Published in final edited form as:

Atherosclerosis. 2010 October ; 212(2): 589–594. doi:10.1016/j.atherosclerosis.2010.05.016.

Inflammation, Coronary Artery Calcification and Cardiovascular Events in Incident Renal Transplant Recipients

Peter Roe⁽¹⁾, Megan Wolfe⁽²⁾, Marshall Joffe⁽³⁾, and Sylvia E Rosas^{(1),(4)}

⁽¹⁾Renal, Electrolyte and Hypertension Division, Department of Medicine, Philadelphia, Pa, USA

⁽²⁾Department of Medicine and Center for Experimental Therapeutics, Philadelphia, Pa, USA

⁽³⁾Department of Biostatistics, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, Philadelphia, Pa, USA

⁽⁴⁾Philadelphia Veterans Medical Center, Philadelphia, Pa, USA

Abstract

Objective—Coronary artery calcification (CAC) predicts cardiovascular events in the general population. We conducted a prospective study to determine if inflammatory markers were predictive of CAC and if CAC predicted cardiovascular events and mortality in incident renal transplant recipients.

Methods—A prospective cohort of 112 asymptomatic incident renal transplant recipients who had no prior history of coronary artery revascularization or myocardial infarction had coronary calcifications measured early post-transplant and at least 18 months later by Agatston score and volume method.

Results—The mean CAC score was 367.7 (682.3). Inflammatory markers such as WBC and CRP were predictive of CAC severity. Recipients with cardiovascular events (n=11) or death (n=12) during the follow-up period had higher mean [675.1 (669.3) vs. 296.8(669.0), p=0.02] and median [434.8 vs. 28.9, p=0.01] CAC score compared to those without them. Recipients with CAC score less than 100 had a better cumulative survival rate compared to the recipients with CAC score greater than 100 [95.1 vs. 82.3%, p=0.03]. We found a significant unadjusted and adjusted association between CAC score and cardiovascular events and mortality. A quarter (25.9%) of recipients had CAC progression. Coronary calcification progression also predicted cardiovascular events and mortality after adjustment for diabetes, age, dialysis vintage and presence of CAC at time of transplant.

Conclusion—CAC is prevalent in renal recipients and is predictive of cardiovascular events and mortality. Changes in coronary calcification are common and predict clinical outcomes. Inflammatory markers are predictive of CAC severity at time of transplant, but are not predictive of future cardiovascular event or mortality.

Correspondence to Dr. Sylvia E. Rosas, 1st Floor Founders Building, 3400 Spruce Street, Philadelphia, Pa Phone:215-573-5812 Fax 215-615-3447 Sylvia.rosas@uphs.upenn.edu.

¹Peter Roe and Megan Wolfe participated in performance of the research and review of the manuscript. Marshall Joffe participated in data analysis and review of the manuscript. Sylvia E. Rosas participated in obtaining funding, research design, performance of the research, data analysis and manuscript preparation and submission.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Keywords

coronary calcification; EBCT; renal transplant; inflammation; C-reactive protein

Introduction

Coronary artery disease (CAD) is the principal cause of mortality in renal transplant recipients. The optimal pretransplant evaluation for recipients with low to intermediate cardiovascular risk is unknown. Poor exercise tolerance limits the use of stress exercise testing, and dipyridamole-thallium is unreliable in patients with end stage renal disease.¹ De Lima et al² found that 30% of renal transplant candidates with a negative dobutamine stress test had critical coronary lesions by angiogram. Several investigators have found an association between higher coronary artery calcification (CAC) and increased cardiovascular morbidity and mortality in asymptomatic subjects from the general population.^{3, 4} Presence and extent of vascular calcifications are strong predictors of cardiovascular and all-cause mortality in stable, end-stage renal disease patients on hemodialysis.^{5 6.}

CAC can be quantified by electron beam computer tomography (EBCT) and multislice CT and may potentially improve the risk assessment for cardiovascular events and mortality in asymptomatic renal transplant recipients. CAC is present in approximately 2/3 of incident renal transplant recipients as reported by our group and others.^{7, 8.} Post-transplant blood pressure and estimated glomerular filtration rate, Caucasian race, body mass index and baseline CAC score were independent predictors of CAC progression.⁹ However, there are no prospective studies to determine the predictive value of CAC for cardiovascular events and mortality in renal transplant recipients.

