical data analysis

The SAS software package (version 9.4, SAS Institute) at Fukuoka University (Fukuoka, Japan) was used for statistical data analysis. Categorical variables are presented as numbers and percentages. Continuous variables with a normal distribution are presented as mean ± SD. If continuous variables do not show a normal distribution, they are presented as median values and interquartile range (IQR). The chi-square test or Fisher's exact test was used to compare frequency distributions of categorical variables between two groups. Differences in continuous variables with a normal distribution were compared by the Student *t* test. Wilcoxon's signed-rank sum test was used if the continuous variables showed skewed distributions. To examine the correlations among continuous variables including eGFR and IVUS parameters, the Spearman correlation or Pearson correlation was used according to the distributions of the variables. A multivariate regression analysis was conducted among conventional risk factors [age, male gender, body mass index (BMI) and current smoking] and LDL-C levels to identify the factors that were related to the percentages of lipid volume and fibrosis volume of coronary plaque. A p value less than 0.05 was considered to be significant unless indicated otherwise.

Results

Characteristics of the patients and clinical laboratory data

The patient characteristics in the present study are shown in Table 1. Patients with CKD were significantly older than those without CKD [median (IQR): 70 years (66–78 years) vs. 68 years (59–72 years), $p = 0.001$]. There were no

significant differences in the frequencies of dyslipidemia, current smoking or history of myocardial infarction and PCI between the groups. The frequencies of the use of glinide, β-blocker and diuretics in the CKD group were significantly higher than those in the non-CKD group. The frequency of the use of biguanide in the non-CKD group was significantly higher than that in the CKD group.

Table 2 shows the clinical laboratory data of the patients in this study. There were no significant differences in LDL-C, HDL-C, HbA_{1c} or FBS levels, while the TG level in the CKD group was significantly higher than that in the non-CKD group [median (IQR): 146 mg/dl (90–224 mg/dl) vs. 113 mg/dl (78–151 mg/dl), $p = 0.005$]. Systolic and diastolic blood pressures were similar between the groups. LVEF in the CKD group was significantly lower than that in the non-CKD group (59.7% ± 13.1% vs. 64.5% ± 11.9%, $p = 0.04$).

Gray-scale and IB IVUS parameters at the non-culprit segment

Table 3 shows the gray-scale and IB IVUS parameters at the non-culprit segment. Although TAV and vessel volume in the CKD group were significantly greater than those in the non-CKD group [median (IQR): 68.9 mm^3 (43.1–97.3 mm^3) vs. 54.7 mm^3 (32.9–74.0 mm^3), p = 0.004 and 153 mm^3 (106–193 mm^3) vs. 130 mm^3 (78–168 mm^3), p = 0.01, respectively], there was no significant difference in PAV

Table 1 Patient characteristics

	All patients ($n = 202$)	CKD group ($n = 106$)	Non-CK group ($n = 96$)	p value (CKD vs. non-CKD)
Age (years)	69 (63–75)	70 (66–78)	68 (59–72)	0.001
Male gender, *n* (%)	153 (76)	77 (73)	76 (79)	0.36
BMI (kg/m^2)	24.5 (22.6–27.1)	24.3 (22.9–26.5)	24.6 (22.1–27.4)	0.83
Dyslipidemia, *n* (%)	185 (92)	98 (93)	87 (91)	0.83
Current smoking, *n* (%)	40 (20)	17 (16)	23 (24)	0.22
Previous MI, *n* (%)	52 (26)	31 (29)	21 (22)	0.30
Previous PCI, *n* (%)	99 (49)	57 (54)	42 (44)	0.20
Previous CABG, *n* (%)	0 (0)	0 (0)	0 (0)	–
# of diseased vessels, *n*				
1/2/3	99/57/46	51/35/20	48/22/26	0.19
Target vessel, *n*				
RCA/LAD/LCx/LMT	76/88/42/3	38/44/22/2	38/37/20/1	0.92
Medications, *n* (%)				
Statin	191 (95)	100 (94)	91 (95)	1.0
Fibrate	0 (0)	0 (0)	0 (0)	–
Ezetimibe	7 (3)	6 (6)	1 (1)	0.12
EPA	20 (10)	13 (12)	7 (7)	0.34
Insulin	60 (30)	33 (31)	27 (28)	0.75
DPP4 inhibitor	88 (44)	47 (45)	41 (43)	0.88
Biguanide	40 (20)	14 (13)	26 (27)	0.02
Sulfonylurea	43 (21)	20 (19)	23 (24)	0.48
α-GI	60 (30)	25 (24)	35 (36)	0.07
Glinide	8 (4)	8 (8)	0 (0)	0.007
Thiazolidine	26 (13)	9 (8)	17 (18)	0.08
CCB	132 (65)	74 (70)	58 (60)	0.21
ARB	148 (73)	78 (74)	70 (73)	1.0
ACE inhibitor	18 (9)	11 (10)	7 (7)	0.60
β-Blocker	65 (32)	43 (41)	22 (30)	0.01
Diuretics	42 (21)	32 (30)	10 (10)	0.001

