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Renal, cardiovascular and hormonal characteristics of young adults with autosomal dominant polycystic kidney disease

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Renal, cardiovascular and hormonal characteristics of young adults with autosomal dominant polycystic kidney disease. We studied young adults with autosomal dominant polycystic kidney disease (ADPKD) to determine the characteristics that precede renal impairment. Nineteen affected (A) and 20 unaffected (U) offspring from families with ADPKD showed no significant differences in basal glomerular filtration rate (A: mean 97, SD 19; U: 100, SD 23 ml/min/1.73 m^2) or renal functional reserve, but effective renal plasma flow was significantly lower in affected offspring (A: 532, SD 86; U: 605, SD 118 ml/min/1.73 m^2, $P < 0.01$). Plasma renin activity [A: median 26 (95% CI: 15 to 37); U: 14 (11 to 27) μU/ml, $P < 0.05$, one-tailed test] and aldosterone [A: 2.5 (2.0 to 3.0), U: 1.0 (1.5 to 2.0) μg/100 ml, $P < 0.04$, one-tailed test] were increased in affected offspring despite the higher systolic blood pressure (A: mean 123, SD 5; U: 115, SD 3 mm Hg, $P < 0.02$) and significant expansion of total exchangeable sodium (A: 40.8, SD 2.3; U: 38.0, SD 3.5 mmol/kg, $P < 0.01$). The ouabain-sensitive component of red cell sodium efflux was less in affected offspring (A: 0.258; SD 0.040; U: 0.288, SD 0.042 hr^{-1}, $P < 0.04$) and in both groups was correlated inversely with total exchangeable sodium. Echocardiography revealed no difference in left ventricular mass index nor prevalence of mitral valve prolapse. Potential cyst growth factors such as the glucocorticoids and somatomedin C were similar in both affected and unaffected groups. Reduced renal blood flow, renin system activation and increased body sodium precede the major clinical manifestations of ADPKD and may play a central role in the genesis of high blood pressure, and possibly also cyst growth, both of which are important determinants of the clinical course of ADPKD.

Autosomal dominant polycystic kidney disease (ADPKD) is a relatively common genetic disorder characterized predominantly by the growth of renal cysts, resulting in the appearance of clinical symptoms in the fourth or fifth decades of life [1, 2]. End-stage renal failure is a common, but not inevitable consequence of ADPKD, and some studies suggest that the prognosis of the condition may be improving [3, 4]. If this observation is correct, then it may reflect an alteration in environmental factors such as diet or the early detection of disease and prevention of complications such as high blood pressure, that modulate the impact of the primary genetic abnormality. The characterisation of abnormalities at a stage before clinical manifestations are obvious may provide an understanding of the disease process and form the basis for planning logical and effective strategies to prevent or ameliorate the development of renal failure in ADPKD.

Cyst growth, resulting in nephron obstruction and compression [5] has long been accepted as a specific major determinant of renal failure in ADPKD. Studies of renal disease in general have emphasized that glomerular hyperfiltration [6] and high blood pressure [7] may cause non-specific acceleration of kidney damage. At present, studies of glomerular filtration reserve in ADPKD have received little attention [8]. In contrast, high blood pressure has received considerable attention [1, 2, 9–15], although attempts to understand the pathogenesis of high blood pressure in ADPKD have often been confounded by important differences in age, blood pressure, renal function and family history.

In this study we have attempted to minimize the effects of common confounders by careful sampling, so as to focus on early and possibly subtle abnormalities likely to be of relevance to the development and progression of renal failure, in particular, glomerular hyperfiltration, high blood pressure and the growth of cysts.

Methods

Subject selection and genetics

Families were identified from the Scottish registry of families ascertained on the basis of one or more family members diagnosed as suffering ADPKD. This registry contains 41 family pedigrees with a total of 392 offspring and serves as a means of identifying offspring at risk, providing routine testing for ADPKD, including renal ultrasound examination and genetic screening, and supplying information and educational material for family members.