CRP predicts all-cause mortality in renal transplant recipients.¹⁰ We hypothesized that the relationship between CRP and mortality in recipients may be explained by a higher atherosclerotic burden. We conducted the present study to determine if inflammatory markers (white blood cell (WBC), C-reactive protein (CRP), soluble intercellular adhesion molecule (sICAM)) were predictive of CAC in incident renal transplant recipients. Furthermore, we sought to determine if CAC and CAC progression predicted cardiovascular events and mortality in incident renal transplant recipients.

Materials and Methods

We used EBCT to screen for CAC in 112 asymptomatic consecutive renal transplant recipients who had no prior history of coronary artery revascularization or myocardial infarction. Inclusion and exclusion criteria have been described previously.^{8, 9.} In summary, recipients with other solid organ transplant, greater than 300 pounds and who did not speak English were excluded. Recipients had undergone a traditional cardiac work-up prior to transplant surgery as prescribed by their primary physicians or nephrologist. The mean time from transplant to first EBCT scan was 2.6 months with a median of 2 months. Additionally, patients had a complete lipid profile (e.g., total cholesterol, triglycerides, HDL, calculated LDL, apoA-I and apoB), measurements of lipoprotein(a) (Lp (a)), and inflammatory markers (white blood count (WBC), High-sensitive C-reactive protein [hs-crp] and soluble intercellular adhesion molecule [s-ICAM]) performed immediately prior to transplantation before any immunosuppressants were administered. All plasma lipid assays were analyzed using commercially available reagents from Sigma Diagnostics (St. Louis, MO). Hs-CRP protein was measured on the Cobas Fara II autoanalyzer using commercially available reagents from Wako Diagnostics (Richmond, Virginia). We used a sandwich enzyme linked immunosorbent assay commercially available from R&D systems (Minneapolis, MN) to measure s-ICAM. Demographics and past

medical history was obtained from patient interviews and medical chart abstraction. We adhered to the Declaration of Helsinki and to the regulations of the Institutional Review Board and have obtained written informed consent from all subjects.

EBCT

Recipients underwent a single scan performed on a C-150 Imatron scanner (GE, San Francisco, CA). Electrocardiographic triggering of scans was used to ensure that all images were obtained at the same phase in the cardiac cycle. Serial, contiguous, 3-mm thick transverse images were obtained commencing at the root of the aorta cephalad to the coronary sinuses and proceeding caudal to the entire coronary tree. No contrast-enhancing agent was used. Quantity of CAC was based on the calcific area, average density and the number of plaques¹¹. A focus of coronary calcium was defined as a region ≥ 6 adjacent pixels with a computed tomography (CT) number >130 Hounsfield units (HU). A total CAC score was then calculated for each scan by multiplying the area of the focus by a coefficient based on the peak CT number in the focus as originally described by Agatston. This coefficient ranged from 1 to 4, where 1=131 to 200 HU, 2=201 to 300 HU, 3=301 to 400 HU, and 4= ≥ 401 HU. The acquired images were reviewed on a Terarecon workstation using the Aquarius program, version 2.1 (San Francisco, CA).

Eighty-seven subjects had repeat EBCT performed at least 18 months later (median 1.7 years). EBCT was not obtained in the remaining subjects due to: patient refusal or lost to follow-up (n=15), weight > 300 lbs (n=2), death (n=2), coronary artery disease requiring coronary artery bypass grafting post-transplant (n=1), or graft failure prior to second EBCT (n=5). CAC progression or change in coronary calcium was measured as difference between the square root of the calcium volume score between the second and the first CT. Recipients with a difference greater than 2.5 were considered progressors as described previously¹³.

Study endpoints

The primary end points for the study were CVE, defined as coronary artery disease (coronary artery bypass surgery, percutaneous intervention or myocardial infarction), cerebrovascular accident (CVA) or peripheral arterial disease (revascularization or amputation), and all-cause mortality. Death was determined using the National Death Index. Recipients were followed prospectively from the time of transplant to the occurrence of the first CVE and/or death. If there were no events, follow-up was censored for this analysis on 6/30/2009. The average time of follow-up was 6.03 (1.7) years.

Immunosuppression

Our standard immunosuppressive regimen comprised induction with Rabbit antithymocyte globulin, followed by maintenance therapy with calcineurin inhibitor (mostly tacrolimus), mycophenolate mofetil and low dose prednisone.

