IJC Heart & Vasculature 40 (2022) 101048

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.sciencedirect.com/journal/ijc-heart-and-vasculature

Effect and correlation of patent vascular access flow on left ventricular hypertrophy in kidney transplant patients

Eakalak Lukkanalikitkul [a,1], Burabha Pussadhamma [b,1], Anucha Ahooja [c], Phuangpaka Ungprasert [b], Panorkwan Toparkngam [b], Supajit Nawapun [c], Wittawat Takong [c], Ubonrat Toimamueang [d], Sirirat Anutrakulchai [a,*]

[a] Division of Nephrology, Department of Internal Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand
[b] Division of Cardiology, Department of Internal Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand
[c] Department of Radiology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand
[d] Division of Nursing, Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

ARTICLE INFO

Keywords:
Access flow rate
Kidney transplant
Left ventricular hypertrophy
Vascular access

ABSTRACT

Background: Patency of vascular accesses (VA) is associated with left ventricular hypertrophy (LVH) in kidney transplant recipients (KTR). This level of VA flow (VAF) as related to LVH was assessed and an upward level of VA flow recommended for VA closure determined. This recommendation has not been previously reported.
Methods: 123 KTR cohort patients were enrolled between August 2016 and December 2017 and their LVH and LV mass index (LVMI) by echocardiography and VAF by Doppler ultrasound were evaluated at baseline and for a 24-month follow-up period. Associations between VAF and LVH were adjusted for other factors.
Results: Patients with patent VA (55.3%) had significantly greater LVH (47.1 vs. 29.1%, an adjusted odds ratio 2.44, $p = 0.03$) and LVMI (112.15 ± 34.4 vs. 97.55 ± 23.55 g/m^2, $p = 0.009$) when compared with the non-VA group. A positive correlation between VAF rate and LVM was noted ($r = 0.40$, $p < 0.001$). Subgroup analysis revealed the VAF $\geq$ 900 ml/min had risks of LVH 3.61, and 2.86 times compared with the non-VA group and the VAF < 900 ml/min group. After a 24-month follow up, there was no significantly individual change in LVMI in patients with or without VA except 6 patients who lost their VA patency during follow-up time had a significant reduction of LVMI (120.17 ± 52.13 to 80.89 ± 22.72 g/m^2, $p = 0.046$).
Conclusions: Patency of VA in post-KT patients was associated with LVH. There was a significant reduction of LMVI after loss of VA patency. Patients with stable kidney graft function should be considered for VA closure especially if VAF is $\geq$ 900 ml/min.

1. Introduction

Left ventricular hypertrophy (LVH) is commonly observed in patients with chronic kidney disease (CKD) especially in hemodialysis patients [1]. After kidney transplantation (KT), left ventricular mass (LVM) usually decreases, however, the incidence of LVH in KT patients remains high. There are multiple factors that contribute to the persistence of LVH after KT and one of them is the patency of vascular access (VA) [2].

Complications related with VA in post-KT patients were found in 12.5% within 4 years, and 8.1% of them had LVH and congestive heart failure (CHF) [3]. Persistence of VA in post-KT patients was associated with LVH as evidenced by an increase of LVM [4,5] and in the same way, closure of VA significantly decreased LVM [6]. Additionally, a higher rate of VA closure from refractory CHF was found in patients with greater VA blood flow which represented the impact of VA blood flow on cardiac function, not only in the patency of VA [7]. Whether VA blood flow is associated with LVH in KT patients has not been reported.

There is no accepted policy for preserving or ligating VA after successful KT. Preserving VA may have a benefit in that the VA could be used for plasmapheresis in acute rejection treatment or for hemodialysis after allograft loss but the increased risk of VA complications including LVH should be of concern. In light of these inconsistencies, this study was aimed to investigate the association between the patency of VA, including VA blood flow and location, and the effect on cardiac indices

* Corresponding author at: Division of Nephrology, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand.
E-mail address: sirirt_a@kku.ac.th (S. Anutrakulchai).
[1] Eakalak Lukkanalikitkul and Burabha Pussadhamma contributed equally to this paper.

https://doi.org/10.1016/j.ijcha.2022.101048
Received 4 October 2021; Received in revised form 22 April 2022; Accepted 3 May 2022

especially LVH in post-KT patients that may help physicians to decide if VA should be preserved or ligated. Additionally, it was aimed to compare changes of left ventricular mass during a 2 year-follow up period among the KT patients who had preserved VA, current loss of VA or no VA patency groups.

2. Methods

2.1. Study design and population

The cohort study was conducted in the Medical Faculty, Srinagarind Hospital, Khon Kaen University between August 1, 2016 and December 31, 2017 with a 24 months follow-up period. The KT patients included were $\geq$ 18 years of age with a $\geq$ 3 months of post-transplantation and stable graft function defined as a serum creatinine (Cr) level change of $<$ 0.3 mg/dl during 3 months before the enrollment. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki that was approved by the Ethics Committee for Human Research, Faculty of Medicine, Khon Kaen University, Thailand (project number HE 591196) and all patients were provided written informed consents. 141 patients were screened, 18 patients were excluded as being ineligible for echocardiography.

2.2. Data collection

Baseline characteristics and demographic data, e.g., age, sex, comorbid diseases, current medications, date of dialysis initiation, date of transplantation, and immunologic risks, were reviewed and collected from interviews, physical examination, and medical records. Laboratory data, e.g., serum hemoglobin, creatinine, estimated glomerular filtration rates (eGFR) calculated by the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula, glucose, cholesterol, calcium, phosphate, parathyroid hormone (PTH) and immunosuppressive drug levels, recorded in the central laboratory were analyzed as independent variables. The participants had doppler ultrasound of VA, chest radiography (CXR), electrocardiography (ECG), and echocardiography performed on the same day of first examination, and they were followed up by echocardiography for 24 months.

Doppler ultrasounds were performed by 3 trained radiologists in which their reliability and agreements were compatible with only small intra- and interobserver variabilities. A GE Doppler ultrasound machine (General Electric Health Care Company, USA) and linear probe with a 10 MHz frequency was used to assess VA patency and VA blood flow at the anastomotic and puncture sites, 3–5 cm. distant from the anastomosis. The patients were examined in a supine position with no flexion of the elbow. Chest radiography was interpreted blindly by radiologists.

2D echocardiography was conducted by 3 cardiologists with good reliability and agreement of measurements. A Prosound α10 premier (Hitachi Aloka medical, CO.LTD) ultrasound system with a standard imaging transducer was used for echocardiography analysis according to the guidelines of American Society of Echocardiography recommendations and indexed to the body surface area.

LVH was defined by evidence of a cardio-thoracic ratio $>$ 0.5 in chest radiography or an abnormal electrocardiogram by Sokolow-Lyon [8] or Cornell [9] criteria or left ventricular mass indices (LVMI) of $>$ 115 g/m^2 in male and $>$ 95 g/m^2 in female patients [10].

Relative wall thickness (RWT) seen in echocardiography was used to classify LVH into concentric (RWT $>$ 0.42) or eccentric (RWT $\leq$ 0.42) hypertrophy [10].

2.3. Definition of exposures and outcomes

The primary outcomes were associations between patency of VA, VA blood flow and prevalence of LVH in post-KT patients. The secondary outcomes were 1.) associations between patency of VA and other cardiac indices assessed by echocardiography, 2.) other factors related with LVH in KT cases and 3.) changes of left ventricular mass during the 2 year-follow up period among the KT patients who had preserved VA, current loss of VA and no VA patency groups.

