Original Paper

Epicardial Fat Thickness in Patients with Autosomal Dominant Polycystic Kidney Disease

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Keywords

Epicardial fat thickness · Autosomal dominant polycystic kidney disease · Cardiovascular disease · Left ventricular hypertrophy

Abstract

Introduction: Autosomal dominant polycystic kidney disease (ADPKD) is associated with early organ damage such as left ventricular hypertrophy and higher cardiovascular risk when compared to essential hypertension (EH). Epicardial adipose tissue (EAT) is a new cardiovascular risk factor, but its role and correlation with left ventricular mass (LVM) in ADPKD is unknown. **Aims:** we sought to investigate whether EAT is higher and related to LVM indexed by body surface area (LVMI) in hypertensive patients with ADPKD compared to those with EH. **Methods:** We performed ultrasound measurement of EAT thickness, LVM, LVMI, and left atrium size (left atrial volume indexed for body surface, LAVI) in 41 consecutive hypertensive patients with ADPKD, compared to 89 EH patients. **Results:** EAT was significantly higher in the ADPKD group in comparison to EH subjects (9.2 ± 2.9 mm vs. 7.8 ± 1.6 mm, $p < 0.001$), and significantly correlated with LVM, LVMI, and LAVI in the ADPKD group ($r = 0.56$, $p = 0.005$; $r = 0.424$, $p = 0.022$; and $r = 0.48$, $p = <0.001$, respectively). Comparing EAT against body mass index, systolic blood pressure, and age, we found that EAT was the strongest predictor of LVMI ($\beta = 0.42$, $p = 0.007$). **Conclusion:** Our data showed that EAT was higher in ADPKD patients than in EH subjects and independently correlated with LVMI. EAT measurement can be a useful marker for the cardiovascular risk stratification in ADPKD.

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Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic kidney disease, characterized by the formation of cystic dilatation of renal tubules with progressive destruction of renal parenchyma continuing to an early onset of end-stage renal disease [1–3]. ADPKD patients are at higher cardiovascular risk, and cardiovascular death is estimated to be 1.6- to 3.2-fold higher in these patients than in the general population [4, 5]. Hypertension is commonly associated with ADPKD, occurring in 50–70% of patients even before the progression to renal dysfunction [6]. Left ventricular hypertrophy (LVH), a major cardiovascular risk factor, is also frequently observed in patients with ADPKD [7, 8]. Both hypertension and LVH play a crucial role in the development of cardiovascular complications in these patients. Traditional risk factors, such as blood pressure (BP) control, proteinuria, body mass index (BMI), age, renal function, and insulin resistance have all been independently associated with left ventricular mass (LVM) and LVM indexed by body surface area (LVMI) in ADPKD [9–11]. Obesity has recently and independently been associated with progression in early-stage ADPKD [12]. Nevertheless, whether visceral obesity and specifically the adiposity of the heart, namely the epicardial adipose tissue (EAT), can play a role in ADPKD and in the development of LVH in these patients is unexplored. EAT is thought to directly and independently modulate the heart, due to its proximity to the coronary arteries and paracrine interaction with the myocardium [13, 14]. EAT has been shown to correlate with LVMI in conditions of insulin resistance, such as obesity and diabetes [15]. EAT thickness can be easily visualized and measured using standard 2D echocardiography, as first developed and validated by Iacobellis and Willens [16]. Nowadays, the relationship between EAT and LVMI in hypertensive ADPKD patients is unknown. Hence, in this study we sought to investigate whether EAT could be higher and related to LVMI in hypertensive patients with ADPKD compared to those with essential hypertension (EH).

