PANCREAS, BILIARY TRACT, AND LIVER

Liver Involvement in Early Autosomal-Dominant Polycystic Kidney Disease

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BACKGROUND & AIMS: **Polycystic liver disease (PLD), the most common extrarenal manifestation of autosomal-dominant polycystic kidney disease (ADPKD), has become more prevalent as a result of increased life expectancy, improved renal survival, reduced cardiovascular mortality, and renal replacement therapy. No studies have fully characterized PLD in large cohorts. We investigated whether liver and cyst volumes are associated with volume of the hepatic parenchyma, results from liver laboratory tests, and patient-reported outcomes.**

METHODS: **We performed a cross-sectional analysis of baseline liver volumes, measured by magnetic resonance imaging, and their association with demographics, results from liver laboratory and other tests, and quality of life. The data were collected from a randomized, placebo-controlled trial underway at 7 tertiary-care medical centers to determine whether the combination of an angiotensin I–converting enzyme inhibitor and angiotensin II–receptor blocker was superior to the inhibitor alone, and whether low blood pressure (<110/75 mm Hg) was superior to standard blood pressure (120–130/70–80 mm Hg), in delaying renal cystic progression in 558 patients with ADPKD, stages 1 and 2 chronic kidney disease, and hypertension (age, 15–49 y).**

RESULTS: **We found hepatomegaly to be common among patients with ADPKD. Cysts and parenchyma contributed to hepatomegaly. Cysts were more common and liver and cyst volumes were greater in women, increasing with age. Patients with advanced disease had a relative loss of liver parenchyma. We observed small abnormalities in results from liver laboratory tests, and that splenomegaly and hypersplenism were associated with PLD severity. Higher liver volumes were associated with a lower quality of life.**

CONCLUSIONS: **Hepatomegaly is common even in early stage ADPKD and is not accounted for by cysts alone. Parenchymal volumes were larger, compared with liver volumes of patients without ADPKD or with those predicted by standardized equations, even among patients without cysts. The severity of PLD was associated with altered biochemical and hematologic features, as well as quality of life. ClinicalTrials.gov identifier: NCT00283686.**

Keywords: HALT-PKD-A; Hepatic Cyst; CKD; MRI Analysis.

Abbreviations used in this paper: **ADPKD, autosomal-dominant polycystic kidney disease; ALP, alkaline phosphatase; ALT, alanine aminotransferase; BMI, body mass index; BP, blood pressure; BSA(m^2), body surface area (corrected for height); eGFR, estimated glomerular filtration rate; HALT-PKD, Halt Progression of Polycystic Kidney Disease studies; HALT-PKD-A, Halt Progression of Polycystic Kidney Disease Study A; htLCV, height-adjusted liver cyst volume; htLV, height-adjusted total liver volume; htTKV, height-adjusted total kidney volume; htLPV, height-adjusted liver parenchymal volume; LCV, liver cyst volume; LPV, liver parenchymal volume; LV, total liver volume; MRI, magnetic resonance imaging; PLD, polycystic liver disease; QOL, quality of life; SF-36, Short-Form 36.**

1542-3565/$36.00
http://dx.doi.org/10.1016/j.cgh.2014.07.051

Autosomal-dominant polycystic kidney disease (ADPKD) is the most common monogenic kidney disease and the fourth leading cause of end-stage kidney disease worldwide.[1,2] Polycystic liver disease (PLD), arbitrarily defined as the presence of any liver cyst, is its most common extrarenal expression.[3,4] Liver cysts often remain asymptomatic, but some individuals experience chronic manifestations related to progressive liver enlargement, leading to disability and severely impacting quality of life.[5] Symptoms of PLD relate to effects from the volume of hepatic cysts or complications such as cyst hemorrhage, rupture, or infection. Massive hepatomegaly can cause compression of the adjacent gastrointestinal tract, vasculature, and diaphragm. Highly symptomatic PLD has become more common as a result of reduced cardiovascular mortality and extended renal survival and life expectancy on renal replacement therapy.[6–11] Some individuals require interventions including cyst aspiration and/or sclerosis, fenestration and/or combined liver resection/cyst fenestration, hepatic artery embolization, or, in extreme cases, liver or combined liver-kidney transplantation. Several interventional clinical trials with the objective of delaying the progression of PLD have been published.[12–17]