2.4. Statistical analyses

Sample size was calculated based on the 65.4% and 38.3% prevalence of LVH in post-KT patients with and without patent VA [11], the 1:1 proportion with a 0.05 α error and 0.8 of power (1-β). The calculated sample size was 53 patients in each group.

Continuous data were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR). Categorical data were expressed as numbers and percent of total participants. Means difference between the two groups were compared by using the Student's *t*-test for independent variables and the paired *t*-test for dependent variables. ANOVA was applied for comparison of means among more than two groups. The Mann-Whitney *U* test and Wilcoxon signed ranks test were used to compare median values of nonparametric distributed data for independent and dependent outcomes. Comparisons of categorical variables between groups was analyzed by Chi-square test or Fisher's Exact for independent and McNemar test for dependent outcomes. Logistic regression analysis was used to identify factors potentially related with LVH and expressed as odds ratios (OR) and 95% confidence intervals (CI). A cut-off value of VA blood flow predicting LVH was assessed by receiver operating characteristic (ROC) curve analysis and an area under the ROC curve (AUC_{ROC}) was determined. The linearity trend for VA flow rates in association with LVH was analyzed to explore the level of significant risk and correlations between VA flow rates and LVM was demonstrated by Spearman's rank. Statistical analysis was done by using STATA version 17.0 and p-value $<$ 0.05 was considered as a statistical significance.

3. Results

3.1. Baseline characteristics and demographic data

A total of 123 post-KT patients with stable graft function were included (58.5% male). The overall mean age was 43.8 ± 12.1 years and median post-transplant duration was 1.48 years. The 68 patients in the patent VA group were composed of 67 arteriovenous fistulas (AVF) and 1 arteriovenous graft (AVG) and 55 patients who were in the non-patent VA group had 34 previous peritoneal dialyses, 16 VA thromboses, 4 post-AVF closures, and 1 previous hemodialysis via tunnel catheter.

Clinical data demonstrated a significantly higher prevalence of hypertension (91.2% vs. 69.1%, p = 0.002), a longer pre-transplant dialysis vintage [4.90 (2.60–6.78) vs. 3.35 (1.53–5.14) years; p = 0.02] and fewer human leukocyte antigen (HLA) mismatches (1.81 ± 1.06 vs. 2.51 ± 1.60; p = 0.01) in the patent VA group. Laboratory data showed that patients with a patent VA had higher serum LDL-cholesterols (116 ± 35 vs. 102 ± 40 mg/dl; p = 0.03), PTH [118 (78–162) vs. 69 (50–98) pg/ml; p = 0.001], and lower serum phosphate levels (2.96 ± 0.64 vs. 3.22 ± 0.51 mg/dl; p = 0.02). Other baseline characteristics and demographic data were similar between 2 groups (Table 1).

3.2. Associations between patency of VA, VA blood flow and prevalence of LVH

Prevalence of LVH defined by CXR, ECG and echocardiographic methods were 35.8, 44.7 and 39.0%, respectively. Concentric hypertrophy was observed in 23 cases (accounting for 47.9% of total 48 LVH cases compared with 24% concentric remodeling in 75 non-LVH subjects, p = 0.006), and eccentric hypertrophy in the other 25 cases.

Results of the primary outcome revealed that the patent VA group had a significantly greater percentage of LVH evaluated by 2 measurements, echocardiography (47.1% vs. 29.1%, OR 2.17, 95 %CI 1.02–4.60; p = 0.04), and CXR (44.1% vs. 25.5%, OR 2.31, 95 %CI 1.07–5.01; p =

Table 1
Comparisons of baseline characteristic and demographic data in post-kidney transplant patients with and without patent vascular access.

	Without patent VA (n=55)	With patent VA (n=68)	p value
Baseline characteristics			
Age (years), mean ± SD	43.6 ± 13.8	44.0 ± 10.7	NS
Gender - male, n (%)	29 (52.7)	43 (63.2)	NS
Weight (kg), mean ± SD	56.6 ± 11.0	58.9 ± 12.5	NS
Waist circumference (cm), mean ± SD	80.4 ± 11.1	81.8 ± 11.3	NS
Body mass index (kg/m^2), mean ± SD	22.1 ± 3.89	22.0 ± 4.16	NS
SBP (mmHg), mean ± SD	126 ± 13.5	129 ± 16.1	NS
DBP (mmHg), mean ± SD	76.2 ± 10.2	75.9 ± 10.4	NS
Underlying disease, n (%)			
Diabetes mellitus	6 (10.9)	2 (2.9)	NS
Hypertension	38 (69.1)	62 (91.2)	0.002
Glomerular disease	6 (10.9)	10 (14.7)	NS
Renal stones	4 (7.3)	4 (5.9)	NS
Dyslipidemia	20 (36.4)	18 (26.5)	NS
Ischemic heart disease	1 (1.8)	1 (1.5)	NS
Ischemic stroke	0 (0)	2 (2.9)	NS
Renal replacement therapy and transplantation			
Pre-transplant dialysis mode HD / PD (n)	21 / 34	68 / 0	< 0.001
Pre-transplant dialysis vintage (years)			
-Median (25th -75th percentile)	3.35 (1.53-5.14)	4.90 (2.60-6.78)	0.02
-Mean ± SD	3.93 ± 3.33	5.04 ± 3.20	0.07
Post-transplant duration (years)			
-Median (25th -75th percentile)	1.97 (0.83 - 5.76)	0.94 (0.44-3.50)	NS
-Mean ± SD	3.87 ± 4.29	3.11 ± 4.56	NS
Deceased donor, n (%)	49 (87.3)	64 (92.6)	NS
PRA (%), median (25th -75th percentile)	0 (0 -3.5)	0 (0-0)	NS
HLA mismatches, mean ± SD	2.51 ± 1.60	1.81 ± 1.06	0.01
Cold ischemic time (hour), mean ± SD	14.6 ± 6.64	15.4 ± 6.00	NS
Induction with anti-thymocyte globulin, n (%)	2 (3.6)	3 (4.4)	NS
Induction with basiliximab, n (%)	23 (41.8)	29 (42.6)	NS
Delay graft function*, n (%)	8 (14.6)	15 (22.1)	NS
Transplant renal artery stenosis, n (%)	6 (10.9)	6 (8.8)	NS
Acute rejection, n (%)			
- T cell mediated rejection	3 (5.5)	2 (2.9)	NS
- Antibody mediated rejection	5 (9.1)	4 (5.9)	NS
IF/TA, n (%)	1 (1.8)	3 (4.4)	NS
Laboratory data, mean ± SD			
Creatinine (mg/dl)	1.36 ± 0.52	1.51 ± 0.63	NS
eGFR (ml/min/1.73 m^2)	62.8 ± 21.5	58.8 ± 21.4	NS
Hemoglobin (g/dl)	12.4 ± 2.15	12.3 ± 1.96	NS
Glucose (mg/dl)	92.9 ± 20.3	92.1 ± 20.0	NS
Total cholesterol (mg/dl)	171.2 ± 45.0	184.6 ± 38.4	NS
LDL cholesterol (mg/dl)	101.6 ± 40.0	116.1 ± 34.5	0.03
Uric acid (mg/dl)	6.40 ± 1.62	6.49 ± 1.74	NS
Albumin (g/dl)	4.50 ± 0.33	4.39 ± 0.39	NS
Calcium (mg/dl)	9.53 ± 0.56	9.73 ± 0.72	NS
Phosphate (mg/dl)	3.22 ± 0.51	2.96 ± 0.64	0.02
Parathyroid hormone (pg/ml)			
-Median (25th-75th percentile)	69.1 (50.4-97.8)	117.9 (78.1-162)	0.001
-Mean ± SD	81.1 ± 46.5	141.0 ± 101.6	<0.001
Medication, n (%)			
ACEI	3 (5.5)	5 (7.4)	NS
ARB	8 (14.6)	5 (7.4)	NS
Beta blocker	14 (25.5)	16 (23.5)	NS
Calcium channel blocker	23 (41.8)	35 (51.5)	NS
Alpha blocker	7 (12.7)	12 (17.7)	NS
Hydralazine	5 (9.1)	16 (23.5)	NS
Aspirin	6 (10.9)	12 (17.7)	NS
Clopidogrel	6 (10.9)	7 (10.3)	NS
Statin	21 (38.2)	28 (41.2)	NS
Allopurinol	2 (3.6)	3 (4.4)	NS
Immunosuppressive regimen			
Prednisolone, n (%)	55 (100)	67 (98.5)	NS
Tacrolimus, n (%)	47 (85.5)	58 (85.3)	NS
Tacrolimus through level, mean ± SD	4.74 ± 1.48	5.34 ± 2.17	NS
Cyclosporin, n (%)	6 (10.9)	7 (10.3)	NS
Cyclosporin through level, mean ± SD	98.3 ± 30.8	121.3 ± 48.9	NS
Mycophenolate mofetil, n (%)	24 (43.6)	30 (44.1)	NS
Mycophenolic acid, n (%)	31 (56.4)	36 (52.9)	NS

