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Renal volume and cardiovascular risk assessment in normotensive autosomal dominant polycystic kidney disease patients

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Abstract

Cardiovascular disease, closely related to an early appearance of hypertension, is the most common mortality cause among autosomal dominant polycystic kidney disease patients (ADPKD). The development of hypertension is related to an increase in renal volume. Whether the increasing in the renal volume before the onset of hypertension leads to a major cardiovascular risk in ADPKD patients remains unknown.

Observational and cross-sectional study of 62 normotensive ADPKD patients with normal renal function and a group of 28 healthy controls. Renal volume, blood pressure, and renal (urinary albumin excretion), blood vessels (carotid intima media thickness and carotid-femoral pulse wave velocity), and cardiac (left ventricular mass index and diastolic dysfunction parameters) asymptomatic organ damage were determined and were considered as continuous variables. Correlations between renal volume and the other parameters were studied in the ADPKD population, and results were compared with the control group. Blood pressure values and asymptomatic organ damage were used to assess the cardiovascular risk according to renal volume tertiles.

Even though in the normotensive range, ADPKD patients show higher blood pressure and major asymptomatic organ damage than healthy controls. Asymptomatic organ damage is not only related to blood pressure level but also to renal volume. Multivariate regression analysis shows that microalbuminuria is only associated with height adjusted renal volume (htTKV). An htTKV above 480 mL/m represents a 10 times higher prevalence of microalbuminuria (4.8% vs 50%, $P < 0.001$). Normotensive ADPKD patients from the 2nd tertile renal volume group (htTKV > 336 mL/m) show higher urinary albumin excretion, but the 3rd tertile htTKV (htTKV > 469 mL/m) group shows the worst cardiovascular risk profile.

Normotensive ADPKD patients show in the early stages of the disease with slight increase in renal volume, higher cardiovascular risk than healthy controls. An htTKV above 468 mL/m is associated with the greatest increase in cardiovascular risk of normotensive ADPKD patients with normal renal function. Early strategies to slow the progression of the cardiovascular risk of these patients might be beneficial in their long-term cardiovascular survival.

Abbreviations: ADPKD = autosomal dominant polycystic kidney disease, BP = blood pressure, cfPWV = carotid-femoral pulse wave velocity, cIMT = carotid intima-media thickness, 24 h ABPM = 24 hour ambulatory blood pressure monitoring, 24 h dABPM = 24 hour ambulatory diastolic blood pressure, 24 h sABPM = 24 hour ambulatory systolic blood pressure, htTKV = height adjusted total kidney volume, LVMI = left ventricular mass index, oBP = office blood pressure, oDBP = office diastolic blood pressure, oSBP = office systolic blood pressure, PC1 = polycystin 1, PC2 = polycystin 2, UAE = urinary albumin excretion.

Keywords: autosomal dominant polycystic kidney disease, cardiovascular risk, renal volume

1. Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common renal inherited disorder. It affects 1 of each 800 born alive and its autosomal dominant inheritance represents a transmission risk of 50% for each children of an affected individual. Mutations in *PKD1* and *PKD2* genes (encoding for polycystin 1 [PC1] and polycystin 2 [PC2]) lead to the formation and progressive expansion of kidney cysts which ultimately cause kidney enlargement and distortion of renal architecture, thus leading to kidney failure. Nowadays, ADPKD is the cause of renal replacement therapy for 10% of patients who need it.[1] Early in the course of the disease hypertension appears, with 60% of patients being diagnosed with hypertension before any decline in renal function is found.[1,2]

Even though the incidence of cardiovascular disease has dropped in the past decades,[3] thanks to a better control of blood pressure (BP) and to an expansive use of renin angiotensin system inhibitors,[4] it is still the most common mortality cause among ADPKD patients,[3] and it is closely linked to hypertension. Moreover, hypertension has been identified as one of the major determinants for disease progression, together with renal volume

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and type of mutation.[1] On the other hand, an early diagnose and treatment of at risk individuals with an active search and early treatment of hypertension even in childhood for the children of an affected parent has not unfortunately lead to a delay in the mean age of initiation renal replacement therapy.[5] The rise in BP in ADPKD is mainly linked to a higher activity of renin angiontensin system because its activation due to the compression of the expanding cysts over intrarenal vessels.[1,2] A prompt occurrence of asymptomatic organ damage is also related to the cardiovascular mortality of these patients.[6] Previously published studies have shown greater asymptomatic organ damage in normotensive ADPKD patients than in their healthy counterparts[7–10] and also in hypertensive ADPKD than in their essential hypertensive counterparts.[10–13] Renal volume plays a central role in the monitoring of disease progression from the earliest stages.[1] Renal volume has been shown to be larger in hypertensive ADPKD patients than in normotensives.[14] Renal volume and asymptomatic organ damage have been both linked to greater BP values.[11,12] However, the relationship between renal volume and asymptomatic organ damage is unknown in normotensive ADPKD patients. We performed a global cardiovascular risk assessment study to investigate whether renal volume influences the cardiovascular risk stratification in patients with ADPKD before the onset of hypertension.