No studies have fully characterized PLD burden in large cohorts with ADPKD. This characterization is needed because its full clinical impact is not well understood. The HALT Progression of Polycystic Kidney Disease Study A (HALT-PKD-A) is the largest clinical cohort of ADPKD patients with liver and kidney imaging studied to date and comprised 558 individuals with early disease (estimated glomerular filtration rate [eGFR], >60 mL/min/1.73 m^2) and hypertension, prospectively followed up for up to 8 years.[18,19] The objective of this study was to systematically characterize PLD-associated morbidities in this cohort and correlate the extent of PLD assessed by magnetic resonance imaging (MRI) with relevant baseline clinical and laboratory data.

Methods

The HALT-PKD-A trial is multicenter, randomized, placebo-controlled trial to investigate the effect of blockade of the renin-angiotensin-aldosterone system on total kidney volume and renal function in adults with ADPKD; eligibility criteria and protocol design have been published previously.[18] A full description of methods can be found in the Supplementary Methods.

Results

Total liver volume (LV) (available for 534 individuals) (Figure 1*A* and *B*; 267 males; 267 females) was higher in men (2022 ± 740 mL) than in women (1905 ± 859 mL) ($P = .0003$). After height adjustment there was no gender difference: 1115 ± 405 mL/m (males) vs 1141 ± 518 mL/m (females) (Table 1, Figure 1*A*).

Higher Prevalence and Earlier Development of Liver Cysts in Women

Liver cyst volume (LCV) (unadjusted for height) was significantly higher in women (311 ± 763 mL) than in men (122 ± 648 mL) ($P < .0001$) (Table 1, Figure 1*A*). Females had a higher liver cyst prevalence (78.7%) than males (69.3%) ($P = .0137$); the age-adjusted odds ratio was 1.54 ($P = .032$) (Table 1). Older men and women had a higher liver cyst prevalence (44%, 68%, and 84% of women age ≤24, 25–34, and ≥35 y, compared with 17%, 57%, and 79% of men in the same age groups). Eighty-three percent (20 patients) of those with height-adjusted LCV (htLCV) greater than 700 mL/m were women, as compared with 49% (275 of 558) in the entire cohort (Figure 1*B*).

Both Liver Cyst Volume and Liver Parenchymal Volume Contribute to Hepatomegaly

In both sexes, LVs were significantly larger in the ADPKD patients than those reported in a group of potential liver donors and for the general population.[20] By using a standardized equation for Caucasians, LVs also were higher than those predicted for the same HALT-PKD ADPKD patients (Table 2).[20–22] When adjusted for height, height-adjusted liver parenchymal volume (htLPV) was higher in men and htLCV was higher in women (Table 1). To ascertain whether cyst development fully accounts for hepatomegaly, we compared liver parenchymal volume (LPV) in the cohort with observed and expected normal LVs in the general population and found that LPV in our cohort was significantly larger than the LVs in liver transplant living donors ($P < .0001$), LVs reported in healthy controls ($P < .0001$), and predicted LVs in our participants using a standardized equation. Even in those without liver cysts, this was significant ($P < .0001$).[22]

Relative Reduction in Liver Parenchymal Volume in Severe Polycystic Liver Disease

As expected, htLCV correlated positively with height-adjusted total liver volume (htLV), particularly in severe PLD (Figure 1*A*) (females: r = 0.69; males: r = 0.48). After reaching an htLCV threshold of approximately 700 mL/m, htLPV does not continue to increase (Figures 1*B*, 2*A*, and 2*B*). Because most of these cases were women, the trends of htLV, htLCV, and htLPV (in Figure 1*B*) accounted for the lower LPVs in women compared with those without liver cysts (1555 ± 289 vs 1735 ± 448 mL; $P = .0003$) (Table 2). Thus, although LPV was normal or larger compared with healthy normals, in the majority of ADPKD patients, relative reductions in htLPV occurred in a small subset of patients with severe PLD (Figure 1*B*).