Data are presented as number (%) or median (interquartile range)

CKD chronic kidney disease, *BMI* body mass index, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass grafting, *RCA* right coronary artery, *LAD* left anterior descending, *LCx* left circumflex, *LMT* left main trunk, *EPA* eicosapentaenoic acid, *DPP4* dipeptidyl peptidase-4; α-GI, α-glucosidase inhibitor, *CCB* calcium channel blocker, *ARB* angiotensin II receptor blocker, *ACE* angiotensin-converting enzyme

Table 2 Clinical laboratory data

	All patients ($n=202$)	CKD group ($n=106$)	Non-CK group ($n=96$)	p value (CKD vs. non-CKD)
LDL-C (mg/dl)	85 (74–107)	85 (73–105)	88 (75–108)	0.21
HDL-C (mg/dl)	45 (38–54)	43 (37–54)	46 (40–53)	0.19
TG (mg/dl)	121 (84–190)	146 (90–224)	113 (78–151)	0.005
FBS (mg/dl)	109 (94–129)	109 (94–133)	108 (94–124)	0.55
HbA_{1c} (%)	7.0 (6.4–7.9)	7.0 (6.4–7.9)	7.1 (6.6–7.7)	0.42
eGFR (ml/min/1.73m^2)	56.0 ± 21.7	40.0 ± 15.3	73.6 ± 11.8	< 0.001
SBP (mmHg)	130 (118–141)	131 (116–145)	128 (119–138)	0.43
DBP (mmHg)	70 (61–79)	70 (61–77)	69 (61–81)	0.49
LVEF (%)	61.7 ± 12.8	64.5 ± 11.9	59.7 ± 13.1	0.04

Data are presented as mean ±SD or median (interquartile range)

LDL-C low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *TG* triglyceride, *FBS* fasting blood sugar, *HbA_{1c}* hemoglobin A_{1c}, *eGFR* estimate glomerular filtration rate, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *LVEF* left ventricular ejection fraction

between the groups (47.0% ± 11.8% vs. 44.7% ± 11.1%, $p=0.15$). The percentage of lipid volume in the CKD group was significantly higher than that in the non-CKD group [median (IQR): 56.7% (45.4–67.0%) vs. 52.0% (38.3–60.2%), $p=0.03$]. The percentage of fibrosis volume was significantly lower in the CKD group than in the non-CKD group (39.6% ± 12.6% vs. 43.5% ± 11.9%, $p=0.03$). There were no significant differences in the percentages of dense fibrosis volume or calcification volume between the groups.