Offspring were eligible for participation if, at the time of the study, they were between the ages of 16 and 35 years of age, irrespective of serum creatinine or blood pressure. Subjects were excluded if they suffered chronic illness (other than ADPKD), were taking prescribed medication (excluding the oral contraceptive pill) or were pregnant. These criteria resulted in exclusion of only one eligible subject (who was affected) from the families taking part because he had recently commenced antihypertensive treatment.

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Offspring from 21 separate families took part in the study with between one and five siblings (average 2.15) from each. Diagnosis of affected or unaffected status was based upon ultrasound findings. Ultrasonic criteria of the affected state were two or more transonic cysts (>0.5 cm in diameter) with well-defined back walls and some acoustic enhancement in one kidney, and a single cyst in the other.

To complement ultrasound examination, genotypic studies were performed with a probe for the 3'HVR region (the D16S85 locus near alpha globin on the short arm of chromosome 16) to assess linkage to *PKD1* [16]. Genetic risks were obtained using the MLINK sub-routine of the program LINKAGE [17]. For these calculations it was assumed that heterozygous individuals had probabilities of 0.22, 0.66, 0.86, 0.95 and 1.00 of clinical detection in the age groups 0 to 9, 10 to 19, 20 to 29, 30 to 39 and 40+, respectively [18].

Pedigree studies revealed that all affected offspring came from families showing linkage to *PKD1*, although two clinically-affected offspring were considered genetic recombinants because of low calculated genetic risks. Disagreement between clinical and genotypic diagnoses was relatively common in three families that took part in this study. Careful review of clinical data after completion of the study revealed that one of these families (PK33) in fact did not have ADPKD, and the two unaffected offspring from this family have been excluded from all analyses. The two other families (PK49, PK53) from which clinically unaffected offspring had been recruited did appear to have ADPKD indistinguishable phenotypically from other participating families.

Clinical protocol

Offspring were invited to participate in the physiological studies by one investigator (AM) who was aware of their diagnosis. Volunteers were asked specifically not to reveal their diagnosis to the other investigators so as to avoid any potential bias during the study. Selection was designed to provide equal numbers of affected and unaffected offspring; subjects were matched for age and sex.

Subjects were admitted to hospital on their normal diet for a period of two days. Written informed consent was obtained from all volunteers, and the studies were approved by the Western Infirmary Ethics Committee.

On the first day, all subjects had echocardiographic examinations using a Hewlett-Packard Ultrasound Unit with a 2.5 MHz transducer. M-mode recordings were made according to the convention of the American Society of Echocardiography [19], with the use of two-dimensional images to direct the M-mode sweep. These data were used to assess left ventricular posterior wall thickness, interventricular septal thickness and left ventricular diastolic diameter, measured distal to the tips of the mitral valve leaflets at the peak of the R-wave on the electrocardiogram. Measurements were made over three consecutive cardiac cycles, and mean values were calculated. Left ventricular mass was calculated by the cube formula using the Penn convention [20], and corrected for body surface area to yield the left ventricular mass index. The reproducibility of echocardiographic measurements in a single subject was calculated by measuring left ventricular mass on ten occasions in the same healthy volunteer. The coefficient of variation was 2.9%. Late systolic posterior displacement of the mitral valve echo beyond an imaginary line joining the C and D portions of the mitral valve echo was measured, and a displacement of greater than 2.0 mm was taken to suggest mitral valve prolapse [21].

Two-dimensional echocardiographic studies were also performed from the parasternal long-axis and apical four-chamber views. These studies were recorded on tape and reviewed subsequently for evidence of systolic "billowing" of the mitral valve leaflets into the left atrium. The tapes were read independently by two experienced echocardiographers who, in the event of disagreement reached a consensus following joint review of the study.

Subjects were fasted from 9 p.m. on the first day and remained so, other than water during clearance measurements, until the high-protein load at 12:30 p.m. on the following day. On the morning of the second day subjects were woken at 7 a.m. and allowed out of bed briefly. Intravenous cannulae were inserted into the right and left cubital veins. A blood pressure cuff was then attached to the right arm, and blood pressure and pulse rate were measured automatically every half an hour for six hours, by a Copal UA251 Auto-Inflation Digital Sphygmomanometer (Takeda Medical Corporation, Japan) while the subjects remained supine or semi-supine in bed. At the end of each of these half-hour periods, three readings were taken and averaged to calculate the systolic and diastolic blood pressure and pulse rate for each period.