Statistical Analysis

Demographic and laboratory parameters were summarized by means, standard deviations and medians for continuous measures and as percentages for categorical variables. As a binary variable, calcification was defined as a coronary calcium score greater than 10. Clinically meaningful categories of CAC were used as described in other clinical studies^{11, 12} to evaluate the risk of obstructive coronary disease. These included : CAC score less than 10 (minimal), CAC scores between 10 and 100 (mild), CAC scores between 100 and 400 (moderate); CAC scores between 400 and 1000 (severe) and subjects CAC scores greater than 1000 (very severe). For categorical predictors, we compared the median coronary calcium scores for all subjects for a variety of dichotomous demographic and laboratory parameters via nonparametric K-

sample test on the equality of medians. We used ordinal logistic regression to test the association of continuous and categorical variables with CAC groups and quintiles of inflammatory markers. In addition, we used a nonparametric equality-of-medians test for skewed variables such as CAC, Lp (a) and CRP. We used multivariable Cox proportional hazards models to assess whether CAC score was associated independently with cardiovascular events and mortality. First, the unadjusted hazard ratio was determined. Then the hazard ratio was adjusted for various variables significant in the univariate Cox proportional hazards models. A multivariable Cox proportional hazards models was performed to determine if CAC progression predicted cardiovascular events and mortality. Results were considered statistically significant if corresponding p-value was less or equal to 0.05.

Results

Subjects

Patients were mostly white (63%), male (62%) and had a deceased donor renal transplant (61%). Approximately a third of the cohort was African American or black (33.9%). The mean age at the time of transplantation was 48.8 (12.5), with a minimum age of 18.3 years and a maximum age of 72.2 years. The most common cause of renal disease listed was hypertension (54.5%) followed by diabetes (31.5%) and polycystic kidney disease (14.3 %). Diabetes was common (35 %) with the majority of the patients having type 2 diabetes (56%). Approximately a 1/4 of the subjects had never been exposed to dialysis. Their mean calculated GFR at time of transplantation using the MDRD equation was 10.6(3.4) ml/min for those that were not on dialysis. The mean duration of time on renal replacement therapy at the time of EBCT for the remainder of the cohort was 3 (2.7) years. The majority of the patients on dialysis were being treated with hemodialysis (74.1%). Approximately 10 percent of the cohort had a previous kidney transplant.

Past Medical History

A past history of cardiovascular disease defined as cerebrovascular accidents, transient ischemic attacks or peripheral vascular disease was found in 10 (8.9%) subjects. Hypercholesterolemia (27.7%) and hypertension (92.3%) were common prior to transplant. The majority of recipients never smoked (55%) or ever used alcohol (66%); however 9.8% were active smokers at the time of transplantation. The mean BMI was 27.2 (5.7). Obesity defined as BMI greater than 30 was found in 22.5 % prior to transplant.

Lipid abnormalities were very common: elevated total cholesterol (24.8%), elevated triglycerides (26.7%), low HDL (46.8%), and elevated LDL (13.5%). However, elevated novel risk factors such as Lp (a) greater than 15 mg/dl (66%) and CRP greater than 3 mg/L(48%) were more frequent. Family history of coronary artery disease was found in 35.7% of subjects.

The majority of our subjects (80%) had non-invasive or invasive cardiac work-up performed prior to transplantation. Fifteen (13.4%) of our subjects had coronary angiograms performed prior to transplantation.

Coronary Artery Calcification (CAC)—The mean CAC score was 367.7 (682.3) with a median of 70.5. A third of subjects (n=38) had no calcification and 42 had CAC scores <10. However, another third (n=33) had scores greater than 400, which has been associated with obstructive disease in the general population. Twelve of our subjects (10.7%) had scores greater than 1000.

In unadjusted analysis, older age, male gender, increased time on dialysis, presence of diabetes, increased BMI, not having a preemptive transplant, deceased donor transplantation, a history

of hypercholesterolemia, increasing levels of white blood cells, serum levels of glucose, and triglycerides were significantly associated with presence of CAC at time of transplant univariately (see Table 1). There was a borderline association of history of smoking, systolic blood pressure, and CRP (log) with degree of CAC. There was no association between serum calcium, phosphorus, or their byproducts with the degree of CAC at the time of renal transplant.

