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ORIGINAL ARTICLE

Increased arterial inflammation in individuals with stage 3 chronic kidney disease

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Abstract
Purpose While it is well known that patients with chronic kidney disease (CKD) are at increased risk for the development and progression of atherosclerosis, it is not known whether arterial inflammation is increased in mild CKD. The aim of this study was to compare arterial inflammation using ^{18}F-FDG PET/CT in patients with CKD and in matched controls.
Methods This restrospective study included 128 patients undergoing FDG PET/CT imaging for clinical indications, comprising 64 patients with stage 3 CKD and 64 control patients matched by age, gender, and cancer history. CKD was defined according to guidelines using a calculated glomerular filtration rate (eGFR). Arterial inflammation was measured in the ascending aorta as FDG uptake on PET. Background FDG uptake (venous, subcutaneous fat and muscle) were recorded. Coronary artery calcification (CAC) was assessed using the CT images. The impact of CKD on arterial inflammation and CAC was then assessed.
Results Arterial inflammation was higher in patients with CKD than in matched controls (standardized uptake value, SUV: 2.41±0.49 vs. 2.16±0.43; p=0.002). Arterial SUV correlated inversely with eGFR (r=−0.299, p=0.001). Venous SUV was also significantly elevated in patients with CKD, while subcutaneous fat and muscle tissue SUVs did not differ between groups. Moreover, arterial SUV remained significantly elevated in patients with CKD compared to controls after correcting for muscle and fat background, and also remained significant after adjusting for clinical risk factors. Further, CKD was associated with arterial inflammation (SUV) independent of the presence of subclinical atherosclerosis (CAC).
Conclusion Moderate CKD is associated with increased arterial inflammation beyond that of controls. Further, the increased arterial inflammation is independent of presence of subclinical atherosclerosis. Current risk stratification tools may underestimate the presence of atherosclerosis in patients with CKD and thereby the risk of cardiovascular events.

Keywords Atherosclerosis · Chronic kidney disease · FDG PET/CT · Inflammation

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Introduction

Approximately 13 % of adults in the US have chronic kidney disease (CKD), and this figure is projected to rise to 14 % in 2020 and 17 % in 2030 [1]. Patients with CKD are at increased risk for the development and progression of atherosclerosis [2, 3]. Furthermore, CKD is considered an independent risk factor for stroke and myocardial infarction [2, 3]. Although several risk factors such as hypertension, diabetes mellitus and dyslipidemia have been proposed as factors independently

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associated with increased cardiovascular risk in patients with CKD, an unabated and persistent systemic inflammatory state is also thought to be an important contributor [4]. Moreover, previous research has shown that elevated plasma levels of multiple inflammatory biomarkers are significantly associated with arterial calcification in patients with CKD, even after adjusting for traditional risk factors [5].

^{18}F-FDG PET allows accurate noninvasive quantification of inflammation in target tissues [6, 7]. In particular, FDG PET imaging of the arterial wall is a well-established and validated method for assessing the inflammatory burden in atherosclerotic plaques [8–10]. Previous studies have demonstrated that arterial FDG uptake is reproducible and responds to therapies known to reduce atherosclerotic plaque inflammation [10–13]. Arterial ^{18}F-FDG activity correlates with atheroma macrophage density [7], is higher after acute atherothrombotic events [8, 14], and predicts future cardiovascular events [10, 15, 16]. Accordingly, FDG PET/CT can be used as an imaging biomarker of atherosclerotic plaque inflammation of the arterial wall. It is unknown whether arterial inflammation on FDG PET/CT is increased in patients with mild CKD, which might explain the increase in cardiovascular events observed in this population. Therefore, the aim of this study was to assess arterial ^{18}F-FDG activity in patients with and without CKD using PET/CT.

