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Ketosis moderates the effect on kidney volume in dietary interventions for ADPKD—more insights on the KETO ADPKD trial

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Background and Aims: Autosomal-dominant polycystic kidney disease (ADPKD) is the most common monogenic disease leading to kidney failure. Tolvaptan, the only approved targeted treatment strategy, comes with adverse events such as hepatotoxicity and massive polyuria, limiting its use. Novel treatment strategies are urgently needed. Cyst-lining epithelial cells are glucose-dependent and metabolically inflexible. Evidence from polycystic kidney disease (PKD) animal models show that ketogenic dietary interventions (KDI) can ameliorate cyst growth and loss of kidney function. To enable clinical translation of these findings, our group set up a series of trials—from small cohorts and proof of principle studies to our most recent trial KETO-ADPKD, showing that KDIs are feasible and can work as a treatment for ADPKD [1]. This has received a lot of attention. With this post-hoc analyses, we aim to share further in-depth analyses of the factors moderating the effects we see on ADPKD.

Method: KETO-ADPKD is an exploratory randomized and controlled clinical trial (NCT04680780). Sixty-six patients were randomized to 3 months dietary intervention (ketogenic diet [KD] or water fasting [WF]) or the control group. Here, we explore correlations between biochemical readout parameters of ketosis and markers of disease progression.

Results: The KD group shows a promising, yet statistically not significant decline in height-adjusted total kidney volume (htTKV). Patients reaching high biochemical thresholds of ketosis however significantly reduced their htTKV in comparison with the control group (KD −16.3 ml/m, CG + 14.8 ml/m, p-value 0.049). This becomes even clearer when higher thresholds for adherence are administered: In a smaller group requiring not only beta-hydroxybutyrate (BHB) levels ≥0.5 mmol/l but breath acetone ≥5 ppm on 75% of daily measurements, htTKV could be reduced by −17.6 ml/m (KD) vs +14.8 ml/m (CG), p-value 0.026. The significant reduction of liver volume upon KD is not influenced by the level of ketosis. Beneficial effects on estimated glomerular filtration rate (eGFR) can be equally observed in all subsets. Weight loss ≥5% was nor associated with a more significant loss of kidney nor liver volume.

Conclusion: Subgroup analyses of the KETO-ADPKD trial show stronger impact of the dietary intervention with higher ketone body levels. In particular, ketogenesis as a marker of metabolic reprogramming strongly moderates the effects we see on kidney volume. The assessment of renal cyst fractions could further enlighten the effects on cyst burden. This is in line with preclinical data showing that ketosis rather than caloric intake is responsible for the amelioration of disease progression [2].

REFERENCES

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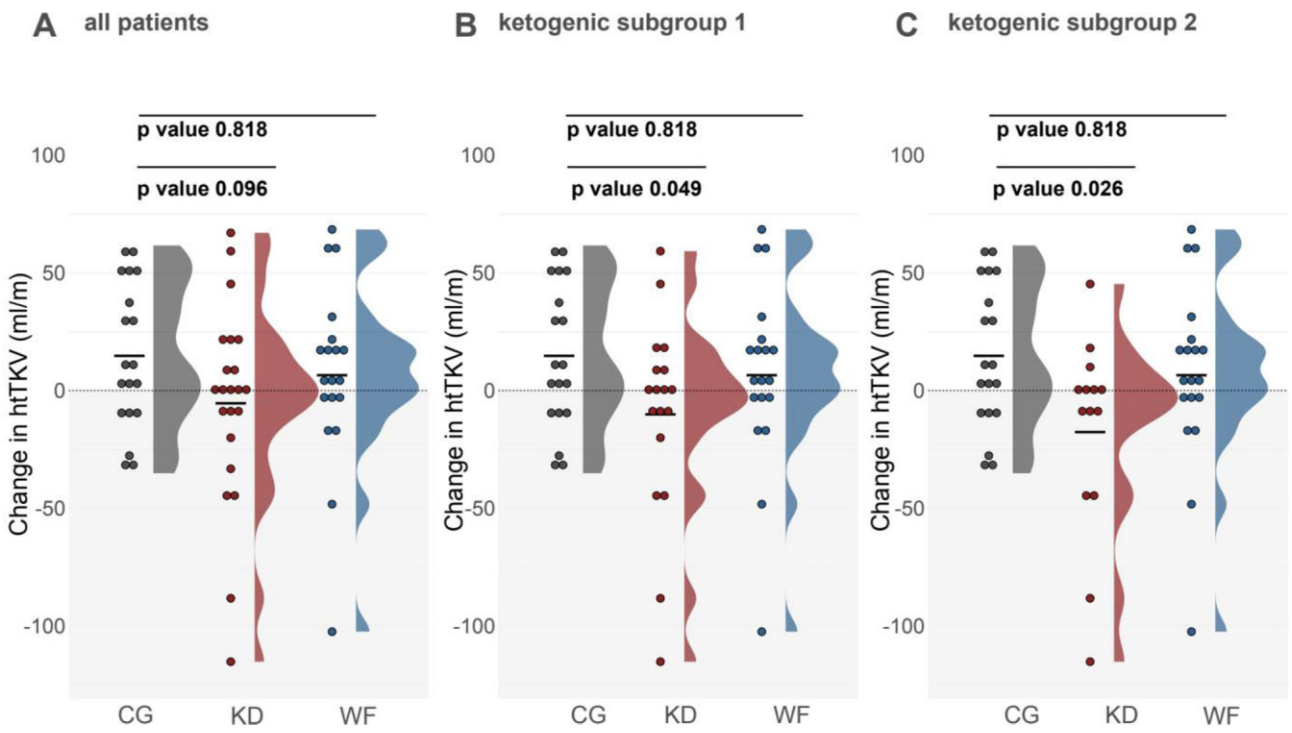

Figure 1: Kidney volume loss is clearly associated with biochemical adherence markers. Changes in htTKV are illustrated from BL to EOT over the course of 3 months KDI. (A) All patients reaching EOT. The mild reduction in htTKV within the KD group cannot be seen within the WF group. Within the control group mean htTKV rises. (B) Subset of n = 51 (19 CG, 19 KD, 19 WF) within the KD group showing elevated BHB levels ≥0.5 mmol/l on at least 2/3 study visits. Here, the level of evidence for a true underlying difference between the KD and CG reaches statistical significance (p-value 0.049) (C) Subset of n = 52 patients (19 CG, 14 KD, 19 WF) reaching a BHB level of ≥0.5 mmol/l at 2/3 on-site visits AND breath acetone levels of ≥5 ppm, showing even more differences in kidney volume (p-value 0.026). Abbr. *BHB, beta-hydroxybuturate; EOT, End of Treatment; htTKV, height adjusted total kidney volume; KD, ketogenic diet; p.p.m, parts per million; WF, water fasting.*