Reassessing Metformin's Potential in Autosomal Dominant Polycystic Kidney Disease (ADPKD): A Call for Further Research

Dear Editor,

I want to express our sincere gratitude for the thoughtful and constructive letter regarding our recent study.[1] In response to the letter, we intend to explore the factors that may have contributed to the nonsignificant findings of our study.

We emphasize that our study was primarily a feasibility assessment and did not have sufficient power or duration to draw definitive conclusions about the metformin efficacy. Due to the limited duration, we were unable to demonstrate a significant reduction in glomerular filtration rate (GFR) with metformin. The use of estimated GFR (eGFR) as an endpoint in participants with well-preserved eGFR requires large trials of long duration because of the slow progression of eGFR in the early stages of autosomal dominant polycystic kidney disease (ADPKD). Alternative clinical trial end points like biomarkers (copeptin) or prognostic enrichment through imaging/genetics can be employed to detect benefit at an earlier stage. Peronne *et al*. calculated the ideal sample size as 700–800 study participants and four to five years of study duration in order to detect a 25% improvement in eGFR decline and 45% reduction in height-adjusted total kidney volume (htTKV) slope.[2]

Lack of metformin for a meaningful beneficial effect on eGFR declines and htTKV could also be explained by the fact that only around half of the patients could tolerate the maximal tolerated dose in our study. This was consistent with the trial of administration of metformin in polycystic kidney disease (TAME-PKD) and Brosnahan *et al*. where compliance to full dose (2 gm/day) metformin was seen in around 50–65% participants[2,3] [Figure 1]. As rightly mentioned by the author, further trials using personalized metformin dosing or extended release (XR) metformin

Landmark trials of Metformin in ADPKD

	Brosnahan	TAME PKD	Venkatasubramanian
Intervention	Metformin (Upto 1gm/day) or Placebo	Metformin (Upto 1gm/day) or Placebo	Metformin (Upto 1gm/day) or Standard of care
Sample size	N=51 Caucasian	N=97 White participants	N=56 Asian
Age	48 years	42 years	43 years
TKV/eGFR	=1229 ml =70	=625-750 =86	=335 =100
Results	Annual eGFR decline was -0.41 vs -3.35 mL/min/1.73 m^2 in metformin vs placebo groups P=0.24	Estimated annual eGFR decline less in metformin (-1.7ml/min/1.73m^2) than placebo (-3) P=0.38	The mean 6 monthly decline in eGFR was −0.7 mL/min/1.73 m^2 in control group and −0.57 mL/min/1.73 m^2in metformin group (p=0.9)
Concerns	Mainly safety study. Only 50% patients tolerated full metformin dose	Only 67% patients tolerated full dose (2 gm/day)	Only 57 % patients tolerated full dose (2 gm/day)

Figure 1: Existing metformin studies in ADPKD. ADPKD: Autosomal dominant polycystic kidney disease, TAME PKD: Trial of administration of metformin in polycystic kidney disease, eGFR: estimated glomerular filtration rate, TKV: Total kidney volume.

formulations should be planned for better patient adherence. We believe that given its potential benefits, metformin could be a promising therapeutic option for ADPKD and should be evaluated in larger clinical trials.

Conflicts of interest: There are no conflicts of interest.

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H5N1 Infection and Kidney Pathology: Is There a Link?

Dear Editor,

Whilst human-to-human avian influenza A virus subtype H5N1 (H5N1) transmission is not yet established, the reemergence of the virus with reported human H5N1 cases in every continent by May 2024 has now sparked fears of another potentially brewing viral pandemic. H5N1-associated kidney pathology has not been studied much since the virus was first isolated from humans in Hong Kong in 1997.

We conducted a scoping literature search through PubMed, Web of Science, EMBASE, Medline-ProQuest, and Google Scholar on publications describing H5N1-associated kidney pathology. Less than ten cases describing kidney pathology in human H5N1 patients have been published, most reported between 1997 and mid-2000s from Hong Kong or China during the first H5N1 outbreak in that period. Acute tubular necrosis was observed in the majority of the published cases.[1–3] There was a three-year-old boy who died of H5N1 infection and, consequently, complications from Reye's syndrome, in which paramortem biopsy identified vacuolation and vesicular changes in the kidney proximal tubules, consistent with Reye's syndrome.[4]

Recent research has studied the links between H5N1 and kidney pathology. Zhang *et al*.[5] immunized BALB/c mice with inactivated H5N1 to prepare monoclonal antibody (mAb) H5-32, where immunohistochemical analysis confirmed that mAb H5-32 cross-reacted with normal human kidney tissue. mAb H5-32 was localized in the cytoplasm of human kidney tubular epithelial cells and its binding fragment size was about 43 kDa. Hence, Zhang *et al*.[5] concluded that the mechanism of binding to human kidney tubular epithelial cells may be a key mechanism of H5N1-induced kidney pathology. With a rising incidence of H5N1 infection worldwide and its plausible links with kidney damage, further investigations are needed to explore and delineate the mechanisms between H5N1 and kidney disease.

Conflicts of interest: There are no conflicts of interest.

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