Materials and methods

Study population

The research protocol was approved by the local Institutional Review Board. Individuals with CKD stage 3 and without known clinically evident atherosclerotic disease (n=64) were identified from a database of patients who had undergone FDG PET/CT imaging for various clinical indications at Massachusetts General Hospital between 2005 and 2012 (Fig. 1). CKD stage 3 status was confirmed as an estimated glomerular filtration rate (eGFR) between 30 and 59 mL/min per 1.73 m^2, calculated by the CKD-EPI (CKD Epidemiology Collaboration) formula, for at least 3 months prior to imaging [17]. The control group included individuals with eGFR >60 mL/min per 1.73 m^2 and no clinical diagnosis of CKD or clinical atherosclerosis, who were consecutively identified from the same database. The CKD subjects were matched 1:1 with controls according to age (±5 years), gender, and cancer history as determined by available clinical notes. PET/CT images were collected and clinical data were removed for a blinded analysis of the images. Exclusion criteria were absence of CT scan, known atherosclerotic disease and immunosuppressive therapy (intravenous and oral administration of corticosteroids, biological therapies and disease-modifying antirheumatic drugs) within 1 month of imaging.

PET/CT image acquisition

Subjects underwent whole-body FDG PET/CT imaging performed according to a clinical protocol using a Biograph 64 (Siemens Healthcare, Forchheim, Germany, or comparable system). All subjects fasted for at least 8 h prior to intravenous injection of ^{18}F-FDG (approximately 370 MBq). After about 60 min, patients and controls were imaged for 15 – 20 min in the supine position. There were no adjustments in injected dose or in acquisition time according to body weight or renal function. PET images were acquired in 3-D mode after obtaining a low-dose, nongated, noncontrast CT scan (120 kV, 50 mA) for attenuation correction.

PET/CT image analysis

PET/CT images were analyzed by an experienced image analyst blinded to the patients' clinical information using previously described methods [18]. FDG uptake was measured within the wall of the ascending aorta in the axial plane starting 1 cm above the origin of the coronary vessels and continuing up to the aortic arch in 5-mm increments (Fig. 2). Arterial FDG uptake was recorded as the mean of maximum standardized uptake values (SUV_{max}) of all the slices.

Mean SUVs were collected from the superior vena cava to obtain an average blood pool background FDG uptake. Due to the impaired renal function in patients with CKD, increased venous retention of FDG, which can result in increased venous background activity, was anticipated. Consequently, mean SUVs were also measured in the subcutaneous adipose tissue (SAT) and the pectoralis major muscle (muscle). Measurement of background FDG uptake (venous and muscle) was performed by placing regions of interest and the average mean SUV was calculated. The background-corrected SUV was calculated as arterial SUV_{max} minus the mean venous SUV (blood-subtracted SUV_{max}, $bsSUV_{max}$) [19].

Coronary calcium score

Images from all patients were quantitatively analyzed for coronary artery calcification (CAC) by an independent investigator blinded to all clinical information and PET data using a dedicated workstation (Leonardo TrueD; Siemens Healthcare, Forchheim, Germany). CAC was assessed using a threshold of 130 HU [20]. The CAC scores were obtained from nongated CT images acquired from a hybrid PET/CT scanner. These scores have been shown to be comparable to those acquired from a dedicated CT scanner [21].

Subject characteristics

The clinical and demographic characteristics of the study subjects are summarized in Table 1. Of the patients with CKD, 28

