Advances in Medical Sciences 60 (2015) 240–245

Contents lists available at ScienceDirect

Advances in Medical Sciences

journal homepage: www.elsevier.com/locate/advms

Original Research Article

Coronary artery calcification and large artery stiffness in renal transplant recipients

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ARTICLE INFO

Article history:
Received 27 January 2015
Accepted 10 April 2015
Available online 24 April 2015

Keywords:
Arterial stiffness
Coronary artery calcification
Pulse wave velocity
Renal transplant

ABSTRACT

Purpose: Coronary artery calcification (CAC) is an independent predictor of cardiovascular (CV) events in renal transplant recipients (RTR). Carotid-femoral pulse wave velocity (PWV), a non-invasive measure of large artery stiffness, also predicts CV events in RTR. The study investigated the relationship between CAC and PWV in RTR and assessed the performance of PWV measurement in predicting CAC.
Patients/methods: The study was performed as cross-sectional analysis in 104 RTR. CAC was determined as total calcium score (CS) and calcium mass (CM). Carotid-femoral PWV was also measured. Sensitivity, specificity and receiver operating characteristic (ROC) curve were used to assess the performance of PWV as diagnostic test for presence of CAC.
Results: CAC was found in 69% of participants. PWV was higher in RTR with CAC than in RTR without CAC (10.2 ± 2.2 vs. 8.6 ± 15; $p < 0.001$). In univariate analysis CS was significantly correlated with age, duration of hypertension, waist circumference, PWV, hemoglobin concentration, and serum glucose. In multiple linear regression analysis CS was independently associated with age only, but not with PWV. Sensitivity and specificity of PWV > 7.6 m/s as cut-off for detecting CAC > 0 was 0.889 and 0.406, respectively. Sensitivity and specificity of PWV > 10.2 m/s as cut-off for detecting severe CAC (CS > 400) was 0.319 and 0.969, respectively.
Conclusions: The study confirmed high prevalence of coronary artery calcification in renal transplant recipients. The study does not support the hypothesis that aortic stiffness is independently associated with coronary artery calcification in RTR. PWV measurement may be useful in excluding severe CAC in RTR.

1. Introduction

Cardiovascular complications are leading cause of death in renal transplant recipients (RTR) [1,2]. Traditional cardiovascular risk factors do not fully explain such high CV risk in RTR [3]. Even exact clinical assessment is not sufficient for identifying RTR of the highest cardiovascular risk. Evaluation of cardiovascular subclinical end-organ damage is useful for reducing CV risk in chronic kidney disease patients [4]. The prognostic significance of several non-invasive cardiovascular markers such as pulse wave velocity (PWV), and coronary artery calcification (CAC) was documented in RTR in recent decade. Carotid-femoral PWV is a most widely used index of large arterial stiffness with well documented predictive value for cardiovascular outcomes [4,5]. PWV measurement is non-invasive procedure with no exposure to radiation. It was shown that carotid-femoral PWV is an independent predictor of cardiovascular (CV) events and total mortality in RTR [6,7]. It was also revealed that CAC is a strong independent predictor of CV events and mortality in RTR [8,9]. Relationship between CAC and PWV was found in CKD patients [10,11] and in non-renal population [12], but has not been investigated separately in RTR yet. The aim of the study was evaluate the relationship between CAC and PWV in renal transplant recipients and to assess performance of PWV measurement in predicting presence of CAC.

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http://dx.doi.org/10.1016/j.advms.2015.04.002
1896-1126/

2. Patients and methods

The study was designed as cross-sectional analysis in renal transplant recipients. The protocol of the study was accepted by Local Ethics Committee, and informed consent was obtained from each participant. One hundred and four consecutive renal transplant recipients were recruited to the study. Exclusion criteria in the study were lack of consent and pregnancy. There were 73 males and 31 females included to the study. The mean duration of kidney transplant follow-up was 38 months (median 32, range from 1 to 172). The underlying renal disease was glomerulonephritis in 64 patients, polycystic kidney disease in 10 patients, diabetic nephropathy in 9 patients, interstitial nephritis in 6, and other in 15 patients. In all subjects clinical assessment was performed. Systolic and diastolic blood pressure (SBP, DBP) were measured in sitting position after a 10-min rest. Pulse pressure (PP = SBP − DBP) was calculated subsequently. Body mass, height, waist circumference, and body mass index (BMI) were assessed. Abdominal obesity was defined as waist circumference ≥102 cm in men and ≥88 cm in women [13]. Fasting blood was collected for laboratory analyses. Patient charts were investigated to analyze immunosuppressive and antihypertensive therapy. In all patients CAC and PWV were also measured.