2. Methods

With the hypothesis that in early stages of ADPKD disease patients show greater asymptomatic organ damage than control population, and that this is linked to renal volume and to an increase of BP, we performed this observational and cross-sectional study in normotensive ADPKD patients.

2.1. Study population

Patients were recruited from the outpatient clinic from 2 University tertiary-care hospitals, Fundació Puigvert and Hospital del Mar, both in Barcelona, Spain. ADPKD diagnostic was based in Pei ultrasonographic criteria,[15] if patients had a positive family history; otherwise patients with bilaterally enlarged kidneys with innumerable cysts in the absence of other findings to suggest a different cystic disease were considered to have ADPKD.[16]

Patients were included if they were not under antihypertensive treatment, and office blood pressure (oBP) and home blood pressure were within the normal range ($\leq$140/90 mm Hg for oBP and $\leq$135/85 mm Hg for home blood pressure) until the last medical visit before the inclusion and had normal renal function [chronic kidney disease-epidemiology collaboration (CKD-EPI) eGFR $>$ 60 mL/min/1.73 m^2]. A group of control subjects (healthy kidney live donors and healthy volunteers) matched by age, gender, and renal function were also studied in the same terms. The inclusion period lasted from July, 2011 to July, 2015.

Patients gave informed consent and protocol was conducted following Helsinki declaration.

2.2. Study protocol

Demographic data and classic cardiovascular risk factors were recorded.

Ultrasound renal volume in mL was measured using the ellipsoid formula.[14] Renal volume was assessed by one experienced radiologist in each center used to follow-up ADPKD patients with ultrasound, using a GeneralElectric LOGIC ultrasound (General Electric Medical Health, Waukesha, WI) with a 3.5 mHz probe. The same protocol was carefully followed by the 2 radiologists. With the patient in either decubitus supine or decubitus oblique position the probe was placed to determine the largest longitudinal axis; after that, the renal hilum was identified using color doppler if necessary and the probe was round 90° to determine transverse and antero-posterior diameter at hilum level in a cross-sectional image of the kidney.[17] Total renal volume resulted from the sum of right and left kidney volumes and was adjusted to height (in meters). Total renal volume adjusted to height (height adjusted total kidney volume [htTKV]) was expressed in mL/m.

oBP was determined with an OMRON M6 device (Omron Corporation, Kyoto, Japan) following the recommendations of the European Society of Hypertension guidelines.[18] A 24 hour ambulatory blood pressure monitoring (24 h ABPM) was performed with a Spacelabs 90207 (Spacelabs Inc., Richmond, WA), or Dyasis Integra (Equimed, Melbourne, Australia) device recording awake, asleep and 24 hour systolic and diastolic BP every 20 minutes during awake hours and every 30 minutes during asleep. Dipping status was also recorded as the night percentage of change of mean BP respect to the awake period. Results regarding BP values were expressed in mm Hg.

Renal (urinary albumin excretion [UAE]), cardiac (left ventricular mass index [LVMI] and diastolic dysfunction parameters), and blood vessels (carotid intima-media thickness [cIMT] and carotid-femoral pulse wave velocity [cfPWV]) asymptomatic organ damage were studied.

Urine albumin/creatinine ratio was expressed in mg/g and resulted from the mean of 3 consecutive 1st morning voids.

An echocardiography was performed with a Vivid 7 or 9 General Electrics ultrasound (General Electric Medical Health) or a Philips EPIQ ultrasound (Philips, Amsterdam, The Netherlands) by 1 cardiologist in each center and images were locally read. Echocardiography was performed following the consensus of the American and European Society of Cardiology.[19] LVMI (in g/m^2) was measured using Deveraux formula. Apical 4-chamber view with pulse doppler at mitral valve edge was used to determine E and A waves. E/A was calculated. Doppler tissue strain at lateral mitral annulus was used to determine Ea wave and E/Ea was calculated.

