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Kidney function decline in polycystic kidney disease – it's not always off the cliff

Autosomal dominant polycystic kidney disease (ADPKD) is a relatively common (estimated to affect 1 in 1000 to 1 in 4000 persons all over the world) inherited disorder that leads to kidney failure in the majority of patients between 40 and 80 years of age. Each child of an affected parent has a 50% chance of inheriting the mutated gene, either *PKD1* or *PKD2*, which account for approximately 95% of cases. At birth the kidneys are usually normal, although they may contain microscopically small cysts, i.e. fluid filled sacs, which then grow over a lifetime into hundreds or thousands of cysts, becoming quite large and destroying the normal kidney tissue. Kidney function usually remains normal until mid-adulthood, but high blood pressure (hypertension) often develops in young adults and contributes to kidney function decline, heart disease and stroke.

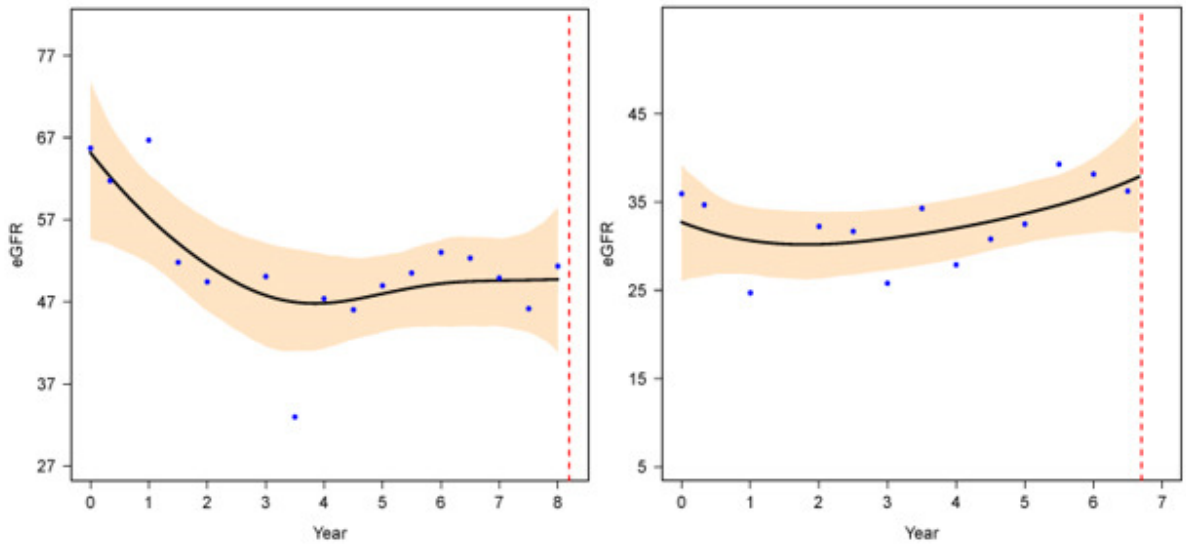

Fig. 1. Examples of kidney function decline in 2 individual patients during the HALT-PKD trial. The blue dots represent individual eGFR estimates (in mL/min/1.73 m2, see text), the black line is the best estimate of the true trajectory over time, derived from 3000 statistical simulations, with 95% confidence intervals in orange. The dotted vertical red line denotes end of study participation for this individual. The left panel shows an example of an initial decline in eGFR being followed by a period of stable kidney function lasting more than 6 years. The right panel shows low but stable kidney function throughout the trial for almost 7 years. (modified from: Brosnahan GM, Abebe KZ, Moore CG, et al., 2018. Patterns of kidney function decline in autosomal dominant polycystic kidney disease: A post hoc analysis from the HALT-PKD trials. Am J Kidney Dis 71(5), 666-676).

There is no cure for this disease; optimal treatment of hypertension has been the focus of research studies. The HALT-PKD trial was the largest study (1044 participants) ever conducted for an extended period (5-8 years) in patients with ADPKD, testing whether more intensive blood pressure treatment can slow the loss of kidney function. There was no difference between the treatment groups, and all participants had well controlled hypertension. We studied individual patterns of kidney function decline because we were

interested to see whether previous observations that kidney function loss, once it has started, is usually rapid and relentless, still hold true.

The HALT-PKD trial determined estimates of kidney function called eGFR (estimated glomerular filtration rate) every 6 months; eGFR is calculated from measured blood values of creatinine, a waste product filtered by the kidneys. eGFR declines from a normal of > 90 mL/min/1.73 m^2 to less than 10. At that point kidney replacement therapy (dialysis or transplantation) becomes necessary. We wanted to determine whether this decline occurs in a steady, linear manner, or with periods of rapid decline and periods of stabilization. Because eGFR estimates are scattered around the true value, we used rigorous statistical analyses to describe the trajectory of kidney function decline for each patient. Examples of individual kidney function "curves" are shown in the Figure 1.

We found that 71% of study participants indeed had a steady, linear decline of eGFR, but 29% had undulating patterns and/or prolonged periods of stable eGFR, even at a reduced level. This is important for patient care because a rush to dialysis or transplantation may not be necessary. In early-stage ADPKD, lower body mass index, smaller kidney volume and milder types of mutations were associated with stable kidney function. In advanced ADPKD some older patients had the most stable kidney function, and approximately three quarters of them had milder types of mutations. Clinical events such as episodes of bloody urine, acute kidney injury or hospitalization (for any cause) were not different between those with stable and unstable kidney function either in early or late ADPKD. Stable patients who had more severe mutations might have other protective genes that mitigate the course of ADPKD.

Although the cysts grow at a fairly constant rate in ADPKD, the rate of kidney function loss is often variable and was overall slower than observed in older studies, possibly due to better control of hypertension. While we still have much to learn about how the mutated genes cause kidney failure, knowing that periods of stable kidney function can occur even after an initial decline is important for patient care. The variability of kidney function loss over time also needs to be considered in clinical trials of new drugs to avoid erroneous conclusions.

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Publication

Patterns of Kidney Function Decline in Autosomal Dominant Polycystic Kidney Disease: A Post Hoc Analysis From the HALT-PKD Trials.
Brosnahan GM, Abebe KZ, Moore CG, Rahbari-Oskoui FF, Bae KT, Grantham JJ, Schrier RW, Braun WE, Chapman AB, Flessner MF, Harris PC, Hogan MC, Perrone RD, Miskulin DC, Steinman TI, Torres VE; HALT-PKD Trial Investigators
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