After the insertion of intravenous cannulae, the subjects remained fully supine for 45 minutes, at the end of which time blood was taken for biochemical, hematological and hormonal tests, including plasma renin activity [22], atrial natriuretic peptide [23], aldosterone [24], deoxycortisol and deoxycorticosterone [25], and cortisol and 18-hydroxycorticosterone which were measured by direct radioimmunoassays following partial purification by paper chromatography. The 18-hydroxycorticosterone antiserum was from Dr. H. Belkien (Klinikum Sleglitz, Berlin, Germany). Somatomedin-C was measured using a radioimmunoassay kit (Nichols Institute Diagnostics, San Juan, Capistrano, California, USA).

The dilutions of ^{24}Na and ^{3}H given about 19 hours before the first blood sample were used to estimate, after correction for overnight urinary isotope excretion, total exchangeable sodium and body water, respectively [26–29]. To ensure adequate tracer equilibration, dilution was remeasured in a second sample taken one hour later. The two estimates of total exchangeable sodium and body water were not significantly different, and individual values were calculated from the average of the two. Identical conclusions were drawn from comparisons of affected and unaffected offspring when exchangeable sodium was expressed either per kilogram of body weight, or as a percentage of the expected normal value for a given surface area [28], and for simplicity only the former data are presented. Plasma volume was estimated from the dilution of a injected bolus of ^{125}I-labelled albumin [29] and also expressed per kilogram body weight.

Intraerythrocytic electrolyte concentrations and the total, ouabain- and frusemide-sensitive transmembrane sodium efflux constants were also measured. For sodium efflux measurements a 6 ml aliquot of each subject's red blood cells (RBC) was loaded with radiosodium by incubating with 25 μCi ^{24}Na in 12 ml tissue culture fluid (TC199, Gibco Ltd, Paisley, Scotland, UK) for four hours. Extracellular ^{24}Na contamination was

removed by three washes in cold TC199. Red blood cells (1 ml) were then resuspended in 1 ml TC199, with or without ouabain (10^{-4} M) or frusemide (10^{-4} M) and incubated at 37°C. This mixture was sampled in triplicate at 8, 16 and 24 minutes after addition of RBC. Each sample was centrifuged through oil at 13,000 g for 20 seconds, and immediately frozen in a mixture of methanol and solid carbon dioxide. The radioactivity of the red cell button and the extracellular fluid (ECF) were measured separately, and the efflux rate constant (ERC) was calculated from the natural logarithm of the radioactivity of the RBC (as a percentage of RBC + ECF radioactivity) plotted against time. Red cell sodium and potassium concentrations were measured in RBC after triple washing in cold (4°C) isotonic choline chloride and lysis in 15 mmol lithium chloride at known hematocrit. Co-efficients of variation (3 estimates within 3 months in each of 12 normal subjects) were 4.8% for ERC, 5.4% for ouabain-sensitive ERC and 4.0% for red cell sodium and potassium concentrations.

Following initial blood sampling, standard constant infusion clearance techniques were used to estimate glomerular filtration rate and renal plasma flow [30], using inulin (50 g/50 ml, Laevosan-Gesellschaft mbh, Linz, Austria) and PAH (2 g/10 ml, MSD, West Point, Pennsylvania, USA), respectively. After a loading dose of inulin (30 g/70 kg) and PAH (0.8 g/70 kg), half of which was given as a rapid bolus injection and the rest over about ten minutes, a constant infusion of inulin (0.96 g/hr) and PAH (0.48 g/hr) was commenced. Each subject was given 5 ml/kg of water to drink at the time of the loading bolus, followed by 1 ml/kg every half hour. One and a half hours were allowed to ensure stable levels before estimating basal clearances based on the known rate of infusion [30], and the plasma levels of inulin [31] and PAH [32]. Three consecutive half-hour estimates of glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were averaged to provide basal control readings for each individual.

The calculations used to derive ERPF assumed an extraction ratio for PAH of 95%, and although we did not measure PAH extraction ratio in this study, previous work [33] suggested that in glomerular or tubulo-interstitial disease, the extraction ratio does not change until PAH clearance rates are significantly reduced (less than about half normal). Based on the observed values of PAH clearance (see below) it seemed that PAH extraction was a valid estimate of ERPF in this study.

