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TAMEing ADPKD with metformin: safe and effective?

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Abstract

The biguanide metformin has been safely and widely used in the treatment of type 2 diabetes mellitus for decades. Preclinical studies have suggested that it may have a role in slowing disease progression in ADPKD. In this issue, Perrone and colleagues report results from the Trial of Administration of Metformin in PKD (TAME PKD) study, a Phase 2 RCT investigating the safety and tolerability of metformin in ADPKD patients with early disease. We discuss the implications of these findings and how they relate to a major Phase 3 trial in ADPKD that will start later this year.

Key words: ADPKD, metformin, AMPK

Commentary

Metformin (dimethyl-biguanide) is the most commonly used oral hypoglycemic agent in the management of Type 2 diabetes mellitus world-wide. Derived from guanidine, a chemical first identified from the plant *Galega officinalis*, a herbal remedy found to lower blood glucose in man, it was first synthesised in the 1920s and has since gained widespread acceptance based on its effectiveness, safety and cost. Metformin is not metabolised in man and is excreted solely through renal excretion. Common side effects include gastrointestinal symptoms such as nausea, loss of appetite, abdominal cramps and occasional vomiting. A rare but serious adverse event is lactic acidosis. This side effect is especially seen in subjects with reduced renal elimination due to low glomerular filtration rate (GFR) and has led to the general safety recommendation that it should not be prescribed in patients with an estimated GFR of <30ml/min/1.73m^2. In cases of vomiting, diarrhoea or other causes of dehydration, metformin should be temporarily withdrawn.

The major mechanism of action of metformin on hepatic glucose production is still debated: there is experimental evidence both for an effect on the cytosolic redox state (inhibiting the redox shuttle enzyme mitochondrial glycerol 3-phosphate dehydrogenase) [1] and on the activation of AMP kinase (AMPK) [2], a major energy sensor within the cell, at therapeutic concentrations (μM). Earlier observations of a direct effect on oxidative phosphorylation (mitochondrial complex 1) have since been attributed to the supra-pharmacological doses (mM) used in these studies: blood therapeutic levels in man are ~10-40μM [3]. An effect of metformin on renal gluconeogenesis has not been established.

The beneficial effect of metformin on ADPKD was first suggested by a study by Takiar et al who reported a reduction of cystic disease by high-dose metformin (300mg/kg/d intraperitoneal) in two severe neonatal *Pkd1* mouse models including a tamoxifen inducible *Pkd1*^{del} conditional knock-out (KO) model. Tamoxifen was given at day 9 and 10 after birth leading to rapidly progressive cystic disease within 1 to 2 weeks [4]. A later study in a zebrafish *pkd2* morphant confirmed similar effects of metformin (2.5-20 mM) on pronephric cyst expansion by inhibiting cell proliferation but also demonstrated additional positive effects on leucocyte infiltration and autophagy [5]. Metformin was shown to activate AMPK as measured by its activated phosphorylated form ($^{pThr\text{-}172}$AMPK) (Figure 1). In MDCK cells, AMPK activation led in turn to the inhibition of the enzyme mTORC1 (mammalian target of rapamycin complex 1) and the CFTR (cystic fibrosis transmembrane regulator) chloride channel, key molecules previously implicated in PKD pathogenesis [4]. Similarly, in a miniature *Pkd1* pig model, metformin had beneficial effects on renal cysts and kidney function after chronic (10-40 months) oral administration (41.7mg/kg/d) [6]. However, a recent study by Leonhard et al that was also performed with metformin (300 mg/kd/d oral) in a tamoxifen inducible conditional *Pkd1*^{del} conditional KO mouse model was surprisingly neutral after 3 months treatment [7]. One obvious difference between this study and the study by Takiar et al was that Leonhard et al gave tamoxifen at day 18 and 19 after birth, which leads to more slowly progressive disease, with end-stage renal failure occurring at a median age of 4 months. Thus, the beneficial effect of metformin could depend on the rate of disease progression, with greater efficacy in more rapidly progressive disease. Another difference between the two studies could lie in the method of drug administration. At first glance, both studies used the same dose i.e. 300 mg/kg/day. However, in the study by Takiar et al,