Relations between clinical data and coronary plaques

The relations between clinical data including eGFR levels, and lipid and fibrosis volume at the non-culprit segment in all of the patients are shown in Table 4. There were no significant associations between the percentages of lipid volume and fibrosis volume, and age, gender, BMI, smoking status, serum levels of LDL-C, HDL-C and TG, FBS and HbA_{1c} levels and systolic and diastolic blood pressures. Figure 2 shows the associations between eGFR levels and gray-scale IVUS parameters in all of the patients. eGFR levels were negatively correlated with TAV ($r=-0.19$, $p=0.006$) and vessel volume ($r=-0.17$, $p=0.01$), while there was no significant correlation between eGFR levels and PAV. In all of the patients, as shown in Table 4 and Fig. 3, eGFR levels were negatively correlated with the percentage of lipid volume ($r=-0.15$, $p=0.03$) and positively correlated with the percentage of fibrosis volume ($r=0.15$, $p=0.04$). There were no significant correlations between eGFR levels and the percentages of dense fibrosis volume and calcification volume (Fig. 3).

Table 5 shows the results of a multivariate regression analysis to identify the factors that were related to the percentages of lipid volume and fibrosis volume at the

Table 3 Gray-scale and IB IVUS parameters

	All patients ($n=202$)	CKD group ($n=106$)	Non-CK group ($n=96$)	p value (CKD vs. non-CKD)
Gray-scale IVUS				
TAV (mm^3)	59.0 (39.5–91.0)	68.9 (43.1–97.3)	54.7 (32.9–74.0)	0.004
Vessel volume (mm^3)	140 (88–181)	153 (106–193)	130 (78–168)	0.01
PAV (%)	45.9 ± 11.5	47.0 ± 11.8	44.7 ± 11.1	0.15
IB IVUS				
Lipid volume (%)	53.3 (43.7–62.6)	56.7 (45.4–67.0)	52.0 (38.3–60.2)	0.03
Fibrosis volume (%)	41.5 ± 12.4	39.6 ± 12.6	43.5 ± 11.9	0.03
Dense fibrosis volume (%)	3.7 (2.3–6.2)	3.3 (2.2–6.2)	4.1 (2.7–6.1)	0.28
Calcification volume (%)	1.3 (0.6–2.6)	1.3 (0.6–2.1)	1.3 (0.6–3.1)	0.53

Data are presented as mean ± SD or median (interquartile range)

IB integrated backscatter, *IVUS* intravascular ultrasound, *TAV* total atheroma volume, *PAV* percent atheroma volume

Table 4 Univariate factors associated with the percentage of lipid volume and fibrosis volume as evaluated by IB IVUS

	Lipid volume (%)		Fibrosis volume (%)	
	r	*p* value	*r*	*p* value
Age	− 0.03	0.68	0.04	0.55
Male gender	0.07	0.31	− 0.02	0.81
BMI	0.09	0.20	− 0.12	0.08
Current smoking	− 0.12	0.09	0.13	0.06
LDL-C	0.03	0.71	− 0.001	0.99
HDL-C	0.07	0.33	− 0.08	0.27
TG	0.07	0.36	− 0.05	0.46
FBS	− 0.11	0.13	0.12	0.10
HbA_{1c}	− 0.03	0.71	− 0.008	0.91
SBP	0.03	0.63	− 0.01	0.84
DBP	0.09	0.23	− 0.06	0.39
eGFR	− 0.15	0.03	0.15	0.04

IB integrated backscatter, *IVUS* intravascular ultrasound, *BMI* body mass index, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *TG* triglyceride, *FBS* fasting blood sugar, HbA_{1c} hemoglobin A_{1c}, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *eGFR* estimate glomerular filtration rate

non-culprit segment. After adjustment for conventional coronary risk factors including LDL-C levels, CKD was found to be an independent predictor associated with increased lipid volume ($\beta = 0.15$, $p = 0.047$) and decreased fibrosis volume ($\beta = -0.16$, $p = 0.03$) in coronary plaques.

Discussion

The present study showed that CKD was significantly associated with increased lipid and decreased fibrous plaque components as assessed by IB IVUS in CAD patients with both DM and HTN. In addition, a lower eGFR was significantly related to increased lipid volume and decreased fibrous volume of coronary plaques. After adjustment for conventional coronary risk factors by a multivariate regression analysis, CKD was identified as an independent predictor associated with increased lipid and decreased fibrosis contents of coronary plaques.