Vascular organ damage was evaluated through cfPWV with Sphygmocor (Atcor Medical, Australia) following the protocol: subjects were examined in supine position after 5 minutes of rest and sequential recordings of the pulses at the carotid and femoral sites via applanation tonometry were determined; these 2 signals were gated using the QRS complex from a simultaneously recorded electrocardiogram. The BP value entered into the SphygmoCor device for the calibration of the pulse waves was the referred as the oBP. The results of cfPWV were expressed in m/s.

cIMT was measured with an Esaote MyLab 25 ultrasound (Esaote, Firenze, Italy) device and a longitudinal high frequency (10 mHz) probe following the Manheim consensus recommendations.[20] With the patient in supine position and with 45° angle of the neck an overview of the structures with the probe placed in transverse axis was performed. Once the bifurcation was identified a 90° round of the probe permitted the identification of white and intima media lines in a longitudinal axis. Bilateral images of the posterior wall of common carotid, bifurcation, and internal carotid arteries were recorded and were further locally read using Siemens Syngo Arterial Health package. The mean of 6

Table 1

Demographic characteristics, blood pressure, and asymptomatic organ damage in autosomal dominant polycystic kidney disease patients and controls.

	ADPKD (n = 62)	Control group (n = 28)	*P*
Age, years	33.9 ± 8.5	32.3 ± 7.5	0.381
Gender (male/female), %	40.3/59.7	42.9/57.1	0.823
BMI, kg/m^2	23.4 ± 3.5	23.5 ± 3.9	0.876
Glucose, mg/dL	89.2 ± 9.2	89.0 ± 6.4	0.932
CT, mg/dL	175.7 ± 29.3	164.2 ± 32.6	0.100
LDL, mg/dL	101.1 ± 27.1	93.6 ± 26.8	0.229
HDL, mg/dL	61.3 ± 15.2	58.7 ± 13.3	0.437
Smoking habit, %	14.5	7.1	0.328
Family history CV event, %	0	3.6	0.138
eGFR, mL/min/1.73 m^2	105.1 ± 14.7	108.3 ± 10.2	0.305
oSBP, mm Hg	123.4 ± 13.0	116.8 ± 13.5	0.032
oDBP, mm Hg	76.8 ± 9.5	71.9 ± 8.3	0.021
24 h sABPM, mm Hg	117.0 ± 11.1	115.4 ± 9.4	0.523
24 h dABPM, mm Hg	76.1 ± 7.4	70.0 ± 6.0	<0.001
UAE, mg/g	10.32 [6.18–22.79]	4.65 [2.36–5.89]	<0.001
cfPWV, m/s	6.76 ± 1.05	6.83 ± 1.17	0.786
cIMT, mm	0.532 ± 0.088	0.473 ± 0.075	0.004
LVMI, g/m^2	90.9 ± 17.7	79.8 ± 17.8	0.008
E/A	1.65 ± 0.50	1.76 ± 0.61	0.391
E/Ea	5.21 ± 1.21	5.18 ± 1.24	0.929

ADPKD = autosomal dominant polycystic kidney disease, BMI = body mass index, cfPWV = carotid-femoral pulse wave velocity, cIMT = carotid intima-media thickness, CT = cholesterol, CV = cardiovascular, eGFR = estimated glomerular filtration rate, 24 h dABPM = 24 hour ambulatory diastolic blood pressure, HDL = high density lipoprotein, 24 h sABPM = 24 hour ambulatory systolic blood pressure, LDL = low density lipoprotein, LVMI = left ventricular mass index, oDBP = office diastolic blood pressure, oSBP = office systolic blood pressure, UAE = urinary albumin excretion.

measurements was recorded as the cIMT. Results are shown in mm.

Morning blood sample was drawn after 30 minutes of decubitus supine position. Basic biochemistry as standard practice was performed. Creatinine (mg/dL) was determined by an enzymatic colorimetric test using kinetic Jaffe Reaction (Cobas 8000-701, Roche). eGFR was calculated using CKD-EPI equation.[21] Aldosterone (pg/mL) and plasmatic renin activity (ng/mL/h) were determined by an immunoturbidimetric assay (LOINC: RIA). The study was approved by the IRB of Fundació Puigvert and Hospital del Mar.

2.3. Sample size and statistical analysis

In a 1:2 model, 30 controls and 60 ADPKD patients were needed to detect differences in diastolic blood pressure (dBP) of at least 4 mm Hg (standard deviation [SD] 6 mm Hg) between patients and controls with an 80% statistical power and an alpha error of 0.05 with a maximum of 10% lost determinations.