Patients and Methods

From January 2015 to April 2016, we enrolled 41 consecutive patients (20 men, 21 women, mean age 44 ± 15 years, age range 19–78 years), who were diagnosed with ADPKD in the Nephrology Unit, Sapienza University of Rome, Italy, and were referred to the Tertiary Centre of Secondary Hypertension Unit, Sapienza University of Rome. Eighty-nine patients with EH were recruited as the control group (mean age 49 ± 12 years, age range 17–82 years). Anthropometric measurements and fasting venous blood samples were obtained from all patients. Clinical BP was measured during the visit according to guidelines [17], and the diagnosis of hypertension was made if systolic BP (SBP) was found to be ≥ 140 mm Hg and diastolic BP (DBP) ≥ 90 mm Hg [17] for three consecutive measurements with the sphygmomanometer by the same investigator. Patients with clinical history or clinical symptoms or electrocardiogram, echocardiographic, and angiographic signs of coronary artery disease, heart failure, cardiomyopathies, or valvular or pericardial diseases were excluded. Patients with cerebrovascular and peripheral artery diseases or hepatic diseases, and patients with a history of cardiovascular or cerebrovascular events, smoking, and drug abuse were excluded. Patients with an established diagnosis of type 2 diabetes were also not included in this study to avoid the possible confounding effects of diabetes on study results. Renal disease was defined as the presence of serum creatinine >1.5 mg/dL, estimated glomerular filtration rate (eGFR) <60 mL/min, or albuminuria >300 mg/24 h. All the study participants followed a regular dietary habit with a salt intake of 140 mEq/day and potassium intake of 50–75 mEq/day. All patients had stable body weight for 6 months before the study.

Diagnosis of EH

EH was defined as BP of 140/90 mm Hg or more in three consecutive measurements (SBP and DBP). Secondary causes of hypertension were all excluded on the basis of clinical, laboratory, and imaging examinations.

Table 1. Anthropometric and clinical parameters in patients with autosomal polycystic kidney disease (ADPKD) and essential hypertension (EH)

	ADPKD (<i>n</i> = 41)	EH (<i>n</i> = 89)	<i>p</i>
Age, years	44±15	49±12	ns
Sex (M/F), <i>n</i>	21:20	49:40	ns
BMI	26±4	26±3	ns
WC, cm	92.6±13	94±15	ns
SBP, mm Hg	141±11	142±15	ns
DBP, mm Hg	87±9	88±10	ns
Creatinine, mg/dL	1.2±0.18	0.9±2	ns
eGFR, mL/min/1.73 m ²	75±15	83±19	ns
FG, mg/dL	92±11	90±15	ns
Na ⁺ , mEq/L	141±3	142±2	ns
K ⁺ , mEq/L	4.5±0.4	4.2±0.4	ns
Uric acid, mg/dL	5.6±1.3	5.3±1.5	ns
TC, mg/dL	183.8±27.7	200.51±37.98	ns
LDL-C, mg/dL	109.9±25.8	120.7±31.5	ns
HDL-C, mg/dL	55.9±15.2	55.9±15.4	ns
TGL, mg/dL	95.6±44.0	99.2±48.9	ns

Data are expressed as means ± standard deviations unless otherwise indicated. BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FG, fasting blood glucose; Na⁺, sodium; K⁺, potassium; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TGL, triglycerides; ns, not significant.

Epicardial Fat Thickness, LVM, and Diastolic Dysfunction

Each subject had a transthoracic 2D-guided M-mode echocardiogram using commercially available equipment (Siemens Sonoline G20). Standard parasternal and apical views were obtained with patients lying in the left lateral decubitus position. All echocardiograms were recorded and analyzed offline for EAT thickness quantification, according to the methodology previously described and validated by Iacobellis et al. [15, 16]. EAT was identified as the echo-free space between the outer wall of the myocardium and the visceral layer of the pericardium. EAT thickness was measured perpendicularly on the free wall of the right ventricle at end-systole in three cardiac cycles. Maximum EAT thickness was measured at the point on the free wall of the right ventricle along the midline of the ultrasound beam, perpendicular to the aortic annulus, which was used as an anatomic landmark for this view. The average value of three cardiac cycles from each echocardiographic view was considered. LVM and LVMi were calculated as previously described [18]. LVH was defined as LVMi of 115 g/m² or more for men and 95 g/m² or more for women [19]; diastolic dysfunction was defined according to the American Society of Echocardiography (ASE) guidelines [20].