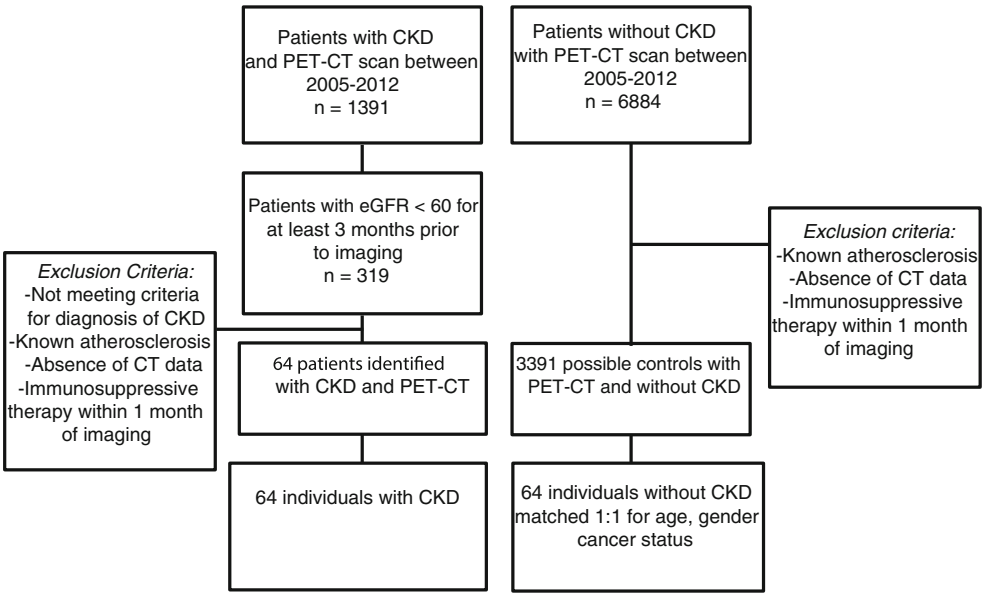

Fig. 1 Study population enrollment

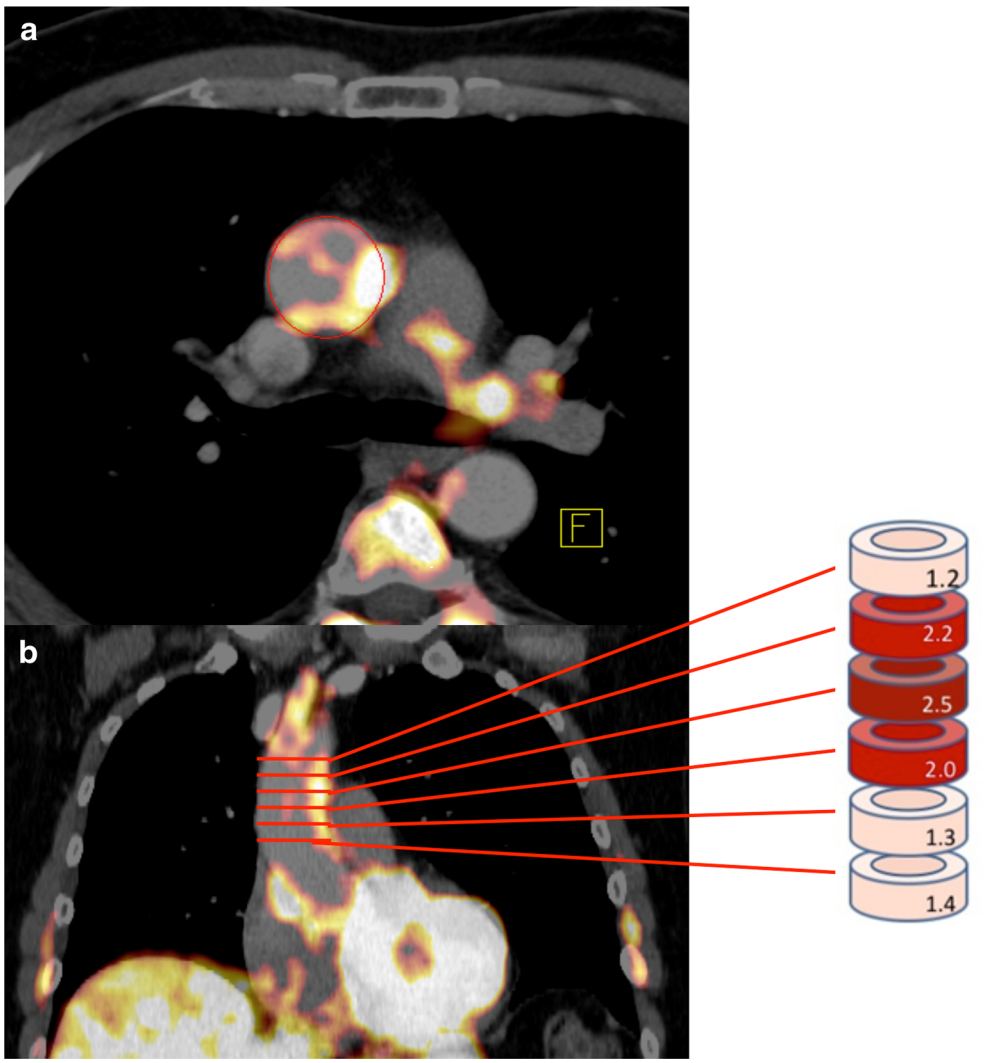

Fig. 2 PET image analysis. SUV is measured in the wall of the ascending aorta in the axial plane (**a**) starting 1 cm above the origin of the coronary vessels and continuing to the bottom of the aortic arch in 5-mm increments (**b**). Arterial FDG uptake was recorded as the mean of maximum standardized uptake values (SUV_{max}) of all the slices

Table 1 Baseline characteristics of study subjects

Characteristic	Overall (n=128)	CKD patients (n=64)	Matched controls (n=64)	p value
Age (years), mean±SD	67.5±9.8	68.6±10.1	66.3±9.4	0.192
Male, *n* (%)	68 (53.1)	34 (53.1)	34 (53.1)	1.000
Body mass index (kg/m^2), mean±SD	28.0±6.6	29.8±7.5	26.3±5.0	0.004
High-density lipoprotein (mg/dL), mean±SD	50.5±15.0	48.7±16.2	52.0±13.9	0.298
Low-density lipoprotein (mg/dL), mean±SD	100.4±32.1	94.6±28.3	105.3±34.4	0.113
Triglycerides (mg/dL), mean±SD	126.8±55.3	133.3±56.5	121.0±54.1	0.283
Total cholesterol (mg/dL), mean±SD	173.9±38.4	166.8±36.1	179.8±39.6	0.101
Current smoker, *n* (%)	13 (10.2)	4 (6.3)	9 (14.1)	0.143