Mean ± SD and median (interquartile range [IQR]) were used to express the results for parametric and nonparametric variables, respectively, and categorical variables results are shown as percentage. Log transformation was applied to those variables not normally distributed. Student *t* test and ANOVA were used to compare means for normally distributed variables while for nonparametric, Mann–Whitney *U* or Kruskal–Wallis were applied for comparisons between 2 or more groups. Differences in categorical variables were studied with Chi-square test. Associations between variables were determined through Pearson correlation or Spearman coefficient. Significant correlations in the bivariate analysis were entered into a multivariate model, and results are expressed as odds ratio (OR) and 95% confidence interval (CI). With receiver operating characteristic curve (ROC) the renal volume cut off point with better sensitivity and specificity to predict asymptomatic organ damage was determined. Bonferroni correction for multiple comparisons was used to compare differences between different groups of ADPKD patients and controls. SPSS 21 (SPSS, Chicago, IL) was used to perform the statistical analysis. *P* values less than 0.05 were considered statistically significant.

3. Results

3.1. Study population characteristics

A total of 62 ADPKD patients and 28 healthy controls were studied. Mean and [IQR] htTKV in ADPKD group was 402 [303–567] mL/m. Renal diameter and renal volume showed a direct and strong correlation ($r = 0.840$, $P < 0.001$), and the mean renal diameter of our population was 13.8 ± 2.0 cm. The mean renal diameter of the control population was 10.2 ± 0.6 cm. The difference in mean renal diameter between ADPKD patients group and control population was statistically significant ($P < 0.001$).

No differences between patients and controls were found for age, gender, or eGFR neither for the classic cardiovascular risk factors (Table 1). Even though in the normal range, ADPKD patients showed higher office systolic (oSBP) and diastolic (oDBP) blood pressure and higher 24 hour ambulatory diastolic blood pressure (24 h dABPM) in the 24 h ABPM. ADPKD patients were also found to have higher UAE, cIMT, and LVMI than controls (Table 1).

Renal volume and function, BP, and asymptomatic organ damage correlations were studied.

htTKV did not show a statistical significant correlation with eGFR using CKD-EPI equation ($r = -0.225$; $P = 0.078$).

htTKV showed a direct correlation with oBP and better correlation with 24 h ABPM BP values. This volume–pressure correlation was not statistically significant with oSBP ($P = 0.097$) and marginally with 24 hour ambulatory systolic blood pressure (24 h sABPM) ($P = 0.031$). The correlation was especially

Table 2

Target renal and vascular organ damage and correlations with renal volume and blood pressure.

	Renal volume	oSBP	oDBP	24 h sABPM	24 h dABPM
Urinary albumin excretion	$r=0.539$	$r=0.162$	$r=0.355$	$r=0.199$	$r=0.308$
	$P<0.001$	$P=0.208$	$P=0.008$	$P=0.366$	$P=0.017$
Carotid-femoral pulse wave velocity	$r=0.365$	$r=0.346$	$r=0.533$	$r=0.425$	$r=0.473$
	$P=0.004$	$P=0.006$	$P=0.001$	$P=0.001$	$P<0.001$
Left ventricular mass index	$r=0.093$	$r=0.401$	$r=0.080$	$r=0.148$	$r=0.257$
	$P=0.471$	$P=0.001$	$P=0.538$	$P=0.259$	$P=0.048$
Carotid intima-media thickness	$r=0.043$	$r=0.190$	$r=0.127$	$r=-0.079$	$r=0.279$
	$P=0.745$	$P=0.146$	$P=0.335$	$P=0.554$	$P=0.034$

24 h dABPM = 24 hour ambulatory diastolic blood pressure, 24 h sABPM = 24 hour ambulatory systolic blood pressure, oDBP = office diastolic blood pressure, oSBP = office systolic blood pressure.

significant with diastolic BPs, both oDBP ($P=0.002$) and 24 h dABPM ($P<0.001$) (Fig. 1). htTKV showed a direct and statistical correlation with aldosterone (61.8 [41.0–111.1] pg/mL) and plasmatic renin activity (0.57 [0.30–0.91] ng/mL/h) ($r=0.273$; $P=0.044$ and $r=0.293$; $P=0.026$) but neither aldosterone ($r=-0.036$; $P=0.792$ for sABPM and $r=0.009$; $P=0.950$ for dABPM) nor plasmatic renin activity ($r=0.238$; $P=0.087$ for sABPM and $r=0.1446$; $P=0.297$ for dABPM) correlated with BP.