Statistical Analysis

All data are expressed as mean ± standard deviation (±SD). Differences between means were assessed by the Student *t* test or the Mann-Whitney U test in nonnormally distributed data for two-sample comparison, or by one-way analysis of variance (ANOVA) applying the Fisher least significant difference post hoc test for multiple comparisons. χ^2 statistics were used to assess differences between categorical variables. Relationships between continuous variables were assessed calculating the Pearson correlation coefficient or the Spearman rank correlation coefficient when appropriate. Multiple linear regression analysis with the “Enter” method was used to identify the statistically significant predicting factors of LVMi. A multivariate logistic regression model was used to identify independent predictors of LVMi. Both of the analyses stated above were undertaken in the entire cohort of patients. We compared the predictive performance of EAT and LVMi as continuous variables using receiver operating characteristic (ROC) curves and by calculating the area under the curves. *p* values < 0.05 were taken as statistically significant. Statistical analysis and ROC curve analysis was performed using the Statistical Package for the Social Sciences (SPSS-PC version 24.0; SPSS Inc., Chicago, IL, USA).

Table 2. Echocardiographic parameters in patients with autosomal polycystic kidney disease (ADPKD) and essential hypertension (EH)

	ADPKD (n = 41)	EH (n = 89)	p
EAT, mm	9.2±2.9	7.8±1.6	<0.001
IVSd, mm	10±1.6	8.3±1.7	<0.001
LVPWd, mm	9.2±1.5	8.3±1.6	<0.001
LAVI, mL/m ²	24±3.9	20.7±4.1	<0.001
LVM, g	181.87±54.9	125.21±25.7	<0.001
LVMi, g/m ²	98.9±31.5	71.9±12.5	<0.001
LVEF, %	61.6±4.6	61.3±4.3	ns
Diastolic dysfunction grade I, n (%)	18 (43)	44 (49)	ns
LVH, n (%)	9 (22)	0	0.001

Data are expressed as means ± standard deviations unless otherwise indicated. EAT, epicardial adipose tissue; IVSd, end-diastolic interventricular septum; LVPWd, end-diastolic left ventricular posterior wall; LAVI, left atrium volume indexed for body surface area; LVM, left ventricle mass; LVMi, left ventricle mass indexed for body surface area; LVH, left ventricular hypertrophy.

Table 3. Multiple regression analysis comparing EAT against age, BMI, SBP, DBP, and WC in predicting LVMi

	β	95% CI inferior limit	95% CI superior limit	p
EAT	0.417	1.220	7.299	0.007
Age	−0.076	−0.749	0.436	0.596
BMI	0.178	−1.057	2.685	0.385
SBP	0.033	−0.435	0.547	0.819

The regression model was obtained after the exclusion of the variables DBP and WC because of a high variance inflation factor which indicates a high level of collinearity; after excluding the collinearity we achieved a regression model with $R^2 = 0.61$. EAT, epicardial adipose tissue; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; WC, waist circumference; LVMi, left ventricular mass indexed by body surface area.

Results

Characteristics of the study patients are summarized in Table 1. The two groups (ADPKD and EH) did not differ by age, sex distribution, BMI, waist circumference (WC), or BP values.

EAT was significantly higher in the ADPKD group compared to the EH group (9.2 ± 2.9 vs. 7.8 ± 1.6 mm, $p < 0.001$), as reported in Table 2. End-diastolic interventricular septum (IVSd), left ventricular posterior wall (LVPWd), left atrial volume indexed for body surface (LAVI), LVM, and LVMi measurements were also higher in the ADPKD group compared to controls ($p < 0.001$). None of the patients with EH had LVH, whereas 9 patients affected by ADPKD presented LVH ($p = 0.001$). No differences in the diastolic parameters were found between the groups (Table 2). In a linear regression model EAT was significantly correlated with LVM and LVMi in the ADPKD group ($r = 0.56$, $p = 0.005$ and $r = 0.424$, $p = 0.022$, respectively). EAT correlated better with both LVM and LVMi than with BMI ($r = -0.19$, $p = 0.25$) and WC ($r = -0.21$, $p = 0.35$). No correlation was found between EAT and LVM/LVMi in the EH group ($r = 0.08$, $p = 0.61$ and $r = 0.003$, $p = 0.98$, respectively). An additional positive correlation was observed between EAT and left atrium size ($r = 0.48$; $p < 0.001$). In a multiple regression

Table 4. Simple correlation matrix for all the continuous variables analyzed in patients with autosomal polycystic kidney disease (ADPKD) (*r*-value)