The cause of the increased prevalence of CAD in individuals with CKD has not yet been fully elucidated, and is likely to be multifactorial. At least some of the increase in cardiovascular events in CKD patients is considered to be associated with the clustering of traditional risk factors for CAD. DM and HTN, which are conventional cardiovascular risk factors, are also the two most common causes of CKD [2, 3]. In patients with DM or HTN, renal dysfunction is related to an increased risk of cardiovascular events [5, 6]. On the other hand, Nakayama et al. investigated the effects of DM and HTN on the risk for CAD in patients with CKD. They reported that patients with diabetic nephropathy or hypertensive nephropathy had a higher risk of cardiovascular events than those with primary renal disease [21].

Coronary plaque formation begins with risk factors for CAD that initiate the process that leads to vascular tissue damage. Oxidative stress can trigger endothelial dysfunction and the inflammatory process. All of these factors are involved in the initiation and development of atherosclerotic diseases [22]. Both DM and HTN are associated with the increased production of free radicals and oxidative

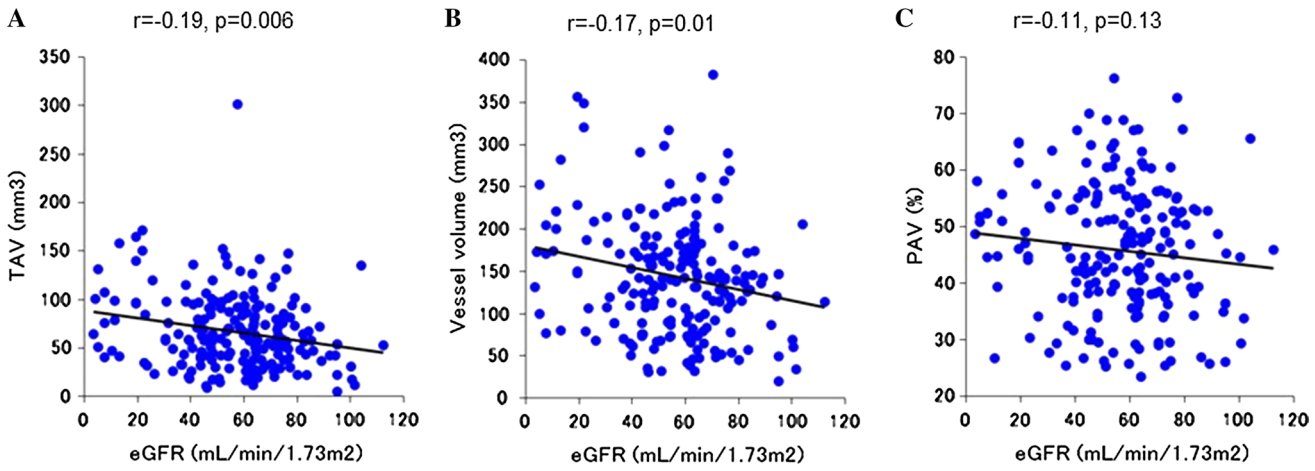

Fig. 2 Associations between eGFR levels and gray-scale IVUS parameters at the non-culprit segments in all of the patients. TAV (**a**), vessel volume (**b**) and PAV (**c**). *eGFR* estimated glomerular filtration rate, *IVUS* intravascular ultrasound, *TAV* total atheroma volume, *PAV* percent atheroma volume