Table 2 shows correlations of asymptomatic organ damage with renal volume and BP. Cardiac asymptomatic organ damage was associated with BP. LVMI was positively correlated with oSBP ($r=0.401$; $P=0.001$) and with 24 h sABPM ($r=0.257$; $P=0.048$). E/A was correlated with oDBP ($r=-0.466$; $P<0.001$). cIMT was only weakly correlated with 24 h dABMP ($r=0.279$, $P=0.034$). UAE and cfPWV showed a strong direct correlation with renal volume (Table 2). UAE was directly correlated with DBP (office and 24 hour), but not with SBP. cfPWV showed a strong direct correlation with all BP measurements (Table 2).

The relationship between renal function and subclinical organ damage was also studied. Renal function showed an inverse correlation with cfPWV ($r=-0.411$; $P=0.001$), cIMT ($r=-0.291$; $P=0.024$), and UAE ($r=-0.264$; $P=0.038$).

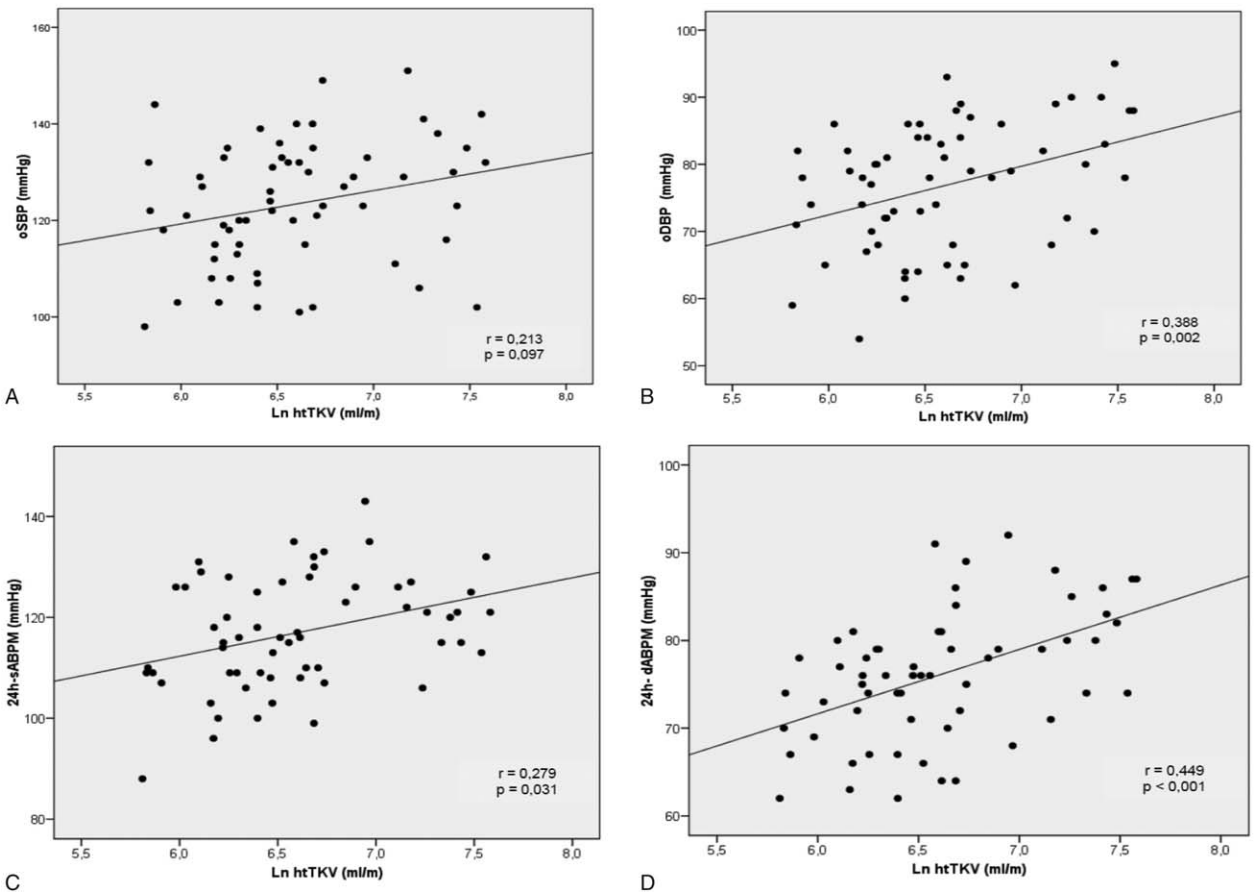

Figure 1. Correlations between htTKV and blood pressure. (A) oSBP and htTKV. (B) oDBP and htTKV. (C) 24 h sABPM and htTKV. (D) 24 h dABPM and htTKV. 24 h dABPM = 24 hour ambulatory diastolic blood pressure, 24 h sABPM = 24 hour ambulatory systolic blood pressure, htTKV = height adjusted total kidney volume, oDBP = office diastolic blood pressure, oSBP = office systolic blood pressure.