Inflammatory Markers

The mean CRP level was 4.08(5.96) mg/L with a median of 2.54 mg/L. The median CAC increased per quintile of CRP levels (Table 2). The median CAC score in the lower quintile was 7.5 compared to 203.2 in the highest CRP quintile. The mean s-ICAM was 282.1 (80.55) ng/mL with a median of 282.3 ng/mL. There was no statistical significant association between levels of s-ICAM and degree of CAC. The mean (SD) of WBC was 6.8(2.2) with a median of 6.5. The median CAC increased per quintile of WBC levels at time of transplant (Table 2). For example the median CAC score in the lower quintile was 10.3 compared to 201.4 in the WBC upper quintile.

There was a mild correlation between CRP levels and WBC count ($r=0.37$). However, there was no correlation between s-ICAM and WBC count or CRP levels ($r=0.01$ and $r=0.02$, respectively). Subjects with hs-CRP greater than 3 mg/L had higher triglycerides [223.1(216.1) vs. 150.62 (88.19), $p=0.02$] and WBC levels [6.3(1.7) vs. 7.2 (2.4), $p=0.05$] compared to those subjects with hs-CRP lower than 3 mg/L. We found no unadjusted association between CRP, sICAM and white blood cell count with the annualized rate of CAC progression. After adjusting for variables that we found in our previous work to be associated with progression⁹ such as diastolic blood pressure and eGFR at 3 months post-transplant, BMI, Caucasian race and baseline CAC score, none of the inflammatory markers above reached statistical significance.

Cardiovascular Events and Death

There have been 11 cardiovascular events and 12 deaths during the average 6.03 (1.7) years of follow-up in 21 subjects. Two participants had a cardiovascular event and death during the study follow-up period. The average CAC score was higher for recipients with cardiovascular events or death during the follow-up period compared to those without those events [675.1 (669.3) vs. 296.8(669.0), $p=0.02$]. Likewise, the median CAC score was higher for recipients with cardiovascular events and death compared to those without them [434.8 vs. 28.9, $p=0.01$]. There was no difference in mean WBC [7.1(2.8) vs. 6.7(2.0), $p=0.24$], median CRP [3.1 vs 2.4, $p=0.52$] or mean sICAM in recipients with cardiovascular events and death compared to those without them at time of transplantation

Figure 1 illustrates that recipients without CAC had better survival than those with CAC at time of transplantation. Recipients with CAC score less than 100 had a higher cumulative survival rate compared to the recipients with CAC score greater than 100 [95.1 vs. 82.3%, $p=0.03$]. Similar results were found if cardiovascular events were also included [90.2 vs. 70.6%, $p=0.01$]. We found a significant unadjusted association between CAC score and cardiovascular events and mortality. After adjustment for multiple confounders this association remained significant (Table 3).

Of the 87 recipients who had a second EBCT, a quarter (25.9%) of recipients met the definition of CAC progressors. CAC progression independently predicted cardiovascular events and mortality along with diabetes and dialysis vintage. (Table 4).

Discussion

Our study is the first to evaluate if CAC and CAC progression predicts cardiovascular events and mortality in asymptomatic renal transplant recipients without a history of coronary revascularization or myocardial infarction. Increasing levels of CRP and WBC at the time of transplantation were associated with increasing CAC score. CAC is prevalent in renal transplant recipients and predictive of cardiovascular events and mortality

In the general population, several investigators have found an association between higher CAC and increased cardiovascular morbidity and mortality in asymptomatic subjects ^{3, 4}. A meta-analysis recently reported relative risks of coronary heart disease of 4.3, 7.2, and 10.8 for CAC values of 100–400, 400–999, and ≥ 1000 , respectively ¹⁴. Matsuoka et al found that CAC measured by EBCT was predictive of death in a cohort of 104 long-standing Japanese dialysis patients. The 5-year cumulative survival rate was 84.2% in the low CAC group (<200) and 67.9% in the high CAC (>200) group.

Several studies have confirmed the correlation between coronary calcification by EBCT and coronary stenosis by coronary angiography in the general population and in end-stage renal disease ¹⁵. Pathologic studies have confirmed the strong correlation between coronary calcification by EBCT and both coronary calcification and atherosclerotic plaque at autopsy ¹⁶. Presence and extent of vascular calcifications are strong predictors of cardiovascular and all-cause mortality in stable long-term hemodialysis patients ^{5, 6}.