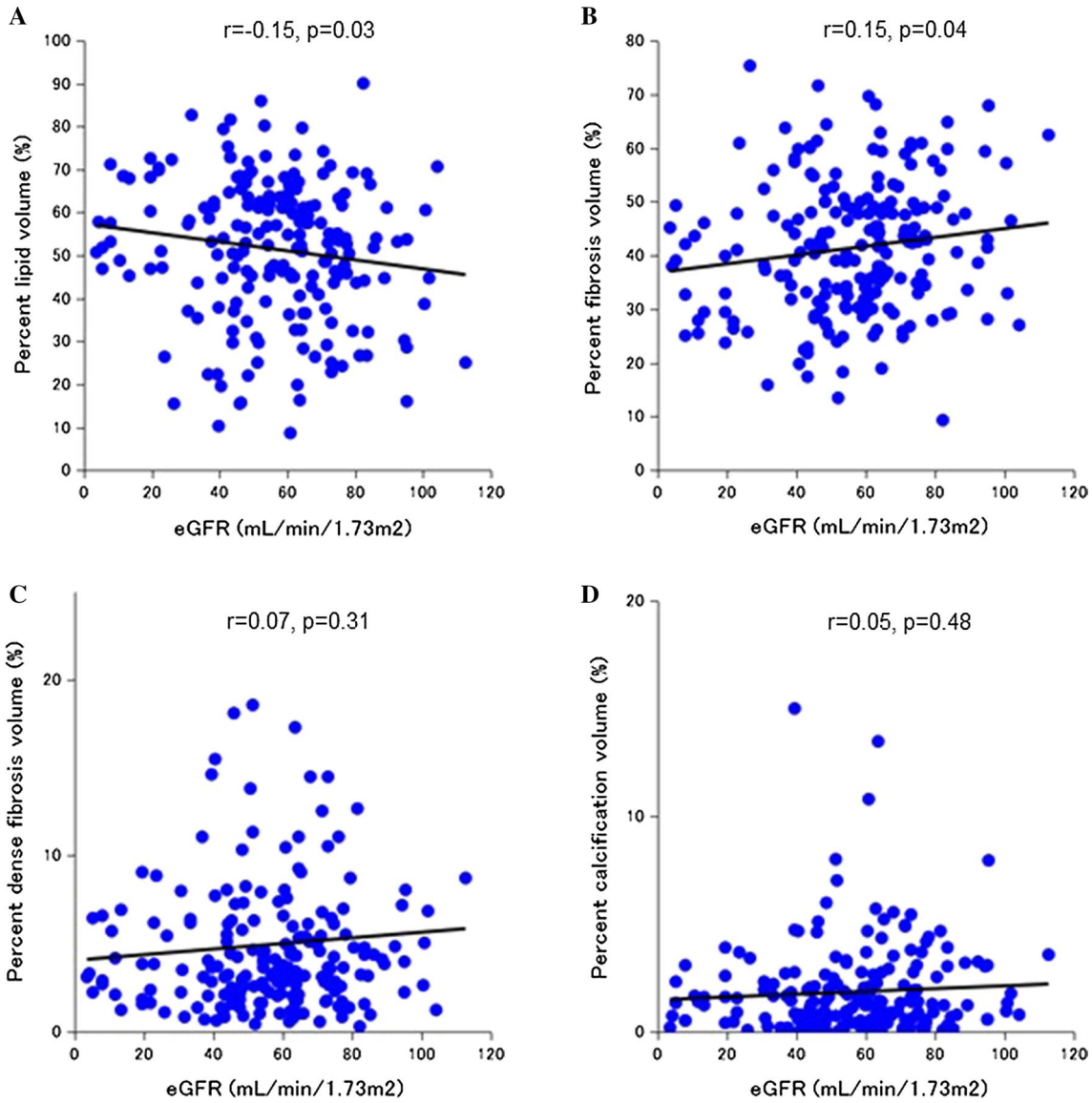

Fig. 3 Associations between eGFR levels and IB IVUS parameters at the non-culprit segments in all of the patients. Lipid volume (**a**), fibrosis volume (**b**), dense fibrosis volume (**c**) and calcification volume (**d**). *eGFR* estimated glomerular filtration rate, *IB* integrated backscatter, *IVUS* intravascular ultrasound

stress, which promote an inflammatory state and endothelial dysfunction [22–24]. Oxidative stress, inflammation and endothelial dysfunction are also involved in the progression of renal injury [25]. It has been reported that endothelial function is more impaired in patients with early-stage CKD than in those without CKD [26], and endothelial dysfunction may be an independent and incremental predictor of cardiovascular events in individuals with CKD [27]. In addition, patients with end-stage renal diseases are subject to enhanced oxidative stress caused by reduced antioxidant systems and increased pro-oxidant activity [28]. These common pathophysiological conditions in patients with DM, HTN and CKD may strongly promote the progression of coronary atherosclerosis.