Age	BMI	WC	SBP	DBP	FG	UricAcid	eGFR	Cr	K ⁺	Na ⁺	TC	HDL-C	LDL-C	TGL	LAVI	LVM	LVMi	EAT
Age	1																	
BMI	0.33*	1																
WC	0.39	0.70**	1															
SBP	0.09	0.24	0.02	1														
DBP	0.30	0.26	0.29	0.62**	1													
FG	0.28	0.28	0.31	0.15	0.01	1												
Uric acid	0.43*	0.39*	0.37	0.18	0.13	0.30	1											
eGFR	-0.64**	-0.24	-0.17	-0.11	-0.12	-0.38*	-0.57**	1										
Cr	0.43**	0.13	0.20	0.09	0.00	0.56**	0.52**	-0.86**	1									
K ⁺	0.30	0.10	0.19	0.06	0.00	0.32*	0.26	-0.35*	0.39*	1								
Na ⁺	-0.30	-0.02	-0.12	0.03	0.14	0.07	-0.46**	0.23	-0.24	0.05	1							
TC	0.26	-0.04	0.00	0.07	0.35*	-0.05	0.27	-0.38*	0.29	0.14	-0.15	1						
HDL-C	0.00	0.02	-0.04	0.24	0.23	-0.22	-0.30	0.19	-0.22	0.21	0.22	0.17	1					
LDL-C	0.21	-0.03	0.07	-0.08	0.20	-0.03	0.37*	-0.38*	0.33	0.04	-0.26	-0.24	-0.43*	1				
TGL	0.20	-0.07	-0.17	0.08	0.15	0.31	0.30	-0.38*	0.30	-0.01	-0.08	0.24	0.17	0.40	1			
LAVI	-0.22	0.04	-0.10	0.16	0.30	-0.25	-0.07	0.08	-0.11	-0.06	0.21	-0.40	-0.03	0.04	0.49*	1		
LVM	-0.04	0.16	-0.19	0.12	0.06	0.27	-0.08	-0.01	-0.04	-0.07	0.10	-0.34	0.03	0.21	0.49*	0.75**	1	
LVMi	-0.03	-0.09	-0.41	0.34	0.07	0.19	0.03	-0.22	0.28	0.16	-0.03	0.08	0.40	0.06	0.21	0.75**	0.56**	1
EAT	0.09	-0.19	-0.21	0.01	0.19	0.17	-0.10	-0.07	0.09	-0.01	-0.05	-0.03	0.11	-0.02	0.48**	0.56**	0.42*	1

BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FG, fasting blood glucose; Na⁺, sodium; K⁺, potassium; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TGL, triglycerides; LAVI, left atrium volume indexed for body surface area; LVM, left ventricle mass; LVMi, left ventricle mass indexed for body surface area; EAT, epicardial adipose tissue. * *p* < 0.05; ** *p* < 0.01.

Fig. 1. ROC curve analysis compares the diagnostic performance of epicardial fat thickness (EAT; **a**) and left ventricular mass indexed by body surface area (LVMI; **b**) to discriminate autosomal dominant polycystic kidney disease. AUC for EAT = 0.639; AUC for LVMI = 0.774.

analysis model including LVMI as dependent variable and EAT, BMI, and WC as independent variables, EAT was the only statistically significant correlate of LVMI ($\beta = 0.59$, $p = 0.036$ vs. $\beta = 0.431$, $p = 0.347$ for BMI and $\beta = -0.563$, $p = 0.225$ for WC). Additional multiple regression analysis comparing EAT against BMI, SBP, and age showed EAT as the only parameter correlating with LVMI (Table 3). Table 4 shows the simple correlation matrix for the continuous variables analyzed. In Figure 1 we report the ROC curve analysis comparing the diagnostic performance of EAT and LVMI to discriminate ADPKD.

Discussion

Cardiovascular complications, including arterial hypertension and myocardial and valvular diseases, represent the major cause of morbidity and mortality in patients with ADPKD [4, 7, 21–24]. In this study we first demonstrated that (1) EAT was higher in patients with ADPKD and hypertension and normal renal function compared to patients with EH and (2) EAT was the strongest correlate of LVMI in patients with ADPKD irrespective of other traditional risk factors such as BMI, WC, and BP. EAT is a novel cardiometabolic risk factor that has been widely linked to LVH, subclinical atherosclerosis, and coronary artery disease [25, 26]. Data on EAT in patients with ADPKD are quite scarce and its relation with LVH was not explored before. However, ultrasound-measured EAT thickness was recently associated with carotid intima-media thickness, a well-accepted marker of subclinical atherosclerosis, in patients with ADPKD [27].