* Delayed graft function was defined as if the patient needed dialysis within 1 week after kidney transplant due to poor graft function. SD: standard deviation; NS: non-significance; VA: vascular access; SBP: systolic blood pressure; DBP: diastolic blood pressure; HD: hemodialysis; PD: peritoneal Dialysis; PRA: panel reactive antibody; HLA: human leukocyte antigen; IF/TA: interstitial fibrosis/tubular atrophy; eGFR: estimated glomerular filtration rate; ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers.

0.03) and a trend of a higher LVH by the ECG method (51.5% vs 36.4%, OR 1.86, 95% CI 0.90–3.84; p = 0.09), as shown in Fig. 1. Fig. 2 compares CXR, EKG and echocardiography between the patients with and without VA.

In the patent VA group, the VA was a forearm shunt in 50 patients (73.5%) and upper arm shunt in 18 patients (26.5%), with the mean diameter of VA at the puncture site was 9.31 ± 4.17 mm. and the mean VA blood flow at the puncture site was 1,192 ± 1,006 ml/min [median 906 (419–1,649 ml/min)]. Interestingly, an increase of every 100 ml/min in VA blood flow at the puncture site was related with an increase in left ventricular mass measured by echocardiography of 2.10 g (95% CI 0.70 – 3.50 g; p = 0.004). VA flow rate positively correlated with left ventricular mass (r = 0.40, p < 0.001) and left ventricular mass index (r = 0.37, p = 0.002) as shown in Fig. 3. On the other hand, the shunt position and diameter of the VA at puncture site were not related to LVH by echocardiography (p = 0.14 and p = 0.43).

In subgroup analysis, patients with a patent VA in which its flow ≥ 900 ml/min (34 patients) had a significantly higher prevalence of LVH by echocardiography compared with patients with patent VA flow < 900 ml/min (34 patients) (OR 2.86, 95 %CI 1.06–7.73; p = 0.04) and patients without a patent VA (55 patients) (OR 3.61, 95 %CI 1.49–8.75; p = 0.004). In the same way, there was significantly higher LVMI in patients with a VA flow ≥ 900 ml/min compared with a VA flow < 900 ml/min (125.1 ± 36.5 vs. 97.1 ± 25.3 g/m^2; p < 0.001). There were no differences in percentages of LVH between patients with VA flow < 900 ml/min and patients without a patent VA (OR 1.55, 95 %CI 0.61–3.95; p = 0.36).

The ROC curve analysis showed VA blood flow rates moderately predicted LVH in KT patients (AUC_{ROC} 0.66, 95% CI 0.58–0.76) as demonstrated in Fig. 4. A cut-off value of VA blood flow ≥ 900 ml/min had a highest sensitivity of 67.9 %, specificity of 70.4 %, positive predictive value 44.2 % and negative predictive value 86.4% in prediction of LVH compared with other cut-off values (Figure S).

3.3. Other factors related with LVH

The other factors related to LVH demonstrated by multivariate analysis were lower hemoglobin (OR 1.28 for every decrease 1 g/dl, 95 %CI 1.02–1.62; p = 0.03), higher SBP (OR 1.05 for every increase 1 mmHg, 95% CI 1.01–1.09; p < 0.01), higher uric acid (OR 1.36 for every higher 1 mg/dl, 95% CI 1.009–1.84; p = 0.043) and higher PTH level (OR 1.007 for every increase of 1 pg/ml, 95 %CI 1.00007–1.01; p = 0.048, Table 2).

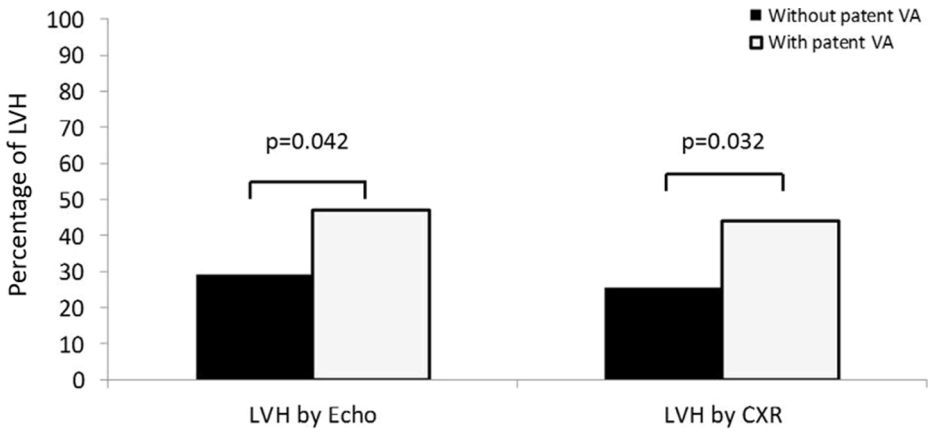

Fig. 1. Prevalence of left ventricular hypertrophy in post-kidney transplant patients with and without patent vascular access evaluated by echocardiography and chest radiography VA: vascular access; LVH: left ventricular hypertrophy; Echo: echocardiography; CXR: chest radiography.