To measure renal functional reserve and provide an indirect assessment of glomerular hyperfiltration [34], at the end of the control period all subjects were given a protein load (60 g/70 kg) in the form of a drink of milk and soybean extract. Blood pressure, pulse, GFR and ERPF were measured every half an hour for a further two hours, until the end of the study.

Statistical analysis

Comparisons of variables between the two offspring groups were made using CIA [35] and SPSS/PC+ [36], and where possible the 95% confidence intervals for the differences between groups have been provided. The chi-square test was used to compare sex distribution and the use of the oral contraceptive pill. Tests of statistical hypotheses were generally made using two-tailed unpaired *t*-tests, but the variables plasma renin activity, atrial natriuretic peptide, corticosteroids and somatomedin C did not show normal distribution and were compared using the nonparametric Mann-Whitney U test. Standard regression analyses were used to analyze the relationship between total exchangeable sodium and ouabain-sensitive erythrocytic sodium efflux. Repeated measures analysis of variance (MANOVA) was used to test for differences in systolic and diastolic blood pressure, pulse rate and the absolute level and change in GFR and ERPF after the protein load, and whether the change in renal function or hemodynamics after the protein load differed between affected and unaffected offspring.

Table 1. Baseline characteristics of unaffected and affected offspring from families with ADPKD

	Unaffected	Affected	95% CI
Number	20	19	
Age *years*	26 (5)	24 (5)	−2 to 5
Male:female ratio	10:10	9:10	−0.29 to 0.34
Oral contraceptive use	4	2	−0.19 to 0.59
Weight *kg*	68.8 (14.2)	66.2 (10.8)	−10.8 to 5.6
Height *m*	168 (10)	172 (8)	−1.6 to 10.2
Body surface area m^2	1.77 (0.21)	1.78 (0.16)	−0.11 to 0.13

Results are mean (SD). The 95% CI is, for sex ratio and oral contraceptive use, the 95% confidence interval for the difference between proportions, and for all other variables, the 95% confidence interval for the difference between means.

Results

The twenty unaffected and 19 affected offspring were matched in terms of sex, age, anthropometric measurements, and use of the oral contraceptive pill (Table 1).

The results of routine hematological and biochemical screening were not significantly different in affected and unaffected offspring. In particular, hemoglobin, hematocrit, plasma electrolytes, urea, urate and liver function indices were similar in the two groups (results not shown). Serum creatinine was the same in both groups: unaffected, mean 80 μmol/liter (range 59 to 107); affected, mean 80 μmol/liter (range 62 to 99).

Renal function and hemodynamics

Measurements of renal function showed that average basal glomerular filtration rates were the same in the two groups (Table 2). However, there was a substantial difference in renal plasma flow; with average levels in affected offspring some 12% lower than unaffected (Table 2).

Following the acute oral protein load, GFR rose significantly by about 10 to 15% in both affected and unaffected offspring (Fig. 1A: MANOVA test of change in GFR with time: $F_{4,34} = 13.8$, $P < 0.001$). Although the GFR of unaffected individuals remained slightly greater than that of affected offspring, the overall difference was not significant throughout the study (MANOVA test of GFR according to diagnosis: $F_{1,37} = 0.57$, $P = 0.454$). The analysis also revealed that the rise in GFR after the protein was similar in affected and unaffected subjects (MANOVA test of interaction between diagnosis and change in GFR with time: $F_{4,34} = 1.07$, $P = 0.385$).

Renal plasma flow also increased following the protein load (Fig. 1B: MANOVA test of change in ERPF with time: $F_{4,34} = 5.5$, $P = 0.002$). As seen during the control period, renal plasma flow remained significantly lower in the affected offspring following the protein load (MANOVA test of overall difference in ERPF according to diagnosis: $F_{1,37} = 11.1$, $P = 0.002$).