Atherosclerosis is an active and complex inflammatory process. Serum lipoprotein (a) [Lp(a)], C-reactive protein (CRP) and soluble intercellular adhesion molecule (s-ICAM) are novel cardiovascular risk factors that have been implicated with the development of cardiovascular disease ^{17–20}. Lp(a) levels increase with mild chronic kidney disease ²¹ and decrease after renal transplantation. CRP and WBC have been proposed as possible biomarkers to be used in cardiovascular risk assessment ²². WBC play a major role in these inflammatory processes. Several epidemiological studies have associated WBC count with risk of symptomatic or fatal coronary heart disease ^{23–24}, acute coronary syndrome ^{23, 25}, congestive heart failure and stroke ²³. This association is independent of smoking and other traditional cardiovascular risk factors ²⁶.

We were unable to find an association between these novel cardiovascular risk factors and CAC. Markers of inflammation such as CRP are elevated in subjects with ESRD ^{27–29} and have been found to be associated with both CVD and overall mortality ^{6, 20, 27}. CRP is a predictor of mortality in hemodialysis patients in prospective studies ²⁸. Pre-transplantation CRP is independently associated with all-cause and cardiovascular mortality ²⁹. Blacher et al found that CRP was associated with vascular calcification measured by ultrasound in a cohort of hemodialysis patients ⁶. However, this has not been a universal finding. In a study of 85 non-diabetic CKD patients not undergoing dialysis, CRP was not found to predict CAC measured by spiral CT ³⁰. Moe et al in a cohort of 71 ESRD patients undergoing dialysis or after renal transplantation was unable to find a statistically significant association ⁷.

This study was limited to a single pre-transplant CRP and WBC measurements in a selected asymptomatic population with no evidence of infection or acute illness at the time the sample was obtained. Relative few cardiovascular events were noted likely secondary to the inclusion criteria as patients with symptomatic or a history of coronary event were not eligible to participate. Parathyroid hormone was not measured as part of the research study. Larger studies are warranted to confirm findings.

In summary, CAC is prevalent in renal transplant recipients. Inflammatory markers such as WBC and CRP are predictive of CAC severity at time of transplant. However, they were not

predictive of future cardiovascular event or mortality. CAC at time of transplantation and CAC progression during the first 18 months post-transplant is predictive of cardiovascular events and mortality.

Acknowledgments

This project was supported in part by National Institutes of Health grants R03 DK 60709 (S.E.R.) and AHA GIA 0655479U (S.E.R.). The project described was supported by Grant Number UL1RR024134 from the National Center for Research Resources. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources or the National Institutes of Health.

Funding American Heart Association- Sylvia E. Rosas

National Institutes of Health – Sylvia E. Rosas

References

1. Marwick TH, Steinmuller DR, Underwood DA, Hobbs RE, Go RT, Swift C, Braun WE. Ineffectiveness of dipyridamole SPECT thallium imaging as a screening technique for coronary artery disease in patients with end-stage renal failure. *Transplantation* 1990;49:100–103. [PubMed: 2300998]
2. De Lima JJ, Sabbaga E, Vieira ML, de Paula FJ, Ianhez LE, Krieger EM, Ramires JA. Coronary angiography is the best predictor of events in renal transplant candidates compared with noninvasive testing. *Hypertension* 2003;42:263–268. [PubMed: 12913060]
3. Arad Y, Spadaro LA, Goodman K, Newstein D, Guerci AD. Prediction of coronary events with electron beam computed tomography. *Journal of the American College of Cardiology* 2000;36:1253–1260. [PubMed: 11028480]
4. Raggi P, Callister TQ, Cooil B, He ZX, Lippolis NJ, Russo DJ, Zelinger A, Mahmarian JJ. Identification of patients at increased risk of first unheralded acute myocardial infarction by electron-beam computed tomography. *Circulation* 2000;101:850–855. [PubMed: 10694523]
5. Matsuoka M, Iseki K, Tamashiro M, Fujimoto N, Higa N, Touma T, Takishita S. Impact of high coronary artery calcification score (CACS) on survival in patients on chronic hemodialysis. *Clin Exp Nephrol* 2004;8:54–58. [PubMed: 15067517]
6. Blacher J, Guerin AP, Pannier B, Marchais SJ, London GM. Arterial calcifications, arterial stiffness, and cardiovascular risk in end-stage renal disease. *Hypertension* 2001;38:938–942. [PubMed: 11641313]
7. Moe SM, O'Neill KD, Fineberg N, Persohn S, Ahmed S, Garrett P, Meyer CA. Assessment of vascular calcification in ESRD patients using spiral CT. *Nephrol Dial Transplant* 2003;18:1152–1158. [PubMed: 12748349]
8. Rosas SE, Mensah K, Weinstein RB, Bellamy SL, Rader DJ. Coronary artery calcification in renal transplant recipients. *Am J Transplant* 2005;5:1942–1947. [PubMed: 15996243]
9. Schankel K, Robinson J, Bloom RD, Guerra C, Rader D, Joffe M, Rosas SE. Determinants of coronary artery calcification progression in renal transplant recipients. *Am J Transplant* 2007;7:2158–2164. [PubMed: 17640315]
10. Winkelmayer WC, Lorenz M, Kramar R, Fodinger M, Horl WH, Sunder-Plassmann G. C-reactive protein and body mass index independently predict mortality in kidney transplant recipients. *Am J Transplant* 2004;4:1148–1154. [PubMed: 15196074]
11. Rumberger JA, Brundage BH, Rader DJ, Kondos G. Electron beam computed tomographic coronary calcium scanning: a review and guidelines for use in asymptomatic persons. *Mayo Clinic Proceedings* 1999;74:243–252. [erratum appears in Mayo Clin Proc 1999 May;74(5):538]. [PubMed: 10089993]
12. Raggi P, Boulay A, Chasan-Taber S, Amin N, Dillon M, Burke SK, Chertow GM. Cardiac calcification in adult hemodialysis patients. A link between end-stage renal disease and cardiovascular disease? *Journal of the American College of Cardiology* 2002;39:695–701. [PubMed: 11849871]
13. Hokanson JE, MacKenzie T, Kinney G, Snell-Bergeon JK, Dabelea D, Ehrlich J, Eckel RH, Rewers M. Evaluating changes in coronary artery calcium: an analytic method that accounts for interscan variability. *AJR Am J Roentgenol* 2004;182:1327–1332. [PubMed: 15100140]