Former smoker, *n* (%)	80 (54.7)	33 (51.6)	37 (57.8)	0.594
Diabetes mellitus, *n* (%)	33 (25.8)	22 (34.4)	11 (17.2)	0.026
Hyperlipidemia, *n* (%)	84 (65.6)	42 (65.6)	42 (65.6)	1.000
Hypertension, *n* (%)	98 (76.6)	56 (87.5)	42 (65.6)	0.003
No active cancer, *n* (%)	45 (35.2)	22 (34.4)	23 (35.9)	0.853
Antihypertensive therapy, *n* (%)	79 (61.7)	52 (81.3)	27 (42.2)	<0.001
Statin therapy, *n* (%)	48 (37.5)	27 (42.2)	21 (32.8)	0.273
eGFR (mL/min/1.73 m^2)	61.0±21.3	42.8±8.6	79.2±13.0	<0.001
Creatinine (mg/dL), mean±SD	1.21±0.41	1.52±0.35	0.89±0.17	<0.001
Framingham risk score, *n* (%)[a]				
Low (10-year risk <10 %)	51 (39.8)	22 (34.4)	29 (45.3)	0.466
Medium (10-year risk 10 – 20 %)	30 (23.4)	14 (21.9)	16 (25.0)	
High (10-year risk >20 %)	11 (8.6)	7 (10.9)	4 (6.3)	

All normally distributed Independent *t* test and chi-squared test for frequencies

[a] Available in 92 subjects

had stage 3A and 36 stage 3B. Significant differences were observed between CKD patients and controls in terms of body mass index (BMI), diabetes mellitus, hypertension, antihypertensive treatment and eGFR.