It is well known that dyslipidemia is involved in the pathogenesis of cardiovascular diseases in CKD. Clearance of chylomicrons, very low density lipoproteins (VLDL) and their remnants is impaired in CKD patients, and this causes a significant increase in TG levels [29, 30]. In fact, the TG level in the CKD group was significantly higher than that in the non-CKD group in this study (Table 2). The accumulation of chylomicrons, VLDL and their remnants in the circulating blood can promote the development of atherosclerosis [31]. Although an elevated LDL-C level is a major risk factor for CAD, most CKD patients show a low or normal

Table 5 Multivariate regression analysis: independent factors associated with the percentages of lipid volume and fibrosis volume as evaluated by IB IVUS

	Lipid volume (%)		Fibrosis volume (%)	
	β	*p* value	*β*	*p* value
Age	− 0.003	0.97	0.01	0.89
Male gender	0.13	0.07	− 0.06	0.37
BMI	0.09	0.25	− 0.11	0.14
Current smoking	− 0.13	0.08	0.13	0.08
LDL-C	0.06	0.41	− 0.03	0.64
CKD	0.15	0.047	− 0.16	0.03

IB integrated backscatter, *IVUS* intravascular ultrasound, *BMI* body mass index, *LDL-C* low-density lipoprotein cholesterol, *CKD* chronic kidney disease

plasma LDL-C concentration [32]. However, low-density lipoprotein (LDL) in these patients consists of highly atherogenic small dense particles due to the elevated TG level in CKD [33]. In addition, it has been reported that oxidized LDL, which has been identified as a potent atherogenic molecule, is increased in individuals with CKD [29, 30]. A low level of HDL-C, a risk factor for CAD, is found in most patients with CKD [32]. In addition, the function of high-density lipoprotein (HDL) may be related to the high incidence of CAD in CKD patients. HDL carries the peripheral cholesterol to the liver, which is called reverse cholesterol transport, and possesses antiinflammatory and antioxidant properties. Impairment of the functions of HDL is considered to be a risk factor for cardiovascular diseases [34, 35], and these functions have been reported to be impaired in CKD patients [29, 30]. The alterations in triglyceride-rich lipoprotein, LDL and HDL metabolism in CKD may contribute to lipid-rich coronary plaque formation.

Several studies have been conducted to investigate the influence of CKD on coronary atherosclerosis. A postmortem study examined the relation of renal function with advanced coronary atherosclerosis defined as American Heart Association type IV (atheroma), type V (fibro-atheroma), or type VI (complicated plaque). As a result, a lower eGFR was related to a high percentage of advanced coronary atherosclerosis [36]. Kashiyama et al. investigated the association between CKD and coronary plaque progression/regression using IVUS after statin treatment. The authors demonstrated that, despite statin therapy, plaque progression was found in patients with eGFR < 60 ml/min/1.73 m^2, whereas plaque regression was observed in patients with eGFR ≥ 60 ml/min/1.73 m^2 [37]. Other studies using IVUS examined the relationship between CKD and coronary plaque components. Miyagi et al. reported that CAD patients who underwent elective PCI with eGFR < 60 ml/min/1.73 m^2 had a higher percentage of lipid volume and a lower percentage of fibrosis volume as evaluated by IB IVUS compared to those with eGFR ≥ 60 ml/min/1.73 m^2 [38]. Another study using IB IVUS showed that the decline in eGFR levels was associated with greater lipid and lower fibrosis components of coronary plaques in CAD patients [11]. In CAD patients with DM, Ogita et al. [12] reported that patients with a lower eGFR level had a greater necrotic core volume as assessed by virtual histology IVUS compared to those with a higher eGFR level. In the present study, we examined the impact of CKD on the tissue characteristics of coronary plaques in higher risk CAD patients who had both DM and HTN. Consistent with the results of previous studies, CKD and a lower eGFR were significantly associated with greater lipid components of coronary plaques. Kakuta et al. [39] examined the relationship between tumor necrosis factor (TNF)-α, which is a well-known potent proinflammatory cytokine, and coronary plaque components as assessed by IVUS. They reported that an elevated serum level of TNF-α was significantly associated with increased lipid and necrotic plaque contents in CAD patients with both type 2 DM and CKD. As mentioned above, the clustering of risk factors for CAD such as DM, HTN, and CKD could more strongly promote oxidative stress, inflammation and endothelial damage, and, as a result, the lipid components of coronary plaque may increase further.

