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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 CKD are at an increased risk for the development and progression of atherosclerosis it is not known whether arterial inflammation is increased in mild CKD. To compare arterial inflammation using 18-F-fluorodeoxyglucose positron emission tomography/computed tomography imaging (FDG-PET/CT) in patients with chronic kidney disease (CKD) with matched controls.

Methods—One hundred twenty-eight individuals undergoing FDG-PET/CT imaging for clinical indications were studied retrospectively: 64 patients with Stage 3 CKD and 64 control patients were matched by age, gender, and cancer history. CKD was defined per guidelines with a calculated glomerular filtration rate (eGFR). Arterial inflammation was measured in the ascending aorta as FDG uptake by PET. Background FDG uptake (venous, subcutaneous fat (SAT) and muscle) were recorded. Coronary artery calcification (CAC) was assessed using the CT images. Thereafter, the impact of CKD on arterial inflammation and CAC was assessed.

Results—Arterial inflammation was higher in patients with CKD compared to 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 among CKD subjects, while SAT and muscle tissue SUVs did not differ between groups. Moreover,

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DISCLOSURES

Jessica Mann, Robert A. Comley and Chek Ing Kiu Weber were employed by, and owned stock in, the pharmaceutical company F. Hoffmann-La Roche Ltd., Basel, Switzerland at the time of study conduct. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Statement of human rights

All procedures performed were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

arterial SUV remained significantly elevated in CKD compared to controls after correcting for muscle or fat background, and further remained a significant after adjusting for clinical risk factors. Further, CKD was associated with arterial inflammation (SUV) independent of the presence of subclinical atherosclerosis (CAC).

Conclusions—Moderate CKD is associated with increased arterial inflammation beyond that of controls. Further, the increased arterial inflammation is associated with higher CAC. Current risk stratification tools may underestimate presence of atherosclerosis in patients with CKD and thereby risk of cardiovascular events.

Keywords

Atherosclerosis; Chronic kidney disease; FDG-PET/CT Inflammation

Introduction

Approximately 13 % of adults in the United States have chronic kidney disease (CKD), this figure is projected to rise to 14% in 2020 and 17% in 2030 [1]. Patients with CKD are at an 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 associated with heightened 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 showed that elevated plasma levels of multiple inflammatory biomarkers were significantly associated with arterial calcification in CKD patients, even after adjusting for traditional risk factors [5].

^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET) allows for accurate non-invasive quantification of inflammation in target tissues [6, 7]. In particular, FDG-PET imaging of the arterial wall is a well-established and validated method to assess inflammatory burden in atherosclerotic plaques [8-10]. Previous studies demonstrated that arterial FDG uptake is reproducible and responds to therapies known to reduce atherosclerotic plaque inflammation [10-13]. Arterial 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 FDG activity in patients with and without CKD using PET/CT.

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 (figure 1). CKD stage 3 status was confirmed as estimated GFR (eGFR) between 30-59 mL/min per 1.73 m^2, calculated by the CKD-EPI (CKD Epidemiology Collaboration) formula, for at least three 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 1:1 matched 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 one month of imaging.

PET/CT Image Acquisition

Subjects underwent whole body FDG-PET/CT imaging performed per clinical protocol using Biograph 64 (Siemens Healthcare, Forchheim, Germany, or comparable system). All subjects fasted for at least 8 hours prior to intravenous FDG injection (approximately 370 MBq). After about 60 minutes, patients and controls were imaged for 15-20 minutes 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 3D mode after obtaining a low-dose, non-gated, non-contrast CT (120 kV, 50 mA) for attenuation correction.

PET/CT Image Analysis

PET/CT images were analyzed by an experienced image analyst while 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 coronary vessels and continuing up to the aortic arch in 5 mm increments (Figure 2). Arterial FDG uptake was recorded as a 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 CKD subjects, increased venous retention of FDG was anticipated which could result in increased venous background activity. 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 (ROI) 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 maximum: bsSUVmax) [19].

Coronary calcium score

All patients were quantitatively analyzed for coronary calcification by an independent investigator blinded to all clinical information and PET data using a dedicated workstation (Leonardo TrueD, Siemens Healthcare, Forchheim, Germany). Assessment of coronary artery calcium (CAC) was performed using a threshold of 130 Hounsfield Units [20]. The CAC scores were obtained from non-gated CT images acquired from a hybrid PET-CT

scanner which 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. 28 patients had CKD stage 3A and 36 CKD stage 3B. Significant differences were observed between CKD subjects and controls in BMI, diabetes mellitus, hypertension, anti-hypertensive treatment and eGFR.