2.1. Coronary artery calcification

To assess CAC a multi-detector row CT scanner (Mx8000, Philips Medical Systems, Cleveland, OH) was used in this study. Patients were scanned in a supine position within a single breath-hold. Scan range was established on a scout image. Scanning was begun from a point approximately 2 cm below the carina to the diaphragm. Nonoverlapping slices were acquired in axial mode (mean number per patient = 48 slices). The collimated and the effective slice thickness was 2.5 mm, scan time was 0.33 s, gantry rotation time was 0.5 s. According to the standard scanner settings, we used filter B (normal), matrix – 512, 120 kVp, and 165 mAs. An average radiation dose given as CTDI was 12.6 mGy per patient. To reduce heart movement artifacts, acquisitions were prospectively electrocardiographically triggered at 60% of the expected next RR interval (AccuSync, Milford, CT). No intravenous beta-blockers were used to reduce the heart rate.

All images were analyzed with dedicated software (Heart Beat-CS vs. 5.0, Philips Medical Systems, Cleveland, OH). According to the Agatston criteria, calcium was defined as a hyperattenuating structure with density of at least 130 HU, and an area of at least 0.5 mm^2 [14]. Such structures were automatically distinguished by the software, and coronary calcifications were manually localized by the investigator. Aortic, valvular, and ostial plaques were excluded.

The CAC measurement included determination of the mass (CM) of the calcifications as well as the total calcium score (CS). CS was calculated according to the Agatston method, based on the area of the calcification and a coefficient related to the peak attenuation of the lesion [14]. CM measurement was calibrated using a dedicated anthropomorphic cardiac CT phantom (QRM, Moehrendorf, Germany). CM of a lesion was calculated based on the measurement of the average attenuation of the calcification, the image noise, and the average attenuation of standard calibration insert [15]. Patients with CS > 0 were considered as having CAC and patients with CS > 400 were considered as having severe CAC [16].

2.2. Pulse wave velocity measurement

Carotid-femoral PWV was measured using Complior® device (Artech Medical, Pantin, France). Two transducers (one positioned over carotid artery and the other one over femoral artery) were used to measure the time delay between pulse waves. Time delay was measured on 10 successive beats, and then averaged. The distance between carotid artery (suprasternal notch) and femoral artery was measured externally. PWV was calculated according to formula: PWV = distance (m)/time delay (s). PWV measurements were taken in duplicate and averaged. All measurements were made by a single operator. The repeatability of PWV measurements was assessed in earlier study [17]. PWV > 10 m/s was considered a marker of organ damage and index of increased risk of cardiovascular events [13].

2.3. Laboratory measurements

Laboratory measurements were performed on Abbott Architect ci8200 analyzer using Abbott Laboratories commercial reagents (Abbott Laboratories, Abbott Park, IL, USA). Additionally, high-sensitive C-reactive protein (hs-CRP) was assessed using BN™ nephelometric method (Dade Behring Inc., Deerfield, IL, USA). Glomerular filtration rate was estimated using abbreviated MDRD formula [$eGFR = 186 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African-American})$] [18].

2.4. Statistical analysis

Statistical analysis was performed using Statistica 7.0 PL software (StatSoft Inc., Tulsa, OK, USA). Distribution of variables was analyzed using Shapiro–Wilk test. Normally distributed variables are presented as mean ± standard deviation (SD) and not normally distributed variables are presented as median and range. Statistical analysis was performed using Student's *t*-test. If variable was not normally distributed *U* Mann–Whitney test was used. Qualitative data were compared with the χ^2-test. Linear correlation between variables was analyzed using Spearman correlation coefficient. Multiple linear regression analysis was also performed. Receiver operating characteristic (ROC) curves were used as a method of evaluating the performance of PWV as a predictor of CAC and severe CAC. p value <0.05 was considered statistically significant.

3. Results

All study subjects were Caucasian. Patients were predominantly male (70%), and received deceased donor kidney transplant (94%). All patients have been on dialysis before KTx, most of them (96%) have been treated with hemodialysis, and 4% with peritoneal dialysis. Immunosuppressive therapy involved cyclosporine in 55 patients, tacrolimus in 42 patients, sirolimus in 4 patients, mycophenolate mofetil in 67, azathioprine in 33 patients, and prednisone in 99 patients. Mean cyclosporine concentration was 149 ± 34 ng/ml and tacrolimus concentration was 9.3 ± 2.4 ng/ml. Antihypertensive medication involved beta-blockers in 80 (77%), calcium antagonists in 66 (63%), angiotensin converting enzyme inhibitors (ACEI) in 14 (13%), diuretics in 4 (4%) and other drugs in 46 (44%).

CAC was found in 72 patients (69%) (CAC+ group). Thirty-three (32%) of study patients had CS > 400, and 23 of them (22% of the study population) had CS > 1000. Median CS value in the whole study group was 40.9 (range 0–3730.7). Median CM was 7.4 mg (range 0–655.4). Among CAC+ patients median CS was 322.5 (range 2.1–3730.7) and median CM was 49.2 mg (range 0.6–655.4). RTR without CAC (CAC = 0; CAC− group) and those with CAC+ were compared. Results are shown in Table 1. Among RTR with CS > 400 the proportion of patients with PWV > 10 was significantly higher than in RTR with CS ≤ 400 (55% vs. 27%; $p < 0.02$). The comparison of RTR with PWV ≤ 10 m/s and with PWV > 10 m/s is presented in Table 2.