14. Greenland P, Bonow RO, Brundage BH, Budoff MJ, Eisenberg MJ, Grundy SM, Lauer MS, Post WS, Raggi P, Redberg RF, Rodgers GP, Shaw LJ, Taylor AJ, Weintraub WS, Harrington RA, Abrams J, Anderson JL, Bates ER, Grines CL, Hlatky MA, Lichtenberg RC, Lindner JR, Pohost GM, Schofield RS, Shubrooks SJ Jr, Stein JH, Tracy CM, Vogel RA, Wesley DJ. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography). *Circulation* 2007;115:402–426. [PubMed: 17220398]
15. Robinson J, Tan AU, Wilensky RL, Matthai W, Munoz M, Rosas SE. Electron-Beam Computerized Tomography Correlates with Coronary Angiogram in Chronic Kidney Disease Patients. *Am J Nephrol* 2007;27:247–252. [PubMed: 17389785]
16. Rumberger J, Simons B, Fitzpatrick L, Sheedy P, Schwartz R. Coronary Artery Calcium Area by Electron-Beam Computed Tomography and Coronary Atherosclerotic Plaque Area: A Histopathologic Correlative Study. *Circulation* 1995;92:2157–2162. [PubMed: 7554196]
17. Ridker PM, Hennekens CH, Roitman-Johnson B, Stampfer MJ, Allen J. Plasma concentration of soluble intercellular adhesion molecule 1 and risks of future myocardial infarction in apparently healthy men. *Lancet* 1998;351:88–92. [PubMed: 9439492]
18. Ridker PM, Stampfer MJ, Rifai N. Novel risk factors for systemic atherosclerosis: a comparison of C-reactive protein, fibrinogen, homocysteine, lipoprotein(a), and standard cholesterol screening as predictors of peripheral arterial disease. *Jama* May 16;2001 285:2481–2485. [PubMed: 11368701]
19. Stenvinkel P, Heimbürger O, Paulter F, Diczfalussy U, Wang T, Berglund L, Jogestrand T. Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure. *Kidney International* 1999;55:1899–1911. [PubMed: 10231453]
20. Zimmermann J, Herrlinger S, Pruy A, Metzger T, Wanner C. Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. *Kidney International* 1999;55:648–658. [PubMed: 9987089]
21. Kronenberg F, Kuen E, Ritz E, Junker R, König P, Kraatz G, Lhotka K, Mann JF, Müller GA, Neyer U, Riegel W, Reigler P, Schwenger V, Von Eckardstein A. Lipoprotein(a) serum concentrations and apolipoprotein(a) phenotypes in mild and moderate renal failure. *Journal of the American Society of Nephrology* 2000;11:105–115. [PubMed: 10616846]
22. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO 3rd, Criqui M, Fadl YY, Fortmann SP, Hong Y, Myers GL, Rifai N, Smith SC Jr, Taubert K, Tracy RP, Vinicor F. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 2003;107:499–511. [PubMed: 12551878]
23. Lee CD, Folsom AR, Nieto FJ, Chambless LE, Shahar E, Wolfe DA. White blood cell count and incidence of coronary heart disease and ischemic stroke and mortality from cardiovascular disease in African-American and White men and women: atherosclerosis risk in communities study. *Am J Epidemiol* 2001;154:758–764. [PubMed: 11590089]
24. Kannel WB, Anderson K, Wilson PW. White blood cell count and cardiovascular disease. Insights from the Framingham Study. *Jama* 1992;267:1253–1256. [PubMed: 1538564]
25. Barron HV, Cannon CP, Murphy SA, Braunwald E, Gibson CM. Association between white blood cell count, epicardial blood flow, myocardial perfusion, and clinical outcomes in the setting of acute myocardial infarction: a thrombolysis in myocardial infarction 10 substudy. *Circulation* 2000;102:2329–2334. [PubMed: 11067784]
26. Brown DW, Giles WH, Croft JB. White blood cell count: an independent predictor of coronary heart disease mortality among a national cohort. *J Clin Epidemiol* 2001;54:316–322. [PubMed: 11223329]
27. Qureshi AR, Alvestrand A, Danielsson A, Divino-Filho JC, Gutierrez A, Lindholm B, Bergstrom J. Factors predicting malnutrition in hemodialysis patients: a cross-sectional study. *Kidney International* 1998;53:773–782. [PubMed: 9507226]
28. Qureshi AR, Alvestrand A, Divino-Filho JC, Gutierrez A, Heimbürger O, Lindholm B, Bergstrom J. Inflammation, malnutrition, and cardiac disease as predictors of mortality in hemodialysis patients. *Journal of the American Society of Nephrology* Jan;2002 13:S28–36. [PubMed: 11792759]