In light of the recently suggested independent role of obesity in the early development of ADPKD, we believe that our findings are of particular interest and novelty [12]. Obesity is a well-established independent risk factor for incident CKD, end-stage renal disease, and a decline in eGFR in the general population. The proinflammatory status commonly described in obesity is considered one of the factors implicated in the development of CKD and also

ADPKD, as recently suggested [12]. Remarkably, EAT is a highly inflammatory fat depot that plays a key pathogenic role in conditions that are not necessarily linked to obesity, such as coronary artery disease and CKD [28]. EAT has a unique proteasome and transcriptome highly enriched in genes encoding for inflammatory factors, as recently described by Iacobellis and colleagues [29]. Ultrasound-measured EAT thickness showed a correlation with circulating inflammatory markers [13, 14, 18]. Hence, based on the proinflammatory properties of EAT and the recently suggested role of obesity-related inflammation in ADPKD, it was somehow anticipated that EAT was higher in these subjects than in those with EH. Future studies exploring EAT inflammatory proteasome and transcriptome in subjects with ADPKD seem to be warranted.

ADPK is commonly associated with increased LVMI and LVH. The development of LVH in patients with ADPKD is likely multifactorial and includes activation of the renin-angiotensin-aldosterone system, increase of sympathetic nervous system activity, endothelial dysfunction, and left ventricular diastolic dysfunction [30]. Our study suggests that EAT can also play a pathogenic role in ADPKD-related LVH. In particular, we found a strong and independent correlation between EAT and LVMI, although ROC curve analysis showed a superiority of LVMI in predicting cardiovascular risk in ADPKD subjects. Although, no conclusion on the cause-effect of the EAT-LVM relation can be drawn from our study, some speculations on the mechanisms can be mentioned. EAT is thought to locally affect the heart throughout the paracrine or vasocrine secretion of proinflammatory and profibrotic cytokines. Other mechanical and biomolecular mechanisms could be also evoked to explain the effect of EAT on the heart. Increased EAT by adding mass to both ventricles increases the work of the heart and then leads to LVH. An infiltration of adipocytes from EAT to the myocardium has also been suggested [31].

Finally, we found and confirmed that the patients with ADPKD and arterial hypertension had higher LVMI left atrium size, IVSd, and LVPWd than EH patients [32]. The correlation between EAT and the left atrium was never detected before in ADPKD patients.

This finding could be of particular interest in light of the growing association between EAT and atrial fibrillation. Mechanical and biochemical factors have been suggested to play a role in this association, although the mechanisms are still unclear [33–35].

EAT thickness can be easily and accurately measured with standard ultrasound in a hypertension work-up, as previously shown by our group [36]. We believe that LVMI and EAT are not interchangeable. They provide two different sets of information that can complement each other. It is an advantage that both can be not invasively obtained. Although this study did not aim to evaluate the superiority of one measurable risk factor over another, EAT could also be a useful diagnostic tool for stratification of the cardiometabolic risk in patients with ADPKD [37].

Conclusions

This study provides novel findings that may have a clinical application for cardiovascular risk assessment in patients with ADPKD. Our data show that EAT is higher in patients with ADPKD than in EH patients with the same pressure load. Therefore, patients with ADPKD could benefit from an early evaluation of EAT.

Study Limitations

No conclusions on cause-effect mechanisms can be drawn from this study. Although our sample size had the power to detect statistically significant differences between the groups, larger and longitudinal studies are warranted. The use of antihypertensive medications could

influence the study results. Global longitudinal strain was not available and therefore could not allow a more accurate assessment of the left ventricular function. To address the potential issue of an operator-dependent procedure, all EAT measurements were performed by the same operator utilizing the same technique.

Statement of Ethics

The study was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study.

Disclosure Statement

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported. This research did not receive any specific grant from any funding agency in the public, commercial, or nonprofit sector.

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