Table 2. Renal, fluid volume and electrolytic characteristics of unaffected and affected offspring from families with ADPKD

	Unaffected	Affected	95% CI
Glomerular filtration rate *ml/min/1.73 m²*	100 (23)	97 (19)	−18 to 10
Effective renal plasma flow *ml/min/1.73 m²*	605 (118)	532 (86)[b]	−140 to −5
Exchangeable sodium *mmol/kg*	38.0 (3.5)	40.8 (2.3)[b]	0.9 to 4.8
Total body water *ml/kg*	573 (71)	594 (64)	−22 to 62
Plasma volume *ml/kg*	39.6 (8.5)	41.7 (4.6)	−2.4 to 6.6
Red cell sodium concentration *mmol/liter*	5.7 (1.7)	5.2 (0.9)	−1.3 to 0.4
Red cell potassium concentration *mmol/liter*	104 (5)	100 (7)	−7 to 1
ERC_t hr^{-1}	0.447 (0.062)	0.412 (0.065)	−0.076 to 0.006
ERC_{os} hr^{-1}	0.288 (0.042)	0.258 (0.040)[a]	−0.056 to −0.002
ERC_{fs} hr^{-1}	0.019 (0.009)	0.020 (0.011)	−0.008 to 0.006

Results are mean (SD). ERC_t, ERC_{os} and ERC_{fs} are the total, ouabain-sensitive and frusemide-sensitive components of the erythrocytic sodium efflux rate constant. The 95% CI is the 95% confidence interval for the difference between means.
[a] $P < 0.05$, [b] $P < 0.005$ compared to unaffected

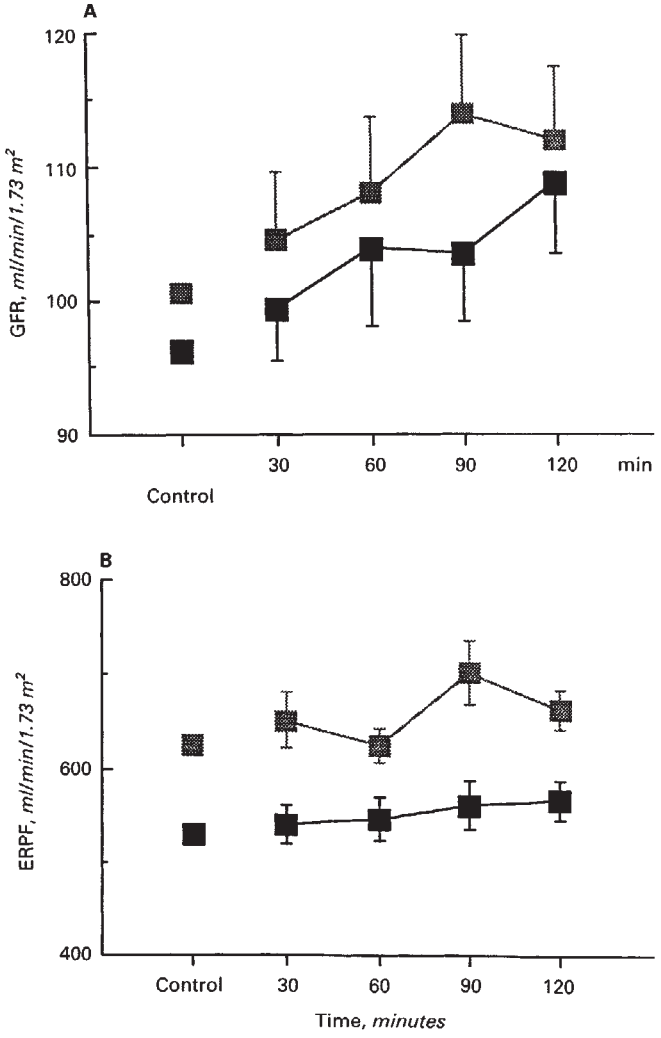

Fig. 1. **(A)** *Glomerular filtration rate (GFR) and* **(B)** *effective renal plasma flow (ERPF) in affected (■) and unaffected (□) offspring before (control) and in the 2 hours after an acute oral protein load.* Data are presented as mean with SEM.

However, no important differences in the change of renal plasma flow after the protein load were detected between the two groups (MANOVA test of interaction between diagnosis and change in ERPF with time: $F_{4,34} = 1.15$, $P = 0.350$).