Statistical analysis

All results are presented as means ± standard deviation (SD) or if not normally distributed as median plus 25th – 75th percentile. Normality of distributions was tested using quantile-quantile plots. Student's *t* test was used to compare normally distributed variables. Fisher's exact test was used for categorical variables. Univariate associations were tested using Pearson's correlation coefficient. Multivariable linear regression was used to evaluate associations between CKD status and arterial SUV_{max} after adjustment for SAT SUV, age and gender, Framingham risk score (FRS) and presence of CAC. No adjustments were made for multiplicity of testing, and no imputation was used for missing values. Reported *p*-values are two-tailed; statistical significance was set at $p<0.05$. All statistical analyses were performed using SPSS version 22.0 (IBM Corp, Armonk, NY).

Results

Background activity

As previously reported and as anticipated, we observed that venous background activity in the CKD group was significantly higher than in the control group (1.23±0.22 vs. 1.13±0.24, $p<0.020$, in 128 subjects). Furthermore, there was a statistically significant negative correlation between venous activity and eGFR ($r=-0.257$, $p=0.005$). In contrast, FDG uptake in SAT was not significantly higher in the CKD group than in the control group (0.23±0.08 vs. 0.22±0.07, $p=0.472$, in 122 subjects), and no statistically significant correlation between SAT activity and eGFR was observed ($r=-0.025$, $p=0.789$). Also, FDG uptake in skeletal muscle (pectoralis major) was not significantly different between the CKD group and the control group (0.51±0.08 vs. 0.49±0.10, $p=0.362$, in 74 subjects), and was not correlated with eGFR ($r=-0.077$, $p=0.515$).

Arterial FDG uptake is higher in patients with CKD

The mean maximal arterial FDG uptake was significantly higher in patients with CKD than in matched controls (SUV

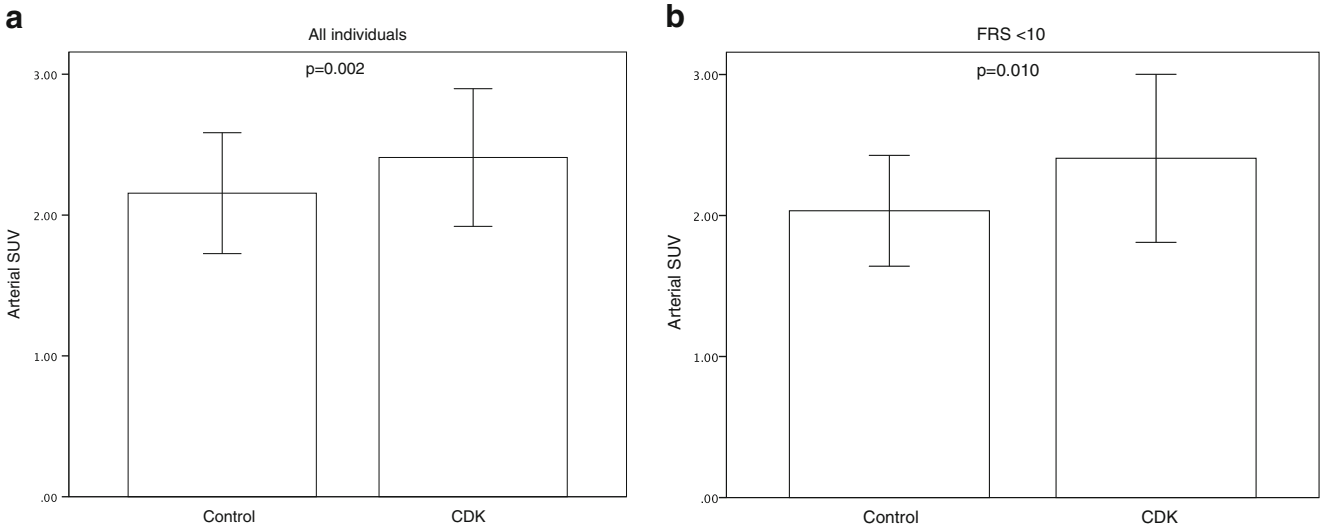

Fig. 3 Differences in arterial SUV between the CKD group and the matched control group in all patients (**a**) and in patients with a low Framingham risk score of <10 (**b**). CKD patients had an increased arterial FDG uptake compared to the control group. *Error bars* represent ±1 standard deviation