Statistical Analysis

All results are presented as mean plus standard deviation (SD) or if not normally distributed as median plus 25^{th} -75^{th} percentile. Normal distribution was tested evaluating Quantile-Quantile plots. Student's t-test was used to compare normal distributed variables. Fisher's exact test was used for categorical variables. Univariate associations were tested using Pearson's correlation coefficients. Multivariable linear regression was used to evaluate associations between CKD status and arterial SUV_{max} after adjustment for SAT SUV, VAT 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 (IBM Corp, Version 22.0. Armonk, NY, USA).

RESULTS

Background activity

As previously reported and as anticipated, we observed that venous background activity in the CKD group was significantly higher compared to the control group (1.23±0.22 vs. 1.13±0.24, p<0.020, in 128). 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 compared to the control group (0.23±0.08 vs. 0.22±0.07, p=0.472, in 122), and no statistically significant correlation between SAT activity and eGFR was observed (r=−0.025, p=0.789). Also, FDG uptake in the skeletal muscle (pectoralis major) was not significantly different between CKD group and the matched controls (0.51±0.08 vs. 0.49±0.10, p=0.362 in 74), and no correlation with eGFR (r= −0.077, p=0.515).

Arterial FDG Uptake (SUV) is higher in individuals with CKD

The mean maximal arterial FDG uptake (SUV) was significantly higher in CKD vs. matched controls (2.41±0.49 vs. 2.16±0.43; p=0.002, Figure 3a). Furthermore, a statistically significant negative correlation between arterial activity and eGFR (r=−0.299, p=0.001) was observed. Blood background corrected SUV (BsSUVmax) was also significantly higher in CKD patients (1.18±0.41 vs. 1.02±0.31; p=0.017). After adjusting for risk factors or background activity (subcutaneous fat or pectoralis muscle SUV) CKD status remained a significant predictor for FDG uptake (Table 2). Furthermore, arterial SUV was significantly

higher in CKD group vs. control group in subjects with a low Framingham Risk Score (FRS<10) (2.41±0.60 vs. 2.03±0.39; p=0.010, Figure 3b).

Relationship between Arterial FDG Uptake and Coronary Calcium Score

We observed a significant increase in arterial inflammation (arterial SUV) in individuals with CKD independent of the presence of subclinical atherosclerosis (presence or absence of CAC, Figure 4). Moreover, CKD significantly associated with arterial inflammation after correcting for the presence of sub-clinical atherosclerosis (Table 2). No significant difference (p=0.183) was observed in the presence of subclinical atherosclerosis in CKD patients compared to controls (positive CAC score 66% vs. 56%, respectively, p=0.183), furthermore, the total CAC scores were similar in 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 this study is that arterial FDG uptake is significantly higher in individuals with CKD compared to matched controls without CKD. This relationship persists within a subset of individuals with a low Framingham Risk Score and after correction for clinical risk factors. Furthermore, we demonstrate that the arterial SUV is associated with CAC in this population. Taken together, these data support the concept that CKD is associated with up-regulated arterial inflammation, which in turn may predispose patients with CKD to atherosclerotic plaque burden beyond that which is predicted by traditional risk assessment tools such as the FRS score.

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 prevalence of extent of vascular calcification was proportional to 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 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 Framingham risk score) to the multivariate regression model. However, we did not observe a significant difference in the presence of CAC when comparing the 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]. 18F-FDG is excreted through the urinary system [27]. Hence, 18F-FDG excretion may be reduced in patient with CKD. Moreover, the kidneys play an important role in glucose homeostasis [28]. Laffon et al.[29] created a theoretic model to assess ^{18}F-FDG uptake in a patient with renal failure. Their model showed that in case of severe renal failure, it takes longer to excrete the tracer, the tracer activity maximizes later and the tissue uptake is greater. We

observed a significantly higher venous background activity in patients with CKD compared to match controls and a negative correlation between eGFR and venous SUV activity. Although the observed differences were significant the absolute difference in venous activity between CKD patients and matched controls was limited. Several possible reasons for the limited magnitude 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 between CKD patients and controls, and as such are 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 us to infer causal relations and we can only speculate on the underlying mechanisms that drive the observed differences. We were also dependent on chart review for data collection, which can results in observational bias. Also, the population size is 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 significant higher prevalence of hypertension, diabetes mellitus and a higher mean BMI, which could potentially contribute 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 CKD and control groups. Furthermore, analysis of coronary artery calcium (CAC) demonstrated that there was no significant between-group difference in the presence of sub-clinical 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

CKD is associated with increased arterial inflammation beyond that of controls. Current risk stratification tools may underestimate 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.