Total exchangeable sodium was significantly elevated in affected compared with unaffected offspring (Table 2). Average total body water and plasma volume were also greater in affected offspring, but the confidence intervals for the differences were relatively wide and included zero. Interestingly, the average 2.8 mmol/kg difference in total exchangeable sodium would be equivalent to an extra 20 ml/kg of extracellular water (at the measured extracellular sodium concentration of 140 mmol/liter), which coincides well with the observed difference in total body water, suggesting expansion of the extracellular space.

Measurements of intracellular sodium and potassium and transmembrane sodium efflux (Table 2) showed that although erythrocytic intracellular electrolyte levels were similar, total efflux rate constants for sodium were greater in unaffected offspring, and this appeared to result from lower rates of ouabain-sensitive efflux in red cells of affected offspring.

Of particular interest was the observed relationship between total exchangeable sodium and the ouabain-sensitive sodium efflux rate constant, as shown in Figure 2. A negative correlation between these two variables was observed in each group of offspring, and the slopes (unaffected: −29.4, SE 18.2; affected: −20.6, SE 13.2) and intercepts (unaffected: 46.5, SE 5.3; affected: 46.2, SE 3.5) of the two regression lines were not significantly different. When considered as a whole the regression of total exchangeable sodium (y) on ouabain-sensitive efflux rate constant (x) was described by the formula: $y = -33.6x + 48.6$, $r = -0.445$, ($F_{1,37} = 9.11$, $P = 0.005$).

Cardiovascular characteristics

The average systolic blood pressure was higher in affected (mean 123, SD 13 mm Hg) than unaffected (115, SD 11 mm Hg) offspring (95% confidence interval for difference = 1 to 15 mm Hg, $P < 0.02$). Diastolic pressure levels tended to be higher in affected (74, SD 9 mm Hg) than unaffected (71, SD 8 mm Hg) offspring, but the confidence interval for the difference was wide (95% CI: −3 to 9 mm Hg). The higher systolic blood pressure of affected offspring was associated with a lower pulse rate compared to unaffected individuals (60, SD 9 vs. 65, SD 7 min^{-1}, 95% CI: −10 to 0, $P < 0.02$).

M-mode echocardiographic estimates of left ventricular mass index did not reveal any significant difference between affected (98, SD 28 g/m^2) and unaffected (92, SD 21 g/m^2) individuals (95% CI: −12 to 23). Similarly, measurements of the degree of late systolic prolapse of the mitral valve leaflets behind the C-D line

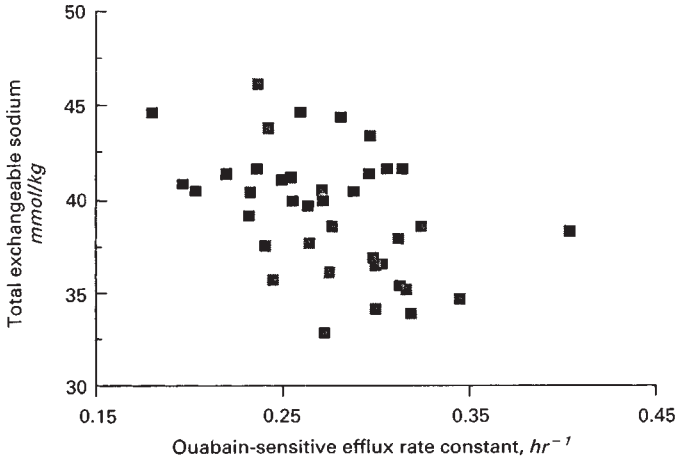

Fig. 2. *The relationship between total exchangeable sodium and the ouabain-sensitive component of the total erythrocytic sodium efflux rate constant in affected (■) and unaffected (□) offspring.*

of the M-mode echocardiogram were on average, not different between the two offspring groups. Nine subjects (3 affected, 6 unaffected) were detected with late systolic posterior displacement of 2.0 mm or greater (none were greater than 3.0 mm), suggesting the possibility of mitral valve prolapse. However, analysis of 2-D echocardiograms revealed evidence of posterior mitral valve leaflet prolapsing into the left atrium in only one of the affected offspring and none of the unaffected subjects.