Table 3

Multivariate analysis for factors associated with the urinary albumin excretion or carotid-femoral pulse wave velocity. Independent variables: age, gender, BMI, blood pressure, eGFR CKD-EPI, and renal volume.

	β	95% CI	*P*
Urinary albumin excretion*			
Age, years	−0.039	−1.467; 1.108	0.781
Gender	−0.040	−22.392; 16.173	0.748
Body mass index, kg/m^2	0.190	−0.768; 4.918	0.149
24 h dABPM, mm Hg	0.024	−1.372; 1.624	0.867
htTKV, mL/m	0.450	0.029; 0.105	<0.001
eGFR CKD-EPI, mL/min/1.73 m^2	−0.141	−1.091; 0.350	0.307
Carotid-femoral pulse wave velocity†			
Age, years	0.004	−0.032; 0.033	0.976
Gender	0.184	−0.111; 0.877	0.126
Body mass index, kg/m^2	0.219	−0.010; 0.136	0.088
24 h dABPM, mm Hg	0.271	−0.001;0.076	0.053
htTKV, mL/m	0.241	0.000; 0.002	0.153
eGFR CKD-EPI, mL/min/1.73 m^2	−0.277	−0.038; −0.001	0.041

BMI = body mass index, CI = confidence interval, CKD-EPI = chronic kidney disease-epidemiology collaboration, 24 h dABPM = 24 hour ambulatory diastolic blood pressure, eGFR = estimated glomerular filtration rate, htTKV = height adjusted total kidney volume.

* r^2 for the model = 0.351

† r^2 for the model = 0.393.

A multivariate regression model which included those variables with significant correlation in bivariate analysis and those with relevant clinical significance was performed for both, UAE and cfPWV. In the UAE model, renal volume became the only variable independently associated with UAE (Table 3). However, the multivariate model for cfPWV showed that eGFR was the only variable independently associated with cfPWV (Table 3).

Twelve ADPKD (19.5%) patients showed microalbuminuria (UAE > 30 mg/g). A ROC curve was performed to determine the renal volume that could better predict the appearance of microalbuminuria. With an area under the curve of 0.840 (95% CI 0.696–0.981, $P < 0.001$) a total height adjusted renal volume ≥480 mL/m had a 50% sensitivity and 95.2% specificity to predict microalbuminuria (Fig. 2).

3.2. Height adjusted renal volume tertiles classification

Since renal volume was associated with asymptomatic organ damage and BP although the latter within normal values, ADPKD patients were divided into renal volume tertiles for further analysis. The thresholds for each renal volume tertile group were: <336 (1st tertile group), 336 to 468 (2nd tertile group), and >468 mL/m (3rd tertile group). Tertiles were compared in terms of BP and asymptomatic organ damage with the control group and among them using Bonferroni correction for multiple comparisons (Table 4). The 1st tertile group did not show any significant difference in cardiovascular risk assessment evaluated by BP and asymptomatic organ damage when compared with the control group. Second tertile group showed a significant increase in 24 h dABPM and in UAE when compared to control group. These differences became more evident in 3rd tertile group, where differences in oBP were also detected and a greater difference in 24 h dABPM as well as in UAE was noticed. Third tertile group also showed significant differences in BP and UAE when compared with 1st and 2nd tertile groups. This results show how 3rd tertile group with an htTKV above 468 mL/m showed a significantly worse cardiovascular profile than controls but also than ADPKD patients with an htTKV below the threshold of 468 mL/m. No differences in renal function were found among renal volume tertiles.