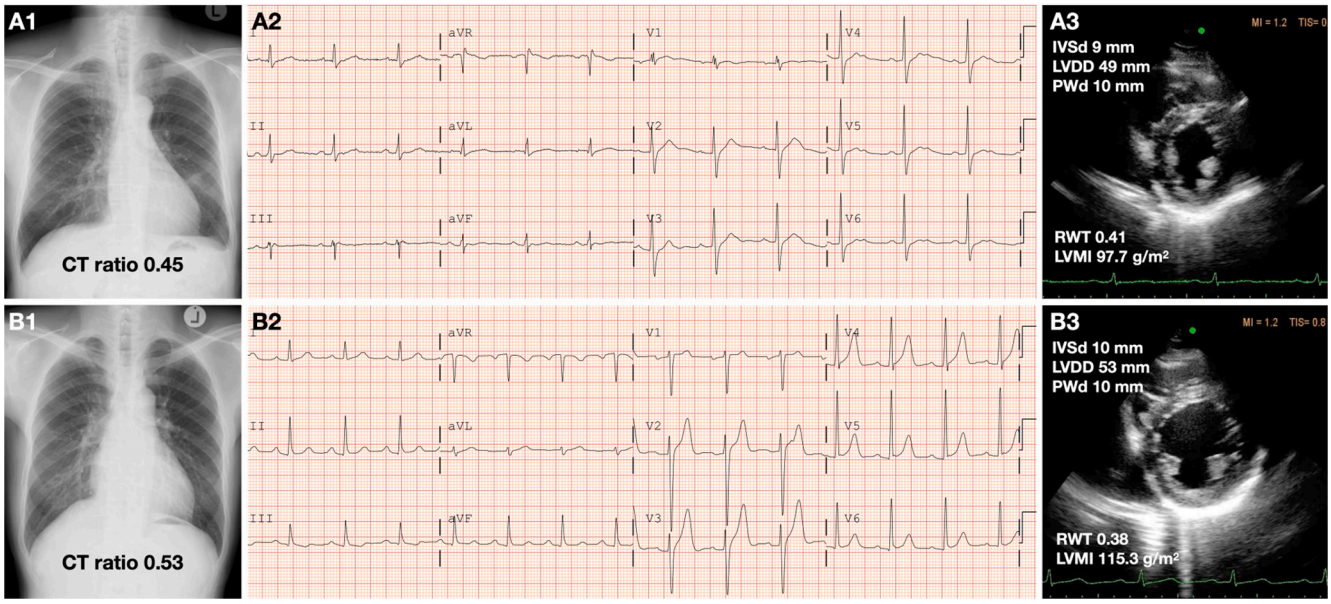

Fig. 2. The comparative chest X-ray (1), electrocardiography (2), and two-dimensional transthoracic echocardiography at end diastole in parasternal short-axis views at the papillary muscle level (3) of representative male patients that show no evidence of cardiomegaly or left ventricular hypertrophy (LVH) from any studies in a patient without patent vascular access (VA) (A), while evidence of slight cardiomegaly or LVH are observed from all studies in patients with patent VA (B). CT, cardiothoracic; IVSd; septal wall thickness at end diastole; LVDD, left ventricular diastolic dimension; LVMI, left ventricular mass index; PWd, posterior wall thickness at end diastole; RWT, relative wall thickness.

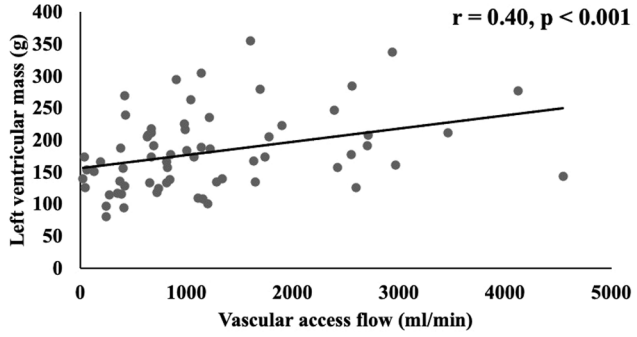

Fig. 3. Positive correlation between vascular access flow and left ventricular mass in kidney transplantation pateints with patent vascular access.

The Fig. 4 reveals AUC_{ROC} data of other factors related with LVH including SBP (AUC_{ROC} 0.70, 95% CI 0.60–0.80), uric acid (AUC_{ROC} 0.61, 95% CI 0.50–0.72), PTH (AUC_{ROC} 0.60, 95% CI 0.48–0.72) and Hb (AUC_{ROC} 0.40, 95% CI 0.29–0.50).

3.4. Associations between patency of VA and cardiac indices assessed by echocardiography

The patent VA group had significantly different cardiac indices assessed by echocardiography compared with the non-patent VA group, *viz.* larger LV diastolic dimensions (LVDD) (50.2 ± 5.88 vs. 47.1 ± 5.47 mm; p = 0.003), LV mass (182.9 ± 62.6 vs. 155.2 ± 42.7 g; p = 0.006), LVMI (112.1 ± 34.5 vs. 97.5 ± 23.5 g/m^2; p = 0.009), higher cardiac output (6.26 ± 1.63 vs. 5.51 ± 1.72 L/min; p = 0.01) and cardiac index (3.91 ± 1.11 vs. 3.42 ± 0.94 L/min/m^2; p = 0.01, Table 3).

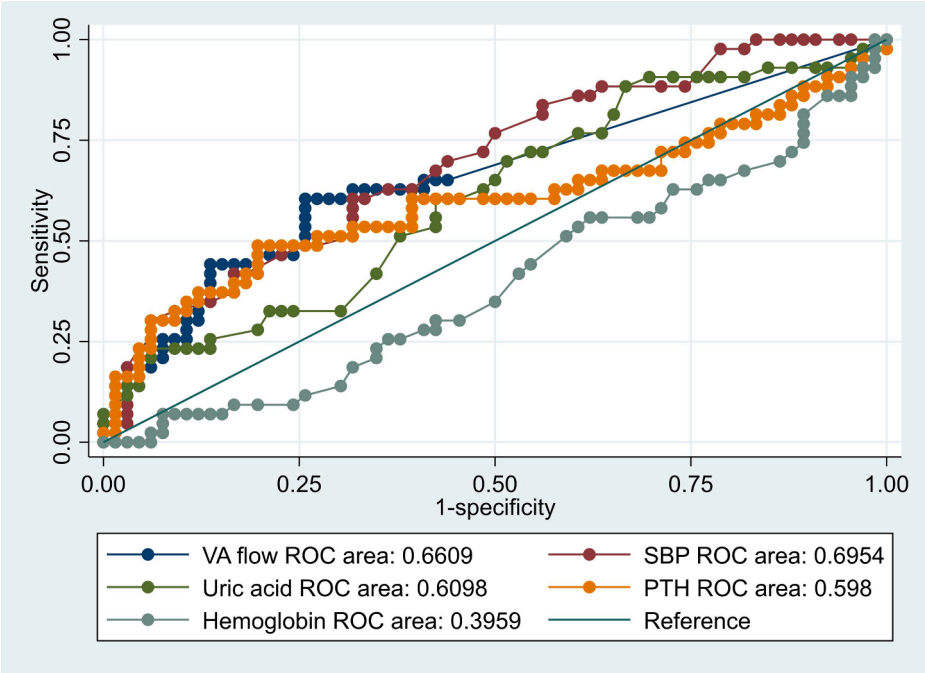

Fig. 4. The receiver operating characteristic (ROC) curve analysis demonstrates levels of area under the ROC curve (AUC_{ROC}) of factors related with left ventricular hypertrophy in post-kidney transplant patients. VA, vascular access; SBP, systolic blood pressure; PTH, parathyroid hormone.

