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Longitudinal Assessment of Left Ventricular Mass in Autosomal Dominant Polycystic Kidney Disease

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Introduction: The high burden of cardiovascular morbidity and mortality in autosomal dominant polycystic kidney disease (ADPKD) is related to development of hypertension and left ventricular hypertrophy. Blood pressure reduction has been shown to reduce left ventricular mass in ADPKD; however, moderators and predictors of response to lower blood pressure are unknown.

Methods: This was a *post hoc* cohort analysis of HALT PKD study A, a randomized placebo controlled trial examining the effect of low blood pressure and single versus dual renin–angiotensin blockade in early ADPKD. Participants were hypertensive ADPKD patients 15 to 49 years of age with estimated glomerular filtration rate (eGFR) $>$ 60 ml/min per 1.73 m^2 across 7 centers in the United States. Predictors included age, sex, baseline eGFR, systolic blood pressure, total kidney volume, serum potassium, and urine sodium, potassium, albumin, and aldosterone. Outcome was left ventricular mass index (LVMI) measured using 1.5-T magnetic resonance imaging at months 0, 24, 48, and 60.

Results: Reduction in LVMI was associated with higher baseline systolic blood pressure and larger kidney volume regardless of blood pressure control group assignment ($P < 0.001$ for both). Male sex and baseline eGFR were associated with a positive annual slope in LVMI ($P < 0.001$ and $P = 0.07$, respectively).

Conclusion: Characteristics associated with higher risk of progression in ADPKD, including higher systolic blood pressure, larger kidney volume, and lower eGFR are associated with improvement in LVMI with intensive blood pressure control, whereas male sex is associated with a smaller slope of reduction in LVMI.

Kidney Int Rep (2018) ■, ■–■; https://doi.org/10.1016/j.ekir.2017.12.011
KEYWORDS: autosomal dominant polycystic kidney disease; hypertension; left ventricular hypertrophy; left ventricular mass index

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Received 20 October 2017; revised 18 December 2017; accepted 23 December 2017; published online 6 January 2018

Progressive growth of kidney cysts increases total kidney volume (TKV) in autosomal dominant polycystic kidney disease (ADPKD). The expansion of cysts is associated with angiotensin-dependent hypertension early in the disease course, before kidney function is substantially reduced. Hypertension results in left ventricular enlargement beginning in

childhood, progressing to overt left ventricular hypertrophy (LVH) in adulthood, which likely contributes to the substantial cardiovascular morbidity and mortality observed in ADPKD.[1–4] Intensive blood pressure (BP) reduction has been shown to reduce left ventricular mass in a small trial of hypertensive ADPKD patients.[5]

The HALT PKD study A was a 2 × 2 factorial, randomized controlled trial that addressed the impact of intensive blockade of the renin–angiotensin–aldosterone system (lisinopril/placebo [angiotensin-converting enzyme inhibitor (ACEi)] vs. lisinopril/telmisartan [ACEi/angiotensin receptor blocker (ACEi/ARB)]) and intensive BP control [95–110/60–75 mm Hg vs. 120–130/70–80 mm Hg]) on TKV in 558 hypertensive subjects with preserved kidney function (estimated glomerular filtration rate [eGFR] >60 ml/min per 1.73 m^2) who were 15 to 49 years of age.[6] The primary results of HALT PKD have been reported previously, and have demonstrated that intensive BP control but not combined ACEi/ARB slowed the growth of TKV. One of the notable secondary outcomes for this study was that left ventricular mass index (LVMI) measured by cardiac magnetic resonance imaging (MRI) was significantly reduced in the intensive BP group.[7]

The HALT study population constitutes the largest cardiac MRI cohort of hypertensive ADPKD patients (total N = 543) to date. Prospective, longitudinal data on the natural evolution of LVMI and factors affecting its response to antihypertensive therapy are lacking. Our primary objective was to evaluate the longitudinal impact of variables, both as moderators and predictors, related to improvement of LVMI with intensive BP control in the HALT PKD study.

MATERIALS AND METHODS

Study Population

The design and implementation of the HALT PKD study and the baseline characteristics of this population have been reported in detail.[6–8] Briefly, the HALT PKD trials were prospective, randomized, double-blind, placebo-controlled, multicenter, intervention trials testing whether multilevel blockade of the renin–angiotensin–aldosterone system using ACEi plus ARB (lisinopril plus telmisartan) combination therapy would delay progression of renal disease compared to ACEi (lisinopril plus placebo) monotherapy in studies A and B, and whether intensive BP control (95–110/60–75 mm Hg) would delay progression as compared with standard control (120–130/70–80 mm Hg) in study A.

All HALT participants were hypertensive as defined by current use of antihypertensive medications for BP control or systolic BP of ≥130 mm Hg and/or a diastolic BP of ≥80 mm Hg on 3 separate readings within the year before baseline. Study A participants were 15 to 49 years of age with eGFR >60 ml/min per 1.73 m^2 and underwent MRI assessment of LVM, renal blood flow, and total kidney volume at the baseline visit (before study intervention) with follow-up measurements performed at 24, 48, and 60 months. A window of ±2 months was allowed for each time period. The protocol for the HALT study was approved by the institutional review board at each study site. The present article reports on study A participants only, as MRI imaging was not performed in study B.

Cardiac MRI

A standardized cardiac MRI protocol using 1.5-T MRI scanner was implemented.[3] De-identified images were stored in the central image analysis center for the HALT PKD study and evaluated centrally using Analyze software system (Mayo Foundation, Biomedical Imaging Resource, Rochester, MN). The myocardial area was defined as the difference between the left ventricular epicardial and endocardial borders during end diastole with the exclusion of papillary muscles. The myocardial area over the entire left ventricle was used to determine the left ventricular volume. Left ventricular mass (LVM) was calculated as the product of left ventricular volume and specific gravity of myocardium (1.05 g/ml). Indexing of LVM was performed using the Dubois formula (using body surface area), which was previously shown to be the most reliable method in this cohort.[3,9] The upper limit of normal for this study was defined as >84.6 g/m^2 for women and >106.2 g/m^2 for men using a previously defined 95th percentile of LVM.[10]

Statistical Methods

Covariates chosen a priori for analysis included age, sex, baseline eGFR, systolic BP, total kidney volume, serum potassium, and urine sodium, potassium, albumin, and aldosterone. Most of these covariates were significant in the univariate analysis conducted on the baseline measurements.[3] We determined whether any baseline covariates moderated the effect of low BP control (vs. standard control) on the slope of LVMI using all available data. Linear mixed models were fit on LVMI as a function of the following predictors: month, month by BP arm interaction, the potential moderator variable, and all resulting 2- and 3-way interactions. If a significant 3-way interaction was found (month by BP arm by moderator), the covariate was classified as a moderator; otherwise the 3-way interaction was removed and the model was rerun to determine whether the 2-way interaction (month by