metformin was given intraperitoneally whereas in the study by Leonhard et al, this was administered orally in drinking water. The oral bio-availability of metformin is 40 to 60%, so the neutral study by Leonhard et al is likely to have provided only half the dose of that by Takiar et al. Importantly, the oral dose of 300 mg/kg/d in mice corresponds approximately to an oral dose of 25 mg/kg/d in humans, i.e. for an 80 kg subject, equivalent to 2000 mg per day [8]. The difference in efficacy between the two experimental studies could therefore also relate to differences in serum metformin levels: therefore it might be important for clinical studies to pursue the highest tolerated dose of 2000 mg/d. Differences in efficacy related to dosing is not a new issue in ADPKD, having been invoked as a possible explanation for positive, high dose experimental studies versus neutral, lower dose clinical trials with mTOR inhibitors.

These early promising preclinical results formed the basis for the Trial of Administration of Metformin in PKD (TAME PKD) study, a Phase 2 double-blind placebo-controlled RCT investigating the safety and tolerability of metformin in ADPKD patients with early disease (eGFR>50ml/min/1.73m^2) which began in 2016 [9]. Ninety-seven patients with ADPKD between 18-60 years of age at two academic centres, were randomised in a 1:1 ratio to receive metformin (1000 mg twice daily) or placebo over a period of 24 months. The patients recruited had a mean age of 42 years and a relatively high mean eGFR at entry of 86 ml/min/1.73m^2 in both groups, suggesting more slowly progressive disease overall. There were more females (78% v 67%) and *PKD1* patients (78.7% v 60.9%) in the metformin group but patients in the placebo group had a greater mean htTKV (751 v 626 ml/m). Only half of the patients could be classified as falling into a higher Mayo htTKV Imaging Class (1C-E), again confirming a lack of enrichment for patients with more rapid disease progression based on the trial design.

Encouragingly, no safety signals of concern (lactic acidosis or clinical hypoglycaemia) or treatment-emergent serious adverse events were detected in this study: lactic acid and vitamin B12 levels were also normal. Despite the Gastrointestinal Symptom Rating Scale (GSRS) being similar between both groups, by the end of the study, 22% of the patients in the metformin group had discontinued medication and 43% of the patients were intolerant of the maximal dose leading to dose reductions: only 35% were still on the prescribed dose of 2000 mg/d. Exploratory secondary end-points showed a trend towards a positive effect of metformin on annualised eGFR slope of 1.37ml/min/1.73m^2 (p=0.2) but an increase in mean annual height-adjusted total kidney volume (htTKV) of 1.68% (p=0.38) and an increase in mean annual height-adjusted total liver volume (htTLV) of 0.39% (p=0.72).

Thus the TAME PKD study achieved its main primary end-point showing that metformin at clinically relevant doses for T2DM (2000 mg/d) is safe in ADPKD patients with early disease (eGFR>60ml/min/1.73m^2). Results of the exploratory secondary end-points were however inconclusive, with non-significant trends for eGFR slope, htTKV and htTLV. Since only a subgroup (35%) of metformin treated patients were able to tolerate the maximal dose prescribed (2000 mg/d), it is possible that a positive effect on kidney or liver volumes could have been missed due to suboptimal dosing. A second possibility could be that the patient cohort recruited had too mild disease to show a detectable effect on disease progression within the study duration. The results on safety and tolerability reported here should nonetheless apply equally to patients with more rapidly progressive disease, as would be the anticipated trial population in a future Phase 3 renoprotection study.

The authors estimate that ~700-800 ADPKD patients will be needed for a four-year Phase 3 RCT to detect a 25% improvement in annualised eGFR slope or a 45% annualised htTKV slope with 80% power, assuming an overall 15% attrition rate. Based on the results of TAME PKD, this could be difficult to achieve without major adjustments in trial design to improve tolerability of the maximal dose (e.g. the use of a slow-release metformin preparation) and enrichment strategies (Mayo Imaging Class) to select patients with more rapidly progressive disease. The question as to what should be an optimal dose for ADPKD remains open. The inclusion of surrogate biomarkers of renal AMPK/mTOR activity (eg urine metabolomics, exosomes) and the measurement of plasma metformin concentrations in a future trial could help to align any observed therapeutic benefits with its proposed mechanisms. Finally, clarifying a potential effect of metformin on TLV in an adequately powered future trial would be an important outcome distinguishing it from tolvaptan.