Hormonal measurements

Plasma renin activity and aldosterone were higher in affected compared with unaffected subjects (Table 3). Because elevated systolic blood pressure and total exchangeable sodium in affected offspring might be expected to suppress the renin-angiotensin-aldosterone axis, we tested the *a priori* hypothesis that plasma renin activity and aldosterone was significantly lower in affected than unaffected individuals and, therefore, report the one-tailed *P* value in Table 3.

No significant differences of cortisol, corticosterone, deoxycortisol, 18-hydroxycorticosterone, deoxycorticosterone or somatomedin C were observed between affected and unaffected offspring (Table 3).

Discussion

In this study young adults with early ADPKD were compared with unaffected offspring to identify characteristics that might precede the development of, and possibly contribute to, the progressive decline in renal function. Special care was taken in designing the study to minimize potentially confounding effects of differences in age, sex and family history.

Relatively narrow limits were set for age, not only to ensure matching, but also to focus on a stage when measured variables were not confounded by the presence of clinical complications such as renal impairment and hypertension, although we observed as reported previously [9], that affected offspring had slightly higher levels of systolic blood pressure than unaffected offspring.

Family history had an important bearing on the choice of controls, as ADPKD families are not necessarily representative of the community in general [37] and comparisons between affected offspring and unrelated normal volunteers might be confounded by such differences. For this reason unaffected offspring were chosen as controls.

Diagnosis in young adults was established primarily by ultrasound, but we also sought to supplement clinical information with genotypic studies, which proved more useful in assessing families rather than individual subjects. We were able to confirm that all affected offspring came from families in which ADPKD was a result of inheritance of *PKD1*, which might be important given the recent suggestion [38] of different clinical manifestations in the minority of ADPKD families not showing linkage to *PKD1*. In our study two families (PK49, PK53) showed relatively high rates of apparent recombination (2 out of 7, and 2 out of 5 informative meioses, respectively), and may be families in which ADPKD is not linked to *PKD1*, although they were not of sufficient size to positively confirm or deny this possibility. By chance, only unaffected offspring were recruited from these two families, and they did not differ substantially from other unaffected offspring. Despite the care taken to establish diagnosis, there remains the possibility that genetic recombination and the delayed appearance of cysts might result in genetically predisposed individuals having been classified as unaffected. We cannot at the moment, gauge the extent of this potential confounding effect.

In young adults, ADPKD did not appear to be associated with detectable renal impairment. However, the demonstration of a normal GFR did not, by itself, exclude the presence of glomerular hyperfiltration, which has been suggested as responsible for progressive decline in renal function in many forms of kidney disease [6]. Nevertheless, we could find no evidence of an inability of the affected kidneys to increase GFR in response to an acute oral protein load, suggesting that, on average, individual glomeruli are not operating at maximal filtration rates in young adults with ADPKD. These findings are not altogether unexpected as the cystic process does not involve primarily the glomeruli, and it has been estimated only 1 to 2% of nephrons contribute to the formation of cysts [5].

Some studies have reported that once renal functional decline in ADPKD is obvious clinically, low protein diets slow the rate of deterioration considerably [39], although others have shown that protein restriction was ineffective [40]. However, our findings would lend no support to the idea that normal basal renal function in young adults with ADPKD belies undetected glomerular hyperfiltration that might justify the recommendation of low protein diets at this age.

Despite normal renal function, young affected offspring had lower renal plasma flow and activation of the renin system. The relationship between these two variables is likely to be complex. Kidney blood flow might be compromized as a result of the physical effects of intrarenal cysts, causing localized ischemia and renin secretion [41]. Renin may in turn exacerbate effects on renal blood flow by causing intrarenal vasoconstriction, as suggested by a recent report showing a large rise in renal plasma flow after ACE inhibition in subjects with ADPKD [41, 42]. In addition to its effects on the renal vasculature, renin may exert effects on the growth of intrarenal cysts, as one recent study [43] observed that the rate of growth of experimental renal cysts is increased when the renin system is activated and reduced when renin is suppressed.