Table 2
Risk factors for left ventricular hypertrophy evaluated by echocardiography.

	Crude OR (95%CI)	p value	Adjusted OR (95%CI)	p value
Patent VA (with/ without)*	2.17 (1.02-4.60)	0.04	2.44 (1.08-5.54)	0.03
Vascular access flow*				
- No VA	1		1	
- VA flow < 900 ml/min	1.55 (0.61-3.95)	0.36	1.29 (0.42-3.95)	0.66
- VA flow ≥ 900 ml/min	3.61 (1.49-8.75)	<0.01	4.12 (1.36-12.5)	0.01
SBP (every increase 1 mmHg)	1.03 (1.005-1.06)	0.02	1.05 (1.01-1.09)	<0.01
Serum Cr (every increase 1 mg/dl)	2.85 (1.37-5.90)	<0.01		
Serum Hb (every decrease 1 g/dl)	1.32 (1.08-1.59)	<0.01	1.28 (1.02-1.62)	0.03
Serum Uric (every increase 1 mg/dl)	1.28 (1.01-1.61)	0.04	1.36 (1.009-1.84)	0.04
Serum PTH (every increase 1 pg/ml)	1.007(1.001-1.01)	0.01	1.007 (1.00007-1.01)	0.048
PRA (every increase 1%)	1.02 (1.00-1.04)	0.03		

* Adjusted with SBP, hemoglobin, uric acid and PTH levels. OR: odd ratio; CI: confident interval; VA: vascular access; SBP: systolic blood pressure; Cr: creatinine; Hb: hemoglobin; PTH: parathyroid hormone; PRA: panel reactive antibody.

Table 3
Cardiac indices evaluated by echocardiography in patients with and without patent vascular access; data presented as mean ± SD.

	Without patent VA (n=55)	Patent VA (n=68)	p value
Estimated mRAP (mmHg)	3.31 ± 1.74	3.22 ± 1.03	NS
RVSP (mmHg)	21.61 ± 4.43	23.31 ± 6.26	NS
LAD (mm)	37.05 ± 6.72	38.72 ± 7.77	NS
LVSD (mm)	9.29 ± 1.82	9.54 ± 2.53	NS
LVDD (mm)	47.09 ± 5.47	50.18 ± 5.88	0.003
LVM (g)	155.2 ± 42.71	182.9 ± 62.58	0.006
LVMI (g/m^2)	97.55 ± 23.55	112.15 ± 34.49	0.009
RWT (mm)	0.41 ± 0.12	0.40 ± 0.13	NS
Stroke volume (ml)	70.91 ± 17.39	80.28 ± 21.28	0.01
LVEF (%)	70.79 ± 6.93	70.45 ± 6.57	NS
Cardiac output (L/min)	5.51 ± 1.72	6.26 ± 1.63	0.01
Cardiac index ($L/min/m^2$)	3.42 ± 0.94	3.91 ± 1.11	0.01
LVOT dimension (mm)	20.40 ± 2.10	20.48 ± 1.89	NS
A velocity (cm/sec)	68.93 ± 19.51	74.61 ± 29.75	NS
E velocity (cm/sec)	70.72 ± 23.65	78.72 ± 30.85	NS
E' velocity (cm/sec)	7.94 ± 2.91	7.90 ± 2.37	NS
E/A	1.08 ± 0.43	1.17 ± 0.37	NS
E/E'	9.54 ± 3.50	10.88 ± 4.46	NS

SD: standard deviation; NS: non-significance; VA: vascular access; mRAP: mean right atrial pressure; RVSP: right ventricular systolic pressure; LAD: left atrial dimension; LVSD: left ventricular systolic dimension; LVDD: left ventricular diastolic dimension; RWT: relative wall thickness; LVEF: left ventricular ejection fraction; LVOT: left ventricular outflow tract.

3.5. Changes of left ventricular mass after 2-year follow-up period

During 2 years of follow up time, 12 participants were withdrawn before the end of study because of 9 deaths (5 patients in the patent VA and 4 patients in the non-patent VA groups) and 3 allograft failures requiring dialysis in the patent VA group. The total 111 cases with 60 cases of patent VA and 51 cases of without VA were followed up for 2 years and during this time, another 6 subjects lost their VAs, i.e., 3 spontaneous losses, 2 surgical closures from AVF aneurysms and 1 from AVF thrombophlebitis, therefore at the end of study total patent VA was observed in 54 patients and non-patent VA in 57 patients. Evidence from the LVMI values evaluated by the second echocardiogram demonstrated 39.6% of total LVH prevalence with the new development of LVH in 12 patients (9 cases in the active patent VA group and 3 cases in the without AV group) and regression of LVH in another 12 subjects (7 cases in the previous VA group in which 6 of them lost their VAs and another 5 cases in the without AV group). Factors related with LVH were functioning VA (OR 2.76, 95 % CI 1.26–6.06, p = 0.01), lower hemoglobin (OR 1.28 for every decrease 1 g/dl, 95% CI 1.05–1.56; p = 0.02) and higher SBP (OR 1.05 for every increase 1 mmHg, 95% CI 1.02–1.09; p = 0.004). The averaged LVMI indices between the patent VA (n = 54) and non-patent VA (n = 57) groups significantly differed (110.70 ± 30.51 vs. 95.33 ±

28.06 g/m^2, p = 0.007). A comparison of individual participants between the first and second times of LVMI parameters in 111 cases, there was no significant change after the 2-year follow-up period (106.61 ± 32.14 vs. 102.81 ± 30.15 g/m^2, p = 0.13). In participants who lost their VA (6 cases), however, a significant decrease of LVMI was observed (baseline mean LVMI 120.17 ± 52.13 vs. followed mean LVMI 80.89 ± 22.72 g/m^2, p = 0.046 and baseline median LVMI 105.5 (81–158) vs. followed median LVMI 72.16 (67 – 84.4) g/m^2, p = 0.03, Fig. 5). No significant changes of baseline and followed LVMI in 54 patients who still had functioning VAs (111.65 ± 33.76 vs. 110.70 ± 30.51 g/m^2, p = 0.81) and in 51 subjects who were previously without patent VAs (99.69 ± 26.35 vs. 97.03 ± 28.33 g/m^2, p = 0.31). Percentages of LVMI change [100 × ((second LVMI- first LVMI)/first LVMI)] among the three groups differed significantly (overall p = 0.01; current loss of VA −27.2 vs. functioning VA 2.94 %, p = 0.008; current loss of VA −27.2 vs. non-patent VA −1.41 %, p = 0.003 and functioning VA 2.94 vs. non-patent VA −1.41 %, p = 0.34).

Additionally, in the patent VA group, 2 cases developed congestive heart failure and 1 case of post-sudden cardiac arrest while no cardiovascular event was reported in the non-patent VA group during this 2-year follow-up period.