2.41±0.49 vs. 2.16±0.43; p=0.002; Fig. 3a). Furthermore, there was a statistically significant negative correlation between arterial activity and eGFR (r=−0.299, p=0.001). The $bsSUV_{max}$ was also significantly higher in CKD patients (1.18±0.41 vs. 1.02±0.31, p=0.017). After adjusting for risk factors and background activity (subcutaneous fat or pectoralis muscle SUV), CKD status remained a significant predictor of FDG uptake (Table 2). Furthermore, arterial SUV was significantly higher in the CKD group than in the control group in subjects with a low FRS of <10 (2.41±0.60 vs. 2.03 ±0.39; p=0.010; Fig. 3b).

Relationship between arterial FDG uptake and coronary calcium score

There was a significant increase in arterial inflammation (arterial SUV) in patients with CKD independent of the presence of subclinical atherosclerosis (presence or absence of CAC, Fig. 4). Moreover, the presence of CKD was significantly associated with arterial inflammation after correcting for the presence of subclinical atherosclerosis (Table 2). There was no significant difference (p=0.183) in the presence of subclinical atherosclerosis between CKD patients and controls (positive CAC score 66 % vs. 56 %, respectively; p= 0.183). Furthermore, the total CAC scores were similar in the CKD and control groups (59.1 [0.0 – 419.8] vs. 15.0 [0.0 – 229.8], p=0.208).

Discussion

To our knowledge this is the first study to investigate arterial inflammation in patients with stage 3 CKD. The principal finding of the study is that arterial FDG uptake was significantly higher in patients with CKD than in matched controls without CKD. This relationship persisted in a subset of patients with a low FRS and after correction for clinical risk factors. Furthermore, arterial SUV was significantly associated with arterial inflammation after correcting for the presence of subclinical atherosclerosis. Taken together, these findings support the concept that CKD is associated with upregulated arterial inflammation, which in turn may predispose patients with CKD to an atherosclerotic plaque burden beyond that predicted by traditional risk assessment tools such as the FRS.

Raggi et al. [22] showed that adult hemodialysis patients have a high prevalence of calcification of the coronary arteries, aorta and cardiac valves and that the severity of vascular calcification was proportional to the prevalence of preexisting cardiovascular disease. Vascular calcifications in CKD patients are mainly related to age, duration of renal disease, and also possibly dyslipidemia [23]. Nonetheless, the complex pathogenesis of vascular calcification in CKD is still not completely understood [24]. In CKD patients we observed

Table 2 Beta coefficients from regression analysis of CKD

SUV_{max}	Beta	Standard error	p-value
Uncorrected	0.253	0.081	0.002
Corrected for venous uptake	0.135	0.066	0.041
Corrected for SAT uptake	0.242	0.081	0.003
Corrected for muscle uptake	0.256	0084	0.003
Corrected for age and gender	0.246	0.082	0.003
Corrected for FRS	0.287	0.101	0.006
Corrected for presence of calcium	0.253	0.082	0.003