Acknowledgments

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F. Hoffmann-La Roche Ltd., Switzerland

Abbreviations

CKD	Chronic Kidney Disease
CT	Computed Tomography
FDG	^{18}F-fluorodeoxyglucose
PET	positron emission tomography

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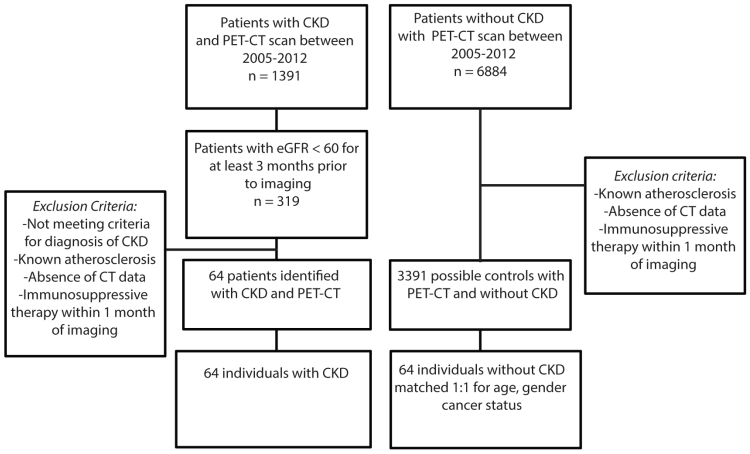

Figure 1.
Flowchart shows study population enrollment

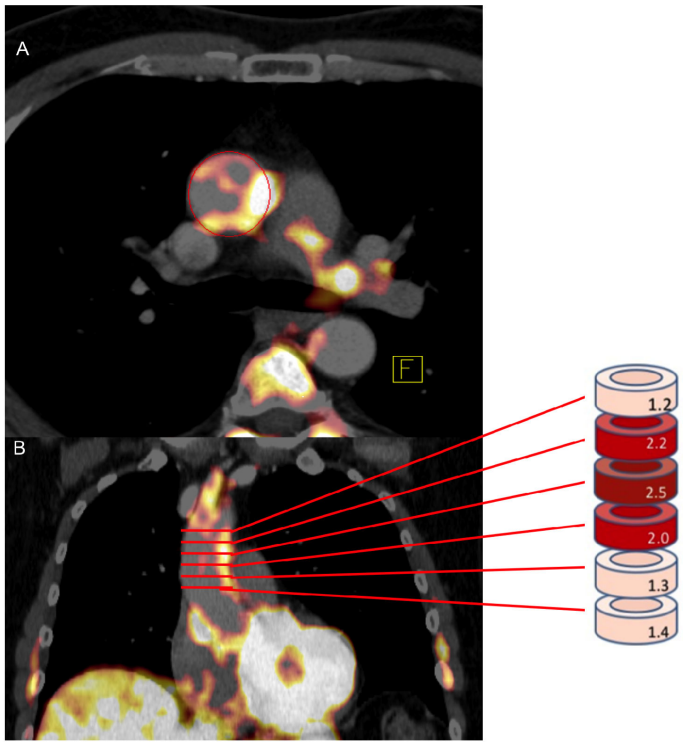

Figure 2.