Table 3. Hormonal characteristics of unaffected and affected offspring from families with ADPKD

	Unaffected	Affected	95% CI
Plasma renin activity *μU/ml*	14.0 (11.0, 26.5)	26.2 (14.5, 36.5)[a]	−2.0 to 22.0
Atrial natriuretic peptide *pg/ml*	29.5 (22.0, 40.5)	34.0 (26.5, 50.0)	−7.0 to 17.0
Aldosterone *μg/100 ml*	2.0 (1.5, 2.0)	2.5 (2.0, 3.0)[a]	0.0 to 1.0
Cortisol *μg/100 ml*	5.5 (4.5, 7.0)	4.5 (3.5, 6.0)	−2.0 to 1.0
11-deoxycortisol *ng/100 ml*	10.5 (6.5, 16.0)	13.0 (8.0, 26.0)	−4.0 to 7.0
Corticosterone *ng/100 ml*	255 (139, 357)	250 (134, 393)	−126 to 143
18-hydroxy-corticosterone *ng/100 ml*	23.8 (17.0, 38.0)	36.0 (16.0, 44.5)	−8.0 to 23.0
Deoxycortisone *ng/100 ml*	8.5 (5.0, 12.0)	8.5 (4.5, 12.0)	−4.0 to 4.0
Somatomedin C *mU/ml*	1.02 (0.79, 1.82)	0.77 (0.56, 1.11)	−0.59 to 0.03

All values are expressed as median with the approximate 95% confidence interval of the median in parentheses. The 95% CI is the approximate 95% confidence interval for the difference in medians.

[a] $P < 0.05$ (one-tailed test) compared to unaffected

The increased total exchangeable sodium in affected offspring is also likely to be the result of activation of the renin system, and might explain the observed difference in systolic blood pressure between affected and unaffected offspring. The observed relationship between total exchangeable sodium and ouabain-sensitive erythrocytic sodium efflux is interesting, and may be indicative of some effect of body sodium on the level of an endogenous inhibitor of the Na,K ATPase pump [44]. The similarity of the relationship for both affected and unaffected offspring suggests a general physiological link [44] between body sodium and circulating inhibitors of Na,K ATPase. Presumably, renin-dependent sodium retention results in generally higher levels of the endogenous inhibitor in affected offspring, which may then have an effect on blood pressure [45, 46].

Despite the difference in systolic blood pressure between affected and unaffected offspring, there was no evidence of cardiac complications such as left ventricular hypertrophy or mitral valve prolapse [47]. This contrasts with a recent report [48] in a much wider age group, in which mitral valve prolapse was especially prevalent in affected offspring, but also more common in unaffected offspring than in the general population, possibly because some families with ADPKD in that study also harbored coincidentally a separate genetic predisposition to mitral valve prolapse [49].

Much experimental evidence implicates corticosteroids in the development and growth of renal cysts. Glucocorticoids have been used to induce cyst growth in vivo [50, 51] and in vitro [51, 52], and the development of renal cysts in a murine genetic model of polycystic disease [53] seems to depend on glucocorticoids [54]. However, the present study revealed no abnormalities of glucocorticoid metabolism in young adults with ADPKD. Nevertheless, our data do not exclude the possibility that glucocorticoids may have been abnormal at a younger age and responsible for the genesis of renal cysts in affected infants, although they do suggest that the continued growth of cysts in adulthood is not dependent on elevated levels of glucocorticoids. The normal levels of somatomedin C in affected offspring also imply that this growth factor is not responsible for the growth of the cysts in young adults with ADPKD.

This study has characterized a group of apparently related abnormalities in young adults with ADPKD that are likely to be important steps in the development and progression of renal disease. Renal failure is not an inevitable consequence of ADPKD and some of these disease phenotypes, although genetic in origin, could be modified by environmental changes such as diet or pharmacological intervention. These matters require further clinical scientific evaluation before any recommendations are justified. The evidence of sodium retention might lead to suggestions of salt restriction, but the resultant rise in renin might adversely affect cyst growth [43]. In view of the heightened activation of the renin system in young adults with ADPKD, the effects of renin system antagonists on the development of high blood pressure and the growth of cysts requires further study. In the future, logical and well-tested preventive strategies may significantly improve the clinical impact of this important genetic condition.

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