From the Thomas Weimbs' Lab:
August 2024--New Research Paper Published on Ketogenic Metabolic Therapy in Polycyctic Kidney Disease
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Summary Highlights

- Polycystic kidney disease leads to increased glycolysis and metabolic disorder
- Ketogenic metabolic therapy may alter disease outcomes by addressing the underlying metabolic disorder
- Both fasting and time-restricted feeding slow or reverse disease progression in rodents
- We show that the metabolite produced during ketosis, β-hydroxybutyrate, alone recapitulates the benefits of fasting

Summary

Autosomal-dominant polycystic kidney disease (PKD) is a common monogenic disease characterized by the formation of fluid-filled renal cysts, loss of mitochondrial function, decreased fatty acid oxidation, increased glycolysis, and likely renal failure. We previously demonstrated that inducing a state of ketosis ameliorates or reverses PKD progression in multiple animal models. In the current study, we expand on those findings and compare time-restricted feeding (TRF) and 48-hour periodic fasting regimens in juvenile and adult polycystic rats. We found that both feeding regimens prevent juvenile disease progression and partially reverse PKD in adults. We hypothesized that the effect of fasting may be regulated by the metabolite β-hydroxybutyrate (BHB), an alternative fuel source produced during ketosis from the breakdown of fatty acids. To explore this, we administered β-hydroxybutyrate (BHB) to both rats and mouse models of PKD. Surprisingly, we found that BHB recapitulated the effects of fasting in these models independent of stereoisomer, suggesting the effects of BHB are largely due to its signaling functions rather than as an alternative fuel source, shedding light on underlying disease mechanisms. Taken together, the results of this study strongly suggest that ketogenic metabolic therapy and BHB supplementation could be used to modify PKD progression and warrant further exploration.

Graphical abstract