29. Varagunam M, Finney H, Trevitt R, Sharples E, McCloskey DJ, Sinnott PJ, Raftery MJ, Yaqoob MM. Pretransplantation levels of C-reactive protein predict all-cause and cardiovascular mortality, but not graft outcome, in kidney transplant recipients. *Am J Kidney Dis* 2004;43:502–507. [PubMed: 14981609]
30. Russo D, Palmiero G, De Blasio AP, Balletta MM, Andreucci VE. Coronary artery calcification in patients with CRF not undergoing dialysis. *Am J Kidney Dis* 2004;44:1024–1030. [PubMed: 15558523]

Figure 1. Mortality and Cardiovascular Event free survival in patients with and without CAC ($p=0.01$)

Table 1

Distribution of demographic and laboratory parameters by calcification group

Coronary Calcification Score	<10 (n=42)	10-<100 (n=19)	100-<400 (n=18)	400-<1000 (n=21)	>1000 (n=12)	P-value
CCS median	0	33.0	200.0	515.7	1747.0	<0.001
Lipoprotein (a) (mg/dl) median	29.8	31.4	21.3	12.6	46.9	0.37
CRP (mg/L) (median)	2.28	2.32	2.24	4.28	3.24	0.09
Female (%)	50.0	47.4	27.8	28.6	16.7	0.01
Caucasian (%)	64.3	73.7	61.1	57.1	50	0.34
Diabetes (%)	20	36.8	44.4	47.6	50	<0.01
Never on Dialysis (%)	33.3	31.6	11.1	23.8	0	0.03
Living donor (%)	61.9	42.1	27.8	23.8	0	<0.001
Never Smoked (%)	64.3	57.9	50	45	41.7	0.07
Hypercholesterolemia(%)	16.7	21.1	50	28.6	45.5	0.03
Age (years) mean (SD)	40.2 (12.0)	51.8 (10.7)	56 (9.3)	56.1 (8.8)	52.3 (9.5)	<0.001
Time on dialysis (years)	1.5 (2.1)	2.3 (3.0)	3.0 (3.0)	2.2(2.3)	4.7(2.2)	<0.01
BMI (kg/m ²)	25.9 (4.7)	26.1(3.6)	28.3(4.9)	28.3(6.0)	27.6(4.1)	0.04
Total cholesterol (mg/dl)	177.1 (43.3)	175.9 (49.0)	167.4 (48.1)	176.9 (41.7)	157.6 (35.9)	0.34
Triglycerides (mg/dl)	159.9 (101.2)	130.5 (47.0)	169.8 (99.6)	296.9 (306.7)	165.2 (80.5)	0.06
HDL (mg/dl)	46.8(19.7)	45.5 (15.4)	47.2 (16.9)	40.5 (16.9)	43.6 (10.9)	0.28
LDL (mg/dl)	98.8 (36.8)	101.1 (37.7)	87.5 (36.2)	90.5 (31.4)	81.0 (29.5)	0.10
Apo A1 (mg/dl)	125.0 (22.4)	125.2 (30.1)	129.4 (29.2)	120.0 (32.6)	116.4 (21.7)	0.41
Apo B (mg/dl)	82.6 (20.8)	80.3 (21.5)	73.6 (22.8)	86.8 (23.4)	74.7 (18.9)	0.59