4. Discussion

LVH is commonly observed in CKD patients especially in chronic dialysis patients. A previous study reported the prevalence of LVH up to 74% and this was related to high cardiovascular mortality [12]. CKD patients had multiple risk factors for LVH including traditional risk factors e.g., age, comorbid diseases, ischemic heart disease, and CKD related risk factors e.g.,volume overload, anemia, malnutrition, uremia [13]. Reported prevalences of LVH assessed by echocardigram in KT recipeints varied from 33 to 67% that might be related with a difference in modes of dialysis before KT and post-transplant duration [14–18], in this study the prevalence of LVH was 39% during the mean 3.45 years of post-KT duration. Previous studies found that KT can improve these risk factors and result in a decrease of LVH prevelence from 67 to 75% in pre-transplant to 37–52.1% in 1 year post-transplant patients and the regression of LVH was related with a reduction of serum Cr and improvement of BP control and anemia [14,15]. Slubowska et al. [16], however, reported that the prevelance of LVH modestly decreased from 51.2% to 50% after 1 year of KT in which about 30% of patients with LVH prior to transplantation had LVH regression after transplantation while 30% of patients had a new onset of LVH after transplantation, similar with the current study in that the prevalence of LVH non-significantly changed from 39% to 39.6% after the 2 year follow-up in which patients with a new onset LVH and LVH regression were equal at about 10.8%. The current *meta*-analysis also demontrated no improvement of left ventricular structure and function after KT [18]. In addition to graft function, hypertension and anemia associated with post-KT LVH, mode of dialysis treatment before transplantation, a history of acute allograft rejection, and patent VA were also related [11]. No association of dialysis mode with LVH was observed in our study, however, presence of VA, low hemoglobin, elevations of: - SBP, uric acid, and PTH were independent risk factors.

The patency of VA was associated with a higher prevalence of LVH (47.1% vs. 29.1%) and an increase in VA blood flow every 100 ml/min was related to an increase in left ventricular mass of 2.10 g. Kolonko et al. [5] also presented that a patent VA increased the risk for LVH in 163 post-transplant patients (66.7% vs. 48.4% OR 2.39; p = 0.01); the reasons of higher LVH prevalence other than the current study may be from the advanced age of a mean of 50 years and a longer dialysis vintage (mean 8.7 years), diabetes millitus (22.6%), and smoking (19.6%) in the study population, however, VA blood flow was not evaluated in this study.

Cridlig et al. [4] studied the effect of VA on cardiac indices in post-KT patients by a match-paired case study (38 patients in each group), the results showed that patent VA was 4.3 times the increased risk for LVH and VA blood flow > 680 ml/min tended to correlate with progression of LVMI (142.6 ± 30.02 vs. 126.9 ± 23.9 g/m^2; p = 0.08). The current study found that VA blood flow correlated with progression of LVMI especialy in patients with VA blood flow ≥ 900 ml/min (125.1 ± 36.5 vs. 97.3 ± 25.7 g/m^2; p < 0.001) that may result from increased cardiac output from high access flow, i.e., cardiac output of the VA blood flow ≥ 900 ml/min.; < 900 ml/min and without VA groups were 6.55 ± 1.81, 5.86 ± 1.33 and 5.51 ± 1.72 L/min (p = 0.03).

Patency of VA led to higher cardiac output as expected, however, it affected predominantly only LVDD and LVM (larger left ventricular size from more volume overload), but had no significant effect on left ventricular diastolic function, right ventricular systolic pressure, and right atrial pressure. Theoretically, high cardiac output could create problems

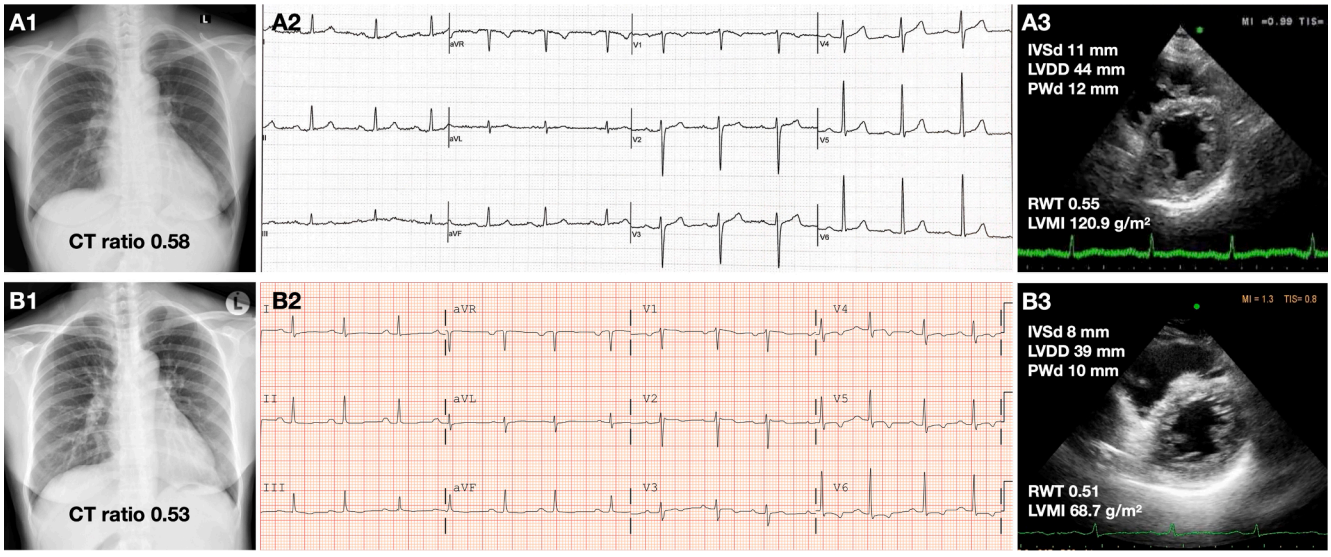

Fig. 5. The comparative chest X-ray (1), electrocardiography (2), and two-dimensional transthoracic echocardiography at end diastole in parasternal short-axis view at papillary muscle level (3) in the female patient before (A) and after loss of vascular access (B) show regressions of left ventricular hypertrophy after loss of vascular access in all studies. CT, cardiothoracic; IVSd; septal wall thickness at end diastole; LVDD, left ventricular diastolic dimension; LVMI, left ventricular mass index; PWd, posterior wall thickness at end diastole; RWT, relative wall thickness.

for both left- and right-sided heart chambers, the isolated left-sided heart problem found in this study (increased LVDD and LVM) might be explained by the common consequence of left-side heart first or up on the degree and duration of increased cardiac output [4,5].

In the current study, it was found that 6 patients who lost their VA function during the follow-up period had a significant decrease LVMI from 120.17 ± 52.13 g/m^2 at baseline to 80.89 ± 22.72 g/m^2 while other patients with no change of VA function (both functioning and non-functioning VA) and had no significant change of LVMI after 2 years of the followup period. This finding was similar with a previous report from Unger P. et al [6] whose study on the effect of AVF closure on LV mass in 17 KT recipients found that there was a significant decrease LVMI from 139 ± 44 g/m^2 to 127 ± 45 g/m^2 and 117 ± 40 g/m^2 at 1 and 21 months after AVF closure compared with no change of LVMI in control groups.

Impaired renal function was correlated with LVH progression which was explained by 3 major pathophysiologic factors;- 1) increased afterload from rising blood pressure, systemic arterial resistance and reduction of vascular compliance, 2) an increased preload from salt and water retention resulting in a hypervolumic state, and 3) factors that were not related to afterload or preload, mainly resulting from oxidative stress, inflammatory cytokines and uremic toxins especially fibroblast growth factor 23 (FGF23) [19,20]. All of these factors had the potential effect of myocardial cell thickening and LV remodeling [13]. Accompanied with results from this current study, increasing SBP and impaired renal function defined by increases in serum Cr, were risk factors for LVH from univariate analysis. After multivariate analysis, however, only increased SBP, not serum Cr, was significantly associatiated with LVH.