SAT subcutaneous adipose tissue, *FRS* framingham risk score

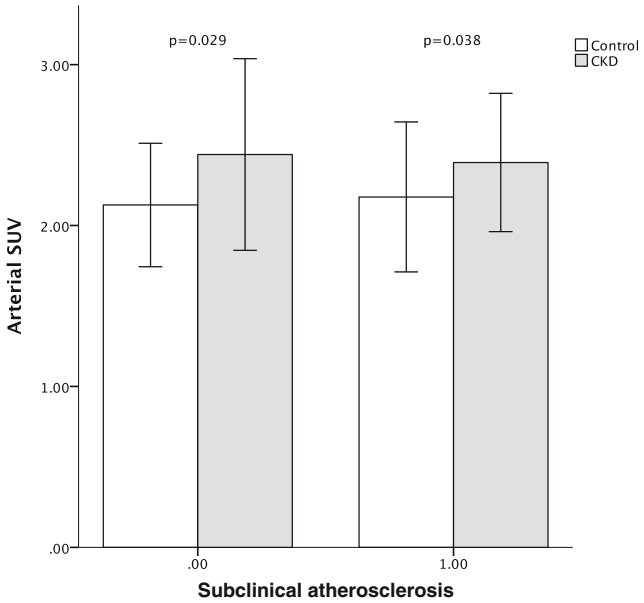

Fig. 4 Differences in arterial SUV between the CKD group and the matched control group in relation to the presence of coronary artery calcification. CKD patients showed significantly higher arterial FDG uptake than controls independent of the presence of CAC. *Error bars* represent ±1 standard deviation

a significant increase in FDG uptake in those with and without subclinical atherosclerosis (e.g., a CAC of 0). Increased arterial inflammation might precede the development of more advanced atherosclerosis and could explain the increased deposition of CAC observed in prior studies [25]. CKD was associated with a significant increase in arterial FDG activity, even after adding clinical risk factors (e.g., age, gender and FRS) to the multivariate regression model. However, we did not observe a significant difference in the presence of CAC between CKD patients with controls. A possible explanation for this could be that we included only patients with moderate kidney disease.

FDG PET is an established technique in neurology, oncology and cardiology [26]. ^{18}F-FDG is excreted through the urinary system [27]. Hence, ^{18}F-FDG excretion may be reduced in patients with CKD. Moreover, the kidneys play an important role in glucose homeostasis [28]. Laffon et al. [29] created a theoretical model to assess ^{18}F-FDG uptake in a patient with renal failure. Their model showed that in the presence of severe renal failure, excretion of the tracer takes longer, the tracer activity maximizes later and the tissue uptake is greater. We observed a significantly higher venous background activity in patients with CKD than in matched controls and a negative correlation between eGFR and venous SUV. Although the observed differences were significant, the absolute difference in venous activity between CKD patients and matched controls was limited. Several possible reasons for this limited difference are: limited time between image acquisition and tracer injection, moderate CKD severity and effect of CKD on insulin sensitivity. SAT and muscle background SUV were similar in CKD patients and controls, and are therefore better suited as a background-corrected SUV measure.

Limitations

The majority of participants had a prior history of treated cancer, which may limit the generalizability of our findings. The retrospective case-control study design does not allow causal relationships to be inferred, and we can only speculate on the underlying mechanisms that drive the observed differences. We also depended on chart review for data collection, which can result in observational bias. Also, the population size was modest and the evaluations of the relationships between CKD and FDG activity were exploratory in nature. Finally, the cohort of patients with mild CKD disease (stage 3) had a significantly higher prevalence of hypertension and diabetes mellitus and higher mean BMI, which could potentially have contributed to the observed difference in arterial inflammation. However, it is also worth noting that despite these small differences in single risk variables, the FRS did not differ between the CKD and control groups. Furthermore, analysis of CAC demonstrated that there was no significant difference between the groups in the presence of subclinical atherosclerosis. Moreover, when the analysis was repeated in the subset of individuals without evident subclinical CAD (those without any CAC), individuals with CKD still had higher arterial inflammation.

Conclusion

Patients with CKD had a greater burden of arterial inflammation than controls. Current risk stratification tools may underestimate the presence of atherosclerosis in patients with CKD. Prospective cohort studies are required to evaluate whether attenuation of the arterial inflammatory process will decrease cardiovascular events in CKD.

Compliance with ethical standards

Funding F. Hoffmann-La Roche Ltd., Switzerland

Conflicts of interest Jessica Mann, Robert A. Comley and Chek Ing Kiu Weber were employed by, and owned stock F. Hoffmann-La Roche Ltd., Basel, Switzerland, at the time of the study.

All other authors have no relationships relevant to the contents of this article to disclose.

Ethical approval All procedures performed were in accordance with the ethical standards of the institutional and national research committee and with the principles of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Infomed consent For this type of study, formal consent is not required.

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