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

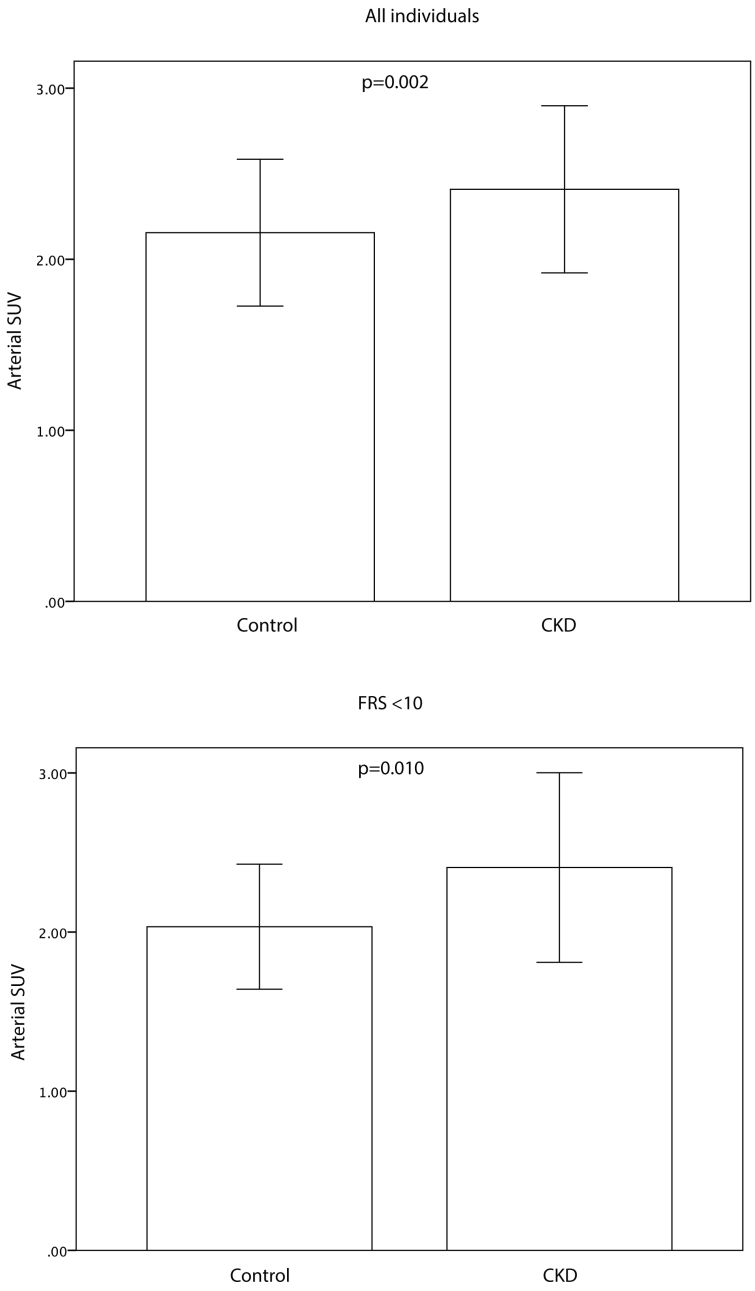

Figure 3.

Differences in Arterial SUV between the CKD group and the matched control group and in all patients (A) and patients with low Framingham risk score (FRS<10) (b). CKD patients had an increased arterial FDG uptake compared to the control group. Error bars represent +/− 1 standard deviation.

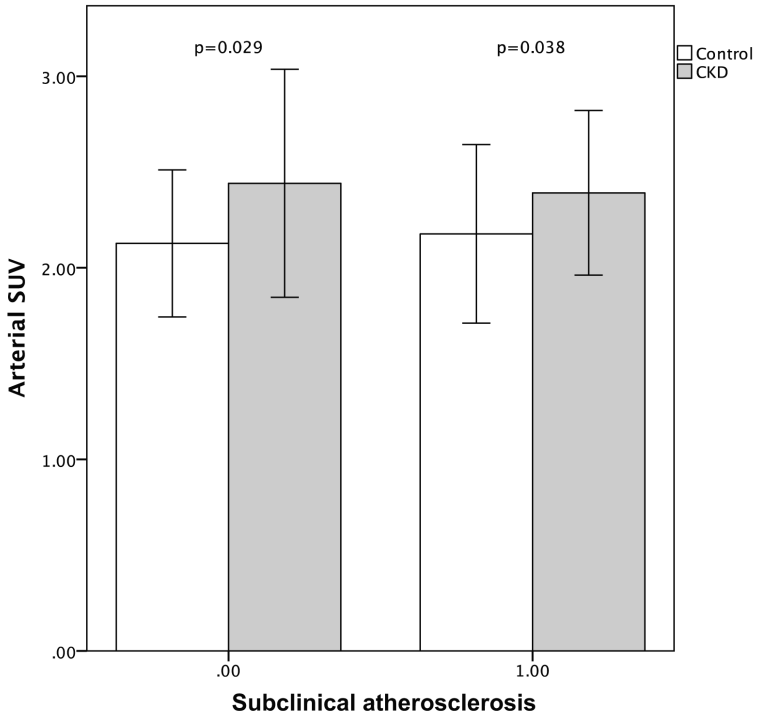

Figure 4.

Differences in Arterial SUV between the CKD group and the matched control group by presence of coronary artery calcification. CKD patients had a significant increased arterial FDG uptake compared to the control group independent of presence of CAC. Error bars represent +/− 1 standard deviation.

Table 1

Baseline Characteristics of Study Subjects

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

BMI, body mass index; eGFR, estimated glomerfular filtration rate. All normally distributed Independent T test and Chi square test for frequencies.

* available in 92 patients

Table 2

Summary of regression analysis for Beta of CKD

	Beta	Standard error	P-value
SUV_{MAX}	0.253	0.081	0.002
SUV_{MAX} Venous corrected	0.135	0.066	0.041
SUV_{MAX} SAT corrected	0.242	0.081	0.003
SUV_{MAX} Muscle corrected	0.256	0084	0.003
SUV_{MAX} Age and gender corrected	0.246	0.082	0.003
SUV_{MAX} FRS corrected	0.287	0.101	0.006
SUV_{MAX} Calcium presence corrected	0.253	0.082	0.003