Hyperuricemia was frequently observed in post-KT patients that might be attributed to a decreased renal urate clearance from impaired renal function and use of diuretics and calcineurin inhibitors, especially cyclosporin [21,22]. The associations between hyperuricemia, renal impairment and LVH in CKD were reported in a previous study [23]. Elevation of serum uric acid level was also associated with several coexisting cardiovascular disease risk factors including obesity, high serum triglycerides, LDL-cholesterol levels and high plasma glucose levels which are parts of the metabolic syndrome [24]. Uric acid itself is also linked to cardiovascular damage by an increase of xanthine oxidase (XO)-derived oxygen free radical production and stimulation of the inflammatory pathway resulting in endothelial dysfunction, vascular smooth muscle cell proliferation and the development of atherosclerosis [25]. Treatment with allopurinol, an XO inhibitor, can reduce oxygen free radical generation and improve peripheral vasodilator capacity [26]. This study confirmed that an increase in serum uric acid level was an independent risk factor for LVH demonstrated by multivariate analyses (OR 1.36 for every higher uric acid level 1 mg/dl, 95% CI 1.009–1.84; p = 0.04). Similar result was reported in the Caliskan et al. [27] study which found that serum uric acid level significantly correlated and could predict LVMI in post-KT patients.

The other factors related to LVH revealed in this study were low hemoglobin and high PTH levels similar to the study of Dzemidzic et al. [28] Consequences of anemia in LVH made possible by chronic tissue hypoxia is accompanied by 1) peripheral vasodilatation from the decreased inhibitory effect of nitric oxide of hemoglobin resulting in a decreased mean arterial pressure and stimulation of the renin angiotensin aldosterone system (RAAS) and sympathetic nervous system (SNS); 2) lactic acidosis that is related to the hyperdynamic state and 3) erythropoietin (EPO) deficiency resulting in defects of cardiac remodeling from loss of the cardiacmyocyte antiapoptotic effect of EPO [29]. PTH levels usually increase after pre-transplantation and decline after succesful KT, however, in some patients PTH levels are still elevated. High PTH levels have been related with previous hyperphosphatemia, Klotho deficiency and an increase in FGF23. These factors were reported as the risk factors for LVH in CKD patients [30,31].

Relationships between the flow of arteriovenous fistula and cardiac output were reported in many studies in hemodialysis patients but there were limited data in post-KT patients. This is the first study that shows a positive correlation between VA blood flow and LV mass in post-KT patients.

There are some limitations of the present study. 1.) The number of enrolled patients who were previously on hemodialysis in the non-patent VA group was less than the patent VA group, however, multivariated analysis adjusted for mode of dialysis confirmed the effect of patent VA on LVH in post-transplant patients. 2.) The current study did not measure serum Klotho, FGF23, N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, and other inflammatory markers that were reported as the risk factors of LVH, therefore, some potential and related factors might be omitted.

5. Conclusion

In conclusion, patent VA in post-KT patients increased cardiac output and cardiac index causing cardiac remodeling by an increase of LVM that turned into LVH and finally, these changes were importantly related to VA blood flow. Post-KT patients with stable graft function should be advised to consider VA closure espcially in cases of VA blood flow ≥ 900 ml/min to prevent LVH progression. Additionally, patients should be monitored for other risk factors of LVH including anemia, high BP, serum Cr, eGFR, serum uric acid, and PTH levels.

Funding

The study was funding supported from the Faculty of Medicine, Khon Kaen University and the Chronic Kidney Disease Prevention in the Northeast of Thailand (CKDNET) project.

CRediT authorship contribution statement

Eakalak Lukkanalikitkul: Conceptualization, Project administration, Data curation, Investigation, Writing – original draft. **Burabha Pussadhamma:** Conceptualization, Project administration, Data curation, Investigation, Writing – review & editing. **Anucha Ahooja:** Investigation. **Phuangpaka Ungprasert:** Investigation. **Panorkwan Toparkngam:** Investigation. **Supajit Nawapun:** Investigation. **Wittawat Takong:** Investigation. **Ubonrat Toimamueang:** . **Sirirat Anutrakulchai:** Conceptualization, Project administration, Data curation, Formal analysis, Investigation, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We would like to acknowledge Prof. James A Will for editing the manuscript via Publication Clinic KKU, Thailand.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2022.101048.

References

[1] J.M. Lopez-Gomez, E. Verde, R. Perez-Garcia, Blood pressure, left ventricular hypertrophy and long-term prognosis in hemodialysis patient, Kidney. Int. 68 (1998) S92–S98, https://doi.org/10.1046/j.1523-1755.1998.06820.x.

[2] D. Hernández, Left ventricular hypertrophy after renal transplantation: new approach to a deadly disorder, Nephrol. Dial. Transplant. 19 (2004) 1682–1686, https://doi.org/10.1093/ndt/gfh283.