4. Discussion

Renal volume clearly correlates with BP in ADPKD patients when hypertension is already diagnosed: hypertensive ADPKD patients have constantly shown larger kidney volumes than those with normotension.[6,14] Previous studies[11,12] failed to demonstrate higher renal volumes in high-normal BP ADPKD patients when

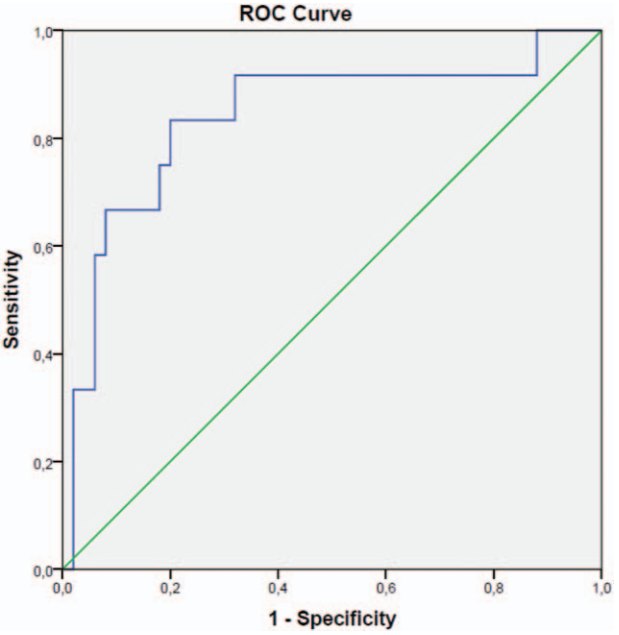

Figure 2. ROC curve for microalbuminuria and height adjusted renal volume. AUC 0.840 (95% CI 0.696–0.981, $P < 0.001$). AUC = area under ROC curve, CI = confidence interval, ROC = receiver operating characteristic curve.

Table 4

Blood pressure and renal, vascular, and cardiac organ damage in ADPKD patients divided into tertiles of height adjusted renal volume.

	Healthy controls (n = 28)	First tertile of renal volume (n = 20) <336 mL	Second tertile of renal volume (n = 21) 336–468 mL	Third tertile of renal volume (n = 21) >468 mL
oSBP, mm Hg	116.8 ± 13.5	118.3 ± 12.2	124.1 ± 11.6	127.5 ± 14.0[*]
oDBP, mm Hg	71.9 ± 8.3	72.9 ± 8.4	76.5 ± 9.5	80.8 ± 9.3[*,‡]
24 h sABPM, mm Hg	115.4 ± 9.4	113.1 ± 11.5	115.7 ± 10.7	121.9 ± 10.4
24 h dABPM, mm Hg	70.0 ± 6.0	72.7 ± 5.6	74.9 ± 7.4[*]	80.2 ± 7.3[†,‡]
cfPWV, m/s	6.8 ± 1.2	6.4 ± 0.7	6.6 ± 0.9	7.3 ± 1.2
cIMT, mm	0.473 ± 0.075	0.534 ± 0.104	0.520 ± 0.051	0.542 ± 0.103
UAE, mg/g	4.6 [2.4–5.9]	7.3 [3.6–14.7]	7.9 [5.9–14.5][*]	22.7 [9.2–70.0][†,‡,§]
LVMI, g/m^2	79.8 ± 17.8	84.2 ± 13.8	94.7 ± 18.1	93.4 ± 19.4
eGFR (CKD-EPI creatinine), mL/min/1–73 m^2	108.3 ± 10.2	106.9 ± 15.1	106.7 ± 11.4	101.8 ± 17.2

ADPKD = autosomal dominant polycystic kidney disease, cfPWV = carotid-femoral pulse wave velocity, cIMT = carotid intima-media thickness, CKD-EPI = chronic kidney disease-epidemiology collaboration, eGFR = estimated glomerular filtration rate, 24 h dABPM = 24 hour ambulatory diastolic blood pressure, 24 h sABPM = 24 hour ambulatory systolic blood pressure, LVMI = left ventricular mass index, oDBP = office diastolic blood pressure, oSBP = office systolic blood pressure, UAE = urinary albumin excretion.

[*] $P < 0.05$ vs control .

[†] $P < 0.001$ vs control.

[‡] $P < 0.05$ 3rd tertile versus 1st tertile.

[§] $P < 0.05$ 3rd tertile versus 2nd tertile.