The clustering of traditional cardiovascular risk factors and the disorders of lipid metabolism in CKD do not fully account for the high incidence of CAD in CKD patients. Several conditions that are related to a decline in renal function are considered to be novel risk factors for CAD. Anemia accompanies worsening renal function as a result of a decline in the production of erythropoietin in the kidney. Anemia has been reported to be associated with an increased risk of cardiovascular events in CKD patients [40–42]. In addition, several factors such as abnormalities of calcium and phosphorus metabolism, altered coagulation factors and impaired vascular stiffness may contribute to an increase in cardiovascular events in individuals with CKD [41, 42]. Furthermore, it is well known that higher albuminuria is an independent predictor of cardiovascular mortality in general population cohorts regardless of eGFR levels [43]. In patients with type 2 DM, albuminuria is also associated with an increased carotid intima-media thickness, which is a surrogate index of general atherosclerosis [44]. Shimbo et al. [45] reported that CAD patients with eGFR 45–59 ml/min/1.73 m^2 and proteinuria had greater lipid volume of coronary plaques as assessed by IB IVUS than those with eGFR > 60 ml/min/1.73 m^2 without proteinuria. We did not examine the relationships between these factors and the tissue characteristics of coronary plaques. Further studies using IVUS will be required to address these issues.

Recently, the relation between blood glucose variability, which is determined by the mean amplitude of glycemic

excursions (MAGE) based on data from a continuous glucose-monitoring system, and coronary plaque vulnerability as evaluated by IVUS was investigated. As a result, high glucose fluctuation strongly contributes to increased coronary plaque vulnerability in patients with acute coronary syndrome or stable CAD [46, 47]. The association between MAGE and coronary plaque contents was not examined in this study. To clarify this point, further research in CKD patients with both DM and HTN should be performed.

This study has several limitations. First, the sample size of the study is relatively small. A more large-scale study with IVUS will be needed to confirm our findings. Second, CAD patients who underwent PCI without IB IVUS examinations or who had unanalyzable IB IVUS images of the non-culprit segment were excluded from this study. Therefore, it is possible that there is a selection bias and our findings may not be applicable to all CAD patients with both DM and HTN. Third, we did not investigate the associations between the changes in renal function and coronary plaque components. A prospective study with serial IB IVUS examinations will be required. Fourth, although coronary plaques with increased lipid components are considered to be vulnerable [8], the vulnerability of plaque also depends on the thickness of the fibrous cap. Optical coherence tomography (OCT) can evaluate thin-cap fibro-atheroma more accurately than IVUS [48, 49]. Therefore, further studies using both IVUS and OCT will be required to examine the associations between vulnerable plaques and CKD more precisely.

In conclusion, among CAD patients with both DM and HTN, CKD was associated with an increased lipid content of coronary atherosclerosis. In these patients who are at very high risk of future cardiovascular events, CKD may contribute to the vulnerability of coronary plaque.

Compliance with ethical standards

Conflict of interest KS and SM are Directors of NPO Clinical and Applied Science, Fukuoka, Japan. KS and SM received a Grant from the Public Interest Incorporated Foundation of "Clinical Research Promotion Foundation" in Fukuoka, Japan, and part of this work was transferred to NPO Clinical and Applied Science, Fukuoka, Japan. KS has an Endowed Department of Molecular Cardiovascular Therapeutics (SM), Fukuoka University, supported by MSD Co., Ltd.

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