Glucose (mg/dl)	89.0 (36.5)	114.7 (72.5)	105.8 (32.3)	139.4 (107.7)	169.0 (170.0)	0.004
SBP (mmHg)	142.9 (21.7)	140.8 (19.8)	148.2 (21.9)	148.6 (26.8)	153.3 (13.9)	0.11
DBP (mmHg)	83.7 (11.8)	80.5 (13.2)	82.2(11.3)	82.5 (16.9)	84.3 (12.6)	0.90
Hemoglobin	12.4 (1.6)	12.4(1.9)	12.3 (1.4)	11.4 (1.4)	12.3 (1.8)	0.13
Calcium (mg/dl)	9.2 (1.1)	8.8 (1.1)	9.6 (0.9)	9.1 (1.1)	9.9 (1.2)	0.19
Phosphate (mg/dl)	5.1 (1.3)	4.8 (1.0)	5.3(1.7)	5.1(1.5)	4.9 (1.2)	0.95
s-ICAM (ng/mL)	283.2(93.3)	281.3 (67.1)	281.3 (53.4)	296.0(92.2)	258.2 (73.2)	0.80

Coronary Calcification Score	<10 (n=42)	10-<100 (n=19)	100-<400 (n=18)	400-<1000 (n=21)	>1000 (n=12)	P-value
WBC count (mm ³)	6.37(1.9)	7.03(2.5)	6.56(1.2)	7.30(2.8)	7.73(2.0)	0.04
Death or Cardiovascular event	2	4	3	6	6	0.006
Death	1	2	2	3	3	0.05

Table 2

Association between CRP and WBC quintiles and coronary calcification

CRP quintiles (mg/L)	Coronary Calcium Score (median)	p-value
<0.85	7.5	0.03
0.85-<2.05	17.5	
2.05-<3.35	78.4	
3.35-<4.76	196.8	
>4.76	255.5	

WBC quintiles (mm3)	Coronary Calcium Score (median)	p-value
<5.2	10.3	0.04
>5.2-6.12	18.6	
>6.12-6.9	98.0	
>6.9-8.14	94.8	
>8.14	201.4	

Table 3

Cox proportional hazards model of coronary calcification predicting cardiovascular events and mortality

Variable	Hazard Ratio	95% Confidence Interval	p-value
Model 1			
CAC score (per 100)	1.05	1.01-1.09	0.01
Model 2			
CAC score (per 100)	1.06	1.02-1.11	0.01
Diabetes	5.9	2.2-15.6	<0.001
Model 3			
CAC score (per 100)	1.05	1.00-1.11	0.045
Diabetes	5.46	1.94-15.3	0.001
Dialysis vintage	1.20	1.04-1.39	0.01
Age	1.03	.98-1.08	0.21
Gender	1.54	0.61-3.90	0.37

Table 4

Cox proportional hazards model of coronary calcification progression predicting cardiovascular events and mortality (n=87)

Variable	Hazard Ratio	95% Confidence Interval	p-value
Model 1			
Change in CAC	1.14	.99-1.32	0.08
Model 2			
Change in CAC	1.25	1.05-1.48	0.01
Diabetes	31.2	3.9-250.3	0.001
Dialysis vintage	1.39	1.11-1.73	0.004

* continuous variable of the difference of square root of the calcification volume