they were compared with strict normotensives. The 24 h ABPM permits a better classification of the BP status compared to oBP, and it may have contributed to the detection of significant renal volume differences among groups even though BP was within the normal range. Our study performed in normotensive ADPKD patients shows a straight correlation between renal volume and BP values from the very early stages of the disease with normal renal function. The rise in BP in ADPKD is mainly linked to a higher activity of renin angiontensin system because its activation due to the compression of the expanding cysts over intrarenal vessels.[1,2] In this study, we have found a positive correlation between renal volume and plasma renin activity and aldosterone levels, even though neither of them correlated with BP levels. This could be hypothesized as an early increase of renin angiotensin system activity linked to the enlargement of renal volume even though significant increases in BP are not yet noticed. Greater asymptomatic organ damage in normotensive ADPKD patients when compared to healthy controls has been shown before,[7–11,14,22] but the relationship between renal volume and asymptomatic organ damage has not been evaluated. We have shown that asymptomatic organ damage is not only associated with BP but also with kidney enlargement. ADPKD patients with slight increases in htTKV (htTKV < 336 mL/m) do not seem to have a worse cardiovascular risk profile than controls. Even though, modest increase of renal volume (2nd tertile htTKV) seems to be associated with significant increases in UAE and dBP when it is evaluated by 24 h ABPM. BP increases parallel to renal volume tertiles, thus showing an association between renal volume and BP even in normotension range patients.

The increase in UAE seems to be independently associated with renal volume. Higher UAE when compared to controls at early stages of the disease with modest htTKV enlargement and normotension could be related to the endothelial dysfunction previously shown in ADPKD patients.[6,23–27] PC1 and PC2 are localized in the primary cilia of nuclear cells, also in the vascular endothelial cells. The optimal function of PC1–PC2 complex is essential for the increase in calcium cytoplasm concentrations which in turn lead to the release of nitric oxide that drives to vasodilation.[27] Dysfunction of the PC1–PC2 complex in ADPKD patients might lead to endothelial dysfunction, UAE being its marker.

Both asymptomatic organ damage and BP values increased with renal volume progression among 2 last tertile groups. The results of this study seem to point to a cut off htTKV of 468 mL/m as the threshold where a clear worsening of the cardiovascular profile starts in normotensive ADPKD patients with normal renal function, even though minor changes in the cardiovascular profile can be already noticed at earlier stages, with htTKV above 336 mL/m. To our knowledge this is the 1st study analyzing global cardiovascular profile (in terms of BP including 24 h ABPM and renal, vascular, and cardiac asymptomatic organ damage) in an early stage of the disease. Moreover, this is apparently the 1st study to show a link between the cardiovascular profile in normotensive ADPKD and the renal volume.

The study has certain limitations: this is a cross-sectional observational study, therefore, we can only describe associations but not causality relationships; the number of patients included is limited; and renal volume was evaluated by ultrasonography. Nowadays, magnetic resonance is the gold standard technique to evaluate renal volume in ADPKD patients. It has been used in all large prospective clinical trials[22,28–33] where renal volume has been pointed as the primary endpoint of the study and changes in renal volume through time must have been carefully evaluated. Recent publications have demonstrated, however, that even though ultrasonographic measurement of renal volume is not appropriate to evaluate kidney volume progression[34] it can be an appropriate method for risk stratification purposes. It is important to point out that ultrasound renal volume and magnetic resonance renal volume correlate well when kidney size is still relatively preserved.[26,34] Indeed, it has also been shown that renal ultrasonographic diameter is a good marker of progression to chronic kidney disease[17] and that more importantly, correlation between renal volume and renal diameter both evaluated by ultrasound is extremely good when renal diameter is less than 17 cm.[17]

In our study, the correlation between renal diameter and renal volume was strong, the mean renal diameter of our population was clearly below 17 cm, and we used kidney volume as a stratification risk factor and not to evaluate volume progression. Therefore, we consider that evaluation of renal volume by ultrasound in this study is sufficient for our purpose. In conclusion, ADPKD patients with normal renal function and normal BP show greater asymptomatic organ damage at early stages with only modest kidney enlargement (renal volume above

336 mL/m) compared with controls despite no differences in BP. Current guidelines in the management of hypertension in ADPKD[16] do not recommend to start antihypertensive treatment before the onset of hypertension and a BP target below 140/90 mm Hg is recommended. Data from the HALT trial[28] show that a very low BP target (<110/75 mm Hg) is not only safe in young ADPKD patients with hypertension but it is also beneficial in slowing kidney enlargement and the progression in renal and cardiac asymptomatic organ damage, which essentially means a better cardiovascular profile.

Adding the results of this study to the evidence of the HALT trial, we could hypothesize that an early treatment of BP (even though in the high-normal range) when a renal volume of 336 mL/m (but certainly when it is above 468 mL/m) is achieved, may prevent a greater worsening of the cardiovascular profile. htTKV above 468 mL/m seems to be a cut off volume pointing toward a deterioration in the cardiovascular profile of ADPKD patients in very early stages. Future studies should evaluate the possible beneficial effects of starting therapeutic strategies to slow the worsening in the cardiovascular profile of ADPKD patients before the onset of hypertension.

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