[3] B. Vajdič Trampuž, R. Ponikvar, A. Kandus, J. Buturović-Ponikvar, Hemodialysis arteriovenous fistula-related complications and surgery in kidney graft recipients, Ther. Apher. Dial. 17 (2013) 444–447, https://doi.org/10.1111/1744-9987.12094.
[4] J. Cridlig, C. Selton-Suty, F. Alla, A. Chodek, A. Pruna, M. Kessler, L. Frimat, Cardiac impact of the arteriovenous fistula after kidney transplantation: a case-controlled, match-paired study, Transpl. Int. 21 (2008) 948–954, https://doi.org/10.1111/j.1432-2277.2008.00707.x.
[5] A. Kolonko, A. Kujawa-Szewieczek, M. Szotowska, P. Kuczera, J. Chudek, A. Więcek, The association of long-functioning hemodialysis vascular access with prevalence of left ventricular hypertrophy in kidney transplant recipients, BioMed. Res. Int. 2014 (2014) 1–6.
[6] P. Unger, K.M. Wissing, L. de Pauw, J. Neubauer, P. van de Borne, Reduction of left ventricular diameter and mass after surgical arteriovenous fistula closure in renal transplant recipients, Transplantation 74 (2002) 73–79, https://doi.org/10.1097/00007890-200207150-00013.
[7] T. Schier, G. Göbel, C. Bösmüller, I. Gruber, M. Tiefenthaler, Incidence of arteriovenous fistula closure due to high-output cardiac failure in kidney-transplanted patients, Clin. Transplant. 27 (2013) 858–865, https://doi.org/10.1111/ctr.12248.
[8] M. Sokolow, T.P. Lyon, The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads, Am. Heart. J. 37 (1949) 161–186, https://doi.org/10.1016/0002-8703(49)90562-1.
[9] P.N. Casale, R.B. Devereux, D.R. Alonso, E. Campo, P. Kligfield, Improved sex-specific criteria of left ventricular hypertrophy for clinical and computer interpretation of electrocardiography: validation with autopsy findings, Circulation 75 (1987) 565–572, https://doi.org/10.1161/01.CIR.75.3.565.
[10] R.M. Lang, L.P. Badano, V. Mor-Avi, J. Afilalo, A. Armstrong, L. Ernande, F. A. Flachskampf, E. Foster, S.A. Goldstein, T. Kuznetsova, P. Lancellotti, D. Muraru, M.H. Picard, E.R. Rietzschel, L. Rudski, K.T. Spencer, W. Tsang, J.U. Voigt, Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging, J. Am. Soc. Echocardiogr. 28 (2015) 1–39, https://doi.org/10.1016/j.echo.2014.10.003.
[11] A.A. El-Husseini, H.A. Sheashaa, N.A. Hassan, F.M. El-Demerdash, M.A. Sobh, M. A. Ghoneim, Echocardiographic changes and risk factors for left ventricular hypertrophy in children and adolescents after renal transplantation, Pediatr. Transplant. 8 (2004) 249–254, https://doi.org/10.1111/j.1399-3046.2004.00159.x.
[12] R.N. Foley, P.S. Parfrey, J.D. Harnett, G.M. Kent, C.J. Martin, D.C. Murray, P. E. Barre, Clinical and echocardiographic disease in patients starting end-stage renal disease therapy, Kidney. Int. 47 (1995) 186–192, https://doi.org/10.1038/ki.1995.22.
[13] L. Di Lullo, A. Gorini, D. Russo, A. Santoboni, C. Ronco, Left ventricular hypertrophy in chronic kidney disease patients: from pathophysiology to treatment, Cardiorenal. Med. 5 (2015) 254–266, https://doi.org/10.1159/000435838.
[14] S.R.C. Ferreira, V.A. Moisés, A. Tavares, A. Pacheco-Silva, Cardiovascular effects of successful renal transplantation: a 1-year sequential study of left ventricular morphology and function, and 24-hour blood pressure profile, Transplantation 74 (2002) 1580–1587, https://doi.org/10.1097/00007890-200212150-00016.
[15] D. Jasminka, S. Rasic, D. Rebic, S. Uncanin, Role of hypertension and anaemia in left ventricular remodelling in patient with renal allograft in the first post-transplant year, Mater. Sociomed. 27 (2015) 104–107, https://doi.org/10.5455/msm.2015.27.104-107.
[16] K. Slubowska, B. Lichodziejewska, P. Pruszczyk, J. Szmidt, M. Durlik, Left ventricular hypertrophy in renal transplant recipients in the first year after transplantation, Transplant. Proc. 46 (2014) 2719–2723, https://doi.org/10.1016/j.transproceed. 2014.08.019.
[17] E. Dounousi, M. Mitsis, K.K. Naka, C. Pappas, L. Lakkas, C. Harisis, K. Pappas, V. Koutlas, I. Tzalavra, G. Spanos, L.K. Michalis, K.C. Siamopoulos, Differences in cardiac structure assessed by echocardiography between renal transplant recipients and chronic kidney disease patients, Transplant. Proc. 46 (2014) 3194–3198, https://doi.org/10.1016/j.transproceed.2014.10.034.
[18] L.C. Pickup, J.P. Law, A. Radhakrishnan, A.M. Price, C. Loutradis, T.O. Smith, N. C. Edwards, R.P. Steeds, J.N. Townend, C.J. Ferro, Changes in left ventricular structure and function associated with renal transplantation: a systematic review and meta-analysis, ESC. Heart. Fail. 8 (2021) 2045–2057, https://doi.org/10.1002/ehf2.13283.
[19] M.-L. Gross, E. Ritz, Hypertrophy and fibrosis in the cardiomyopathy of uremia–beyond coronary heart disease, Semin. Dial. 21 (2008) 308–318, https://doi.org/10.1111/j.1525-139X.2008.00454.x.
[20] E. Ritz, C. Wanner, The challenge of sudden death in dialysis patients, Clin. J. Am. Soc. Nephrol. 3 (2008) 920–929, https://doi.org/10.2215/CJN.04571007.
[21] H.Y. Lin, L.L. Rocher, M.A. McQuillan, S. Schmaltz, T.D. Palella, I.H. Fox, Cyclosporine-induced hyperuricemia and gout, N. Engl. J. Med. 321 (1989) 287–292, https://doi.org/10.1056/NEJM198908033210504.
[22] V.O. Edvardsson, B.A. Kaiser, M.S. Polinsky, J.A. Palmer, R. Quien, H.J. Baluarte, Natural history and etiology of hyperuricemia following pediatric renal transplantation, Pediatr. Nephrol. 9 (1995) 57–60, https://doi.org/10.1007/BF00858973.
[23] S.C. Chen, J.M. Chang, S.M. Yeh, H.M. Su, H.C. Chen, Association of uric acid and left ventricular mass index with renal outcomes in chronic kidney disease, Am. J. Hypertens. 26 (2013) 243–249, https://doi.org/10.1093/ajh/hps020.
[24] S.G. Wannamethee, A.G. Shaper, P.H. Whincup, Serum urate and the risk of major coronary heart disease events. Heart 78 (2) (1997) 147–153.
[25] F. Viazzi, D. Parodi, G. Leoncini, A. Parodi, V. Falqui, E. Ratto, S. Vettoretti, G. P. Bezante, M. Del Sette, G. Deferrari, R. Pontremoli, Serum uric acid and target organ damage in primary hypertension, Hypertension 45 (2005) 991–996, https://doi.org/10.1161/01.HYP.0000161184.10873.ea.
[26] W. Doehner, N. Schoene, M. Rauchhaus, F. Leyva-Leon, D.V. Pavitt, D.A. Reaveley, G. Schuler, A.J. Coats, S.D. Anker, R. Hambrecht, Effects of xanthine oxidase inhibition with allopurinol on endothelial function and peripheral blood flow in hyperuricemic patients with chronic heart failure: results from 2 placebo-controlled studies, Circulation 105 (2002) 2619–2624, https://doi.org/10.1161/01.CIR. 0000017502.58595.ED.
[27] Y. Caliskan, N. Gorgulu, B. Yelken, F. Akturk, H. Yazici, A. Turkmen, M.S. Sever, Serum uric acid level is associated with cardiac hypertrophy in renal transplant recipients, Clin. Transplant. 25 (3) (2011) 368–374.
[28] J. Dzemidzić, S. Rasić, A. Saracević, D. Rebić, S. Uncanin, A. Srna, A. Muslimović, Predictors of left ventricular remodelling in kidney transplant recipients in the first posttransplant year, Bosn. J. Basic. Med. Sci. 10 (2010) S51–S55, https://doi.org/10.17305/bjbms.2010.2649.
[29] R. Latini, M. Brines, F. Fiordaliso, Do non-hemopoietic effects of erythropoietin play a beneficial role in heart failure? Heart Fail Rev 13 (4) (2008) 415–423.
[30] I. Vogt, D. Haffner, M. Leifheit-Nestler, FGF23 and Phosphate-Cardiovascular Toxins in CKD, Toxins (Basel). 11 (2019) 647, https://doi.org/10.3390/toxins11110647.
[31] M. Leifheit-Nestler, R. Große Siemer, K. Flasbart, B. Richter, F. Kirchhoff, W. H. Ziegler, M. Klintschar, J.U. Becker, A. Erbersdobler, C. Aufricht, T. Seeman, D. C. Fischer, C. Faul, D. Haffner, Induction of cardiac FGF23/FGFR4 expression is associated with left ventricular hypertrophy in patients with chronic kidney disease, Nephrol. Dial. Transplant. 31 (2016) 1088–1099, https://doi.org/10.1093/ndt/gfv421.