NADPH oxidase (NOX4) and mitochondrial abnormalities contribute to oxidative stress and endothelial dysfunction in young normotensive patients with autosomal dominant polycystic kidney disease (ADPKD).

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BACKGROUND

Cardiovascular (CV) complications are the main cause of premature morbidity and mortality in patients with autosomal dominant polycystic kidney disease (ADPKD). Endothelial dysfunction (ED) is an independent predictor of CV events. Given its reversibility, it constitutes an attractive target to optimize therapeutic strategies to reduce CV morbidity and mortality. In ADPKD, ED accompanied by oxidative stress (OS) develops early on, preceding the development of hypertension (HTN), CV complications and renal function decline. However, the mechanisms responsible remain unknown. The aim of this study was to determine whether NADPH oxidase (NOX4) and mitochondrial dysfunction contribute to OS and ED preceding HTN in young normotensive patients with ADPKD.

METHODS

Plasma levels of homocysteine (Hcy), as well as plasma and urine levels of 8- isoprostanes, NOX4, and the mtDNA genes cytochrome-c oxidase-3 (COX3) and nicotinamide adenine dinucleotide (NADH) dehydrogenase subunit-1 (ND1), were measured in early (18-30 years, eGFR>90mL/min/1.73m^2) normotensive (<140/90mmHg without antihypertensive medication) patients with ADPKD, and age and gender-matched healthy controls (n=10 each). Total kidney volume (TKV) and renal blood flow (RBF) were measured by MRI.

RESULTS

Blood pressure levels were higher in patients with ADPKD, and HtTKV was twofold higher in ADPKD vs. controls. Yet, eGFR and RBF were similar between the groups (Table). Plasma levels of Hcy were higher in ADPKD compared to controls ($p<0.05$), as were plasma and urine levels of 8-isoprostanes and NOX4 ($p<0.05$). In ADPKD, plasma Hcy, 8-isoprostane, and NOX4 levels correlated directly with HtTKV (R^2 507, 0.485 and 0.599 respectively, $p<0.05$) but the correlation with RBF was not significant. Plasma and urine mtDNA copy number were lower in ADPKD compared to controls, and correlated inversely with HtTKV (R^2 0.397 and 0.392 respectively).

CONCLUSION

Early ADPKD is associated with elevation in Hcy, 8-isoprostane, and NOX4 levels, and decreased mtDNA copy numbers, which precede the reduction in RBF and the development of HTN, and are associated with disease severity. These findings suggest that NOX4 and mitochondrial abnormalities contribute to oxidative stress, endothelial dysfunction, and possibly the development of HTN and disease progression in ADPKD.

Table

	HV	**ADPKD**	*p value*
Number of patients	10	10	N/A
Gender (Female/Male)	6/4	6/4	N/A
Age (years)	23.2 ± 3.2	22.5 ± 3.2	N/A
Systolic blood pressure (mmHg)	114.6 ± 9.0	123.6 ± 11.0	**0.008**
Diastolic blood pressure (mmHg)	70.2 ± 8.4	77.3 ± 8.3	0.063
Serum creatinine (mg/dL)	0.9 ± 0.1	0.8 ± 0.2	0.494
eGFR-CDK-EPI (ml/min/1.73m^2)	104.9 ± 19.3	110.6 ± 12.4	0.411
HtTKV (mL/m)	179 (160 - 189)	347 (270 - 460)	**<0.001**
RBF (cc/min/1.73m^2)	624 ± 100	619 ± 79	0.903