The potential for metformin to slow both kidney and liver disease in early ADPKD remains tantalizingly open. The TAME PKD study takes us one step closer but further steps will need to be taken. In this respect, it is of interest that the IMPEDE-PKD trial is expected to begin enrolling later this year. This international multi-centre study aims to test in 1164 ADPKD patients selected for rapidly progressive disease, whether metformin given as a slow release formulation of 2000 mg/day over two years, will improve the annual loss in estimated GFR compared to placebo (NCT04939935). This well-powered phase 3 trial should be completed in 2026, when we should have a definitive answer as to whether metformin has a role in the future management of ADPKD.

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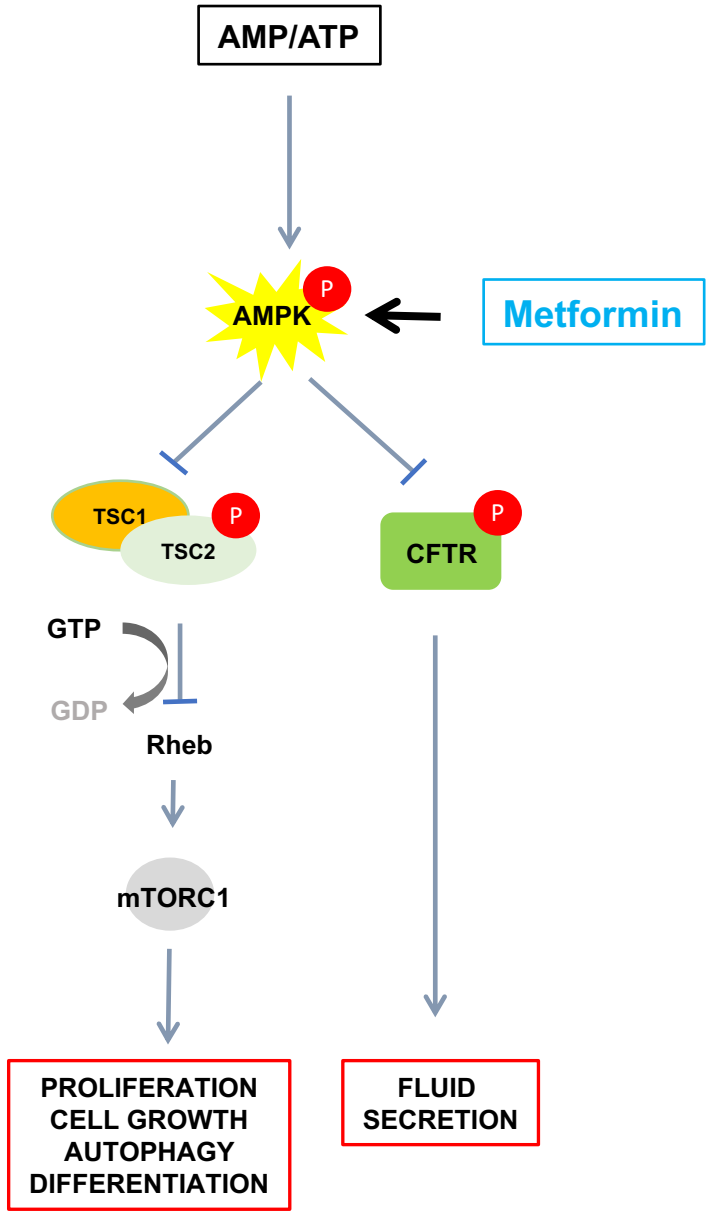

Fig 1: Metformin activates AMPK leading to the inhibition of the mTORC1 enzyme complex and the CFTR chloride channel. This results in the reduced cell proliferation and fluid secretion, major features of ADPKD cystic renal epithelial cells, as well as other cellular changes. The activation of AMPK is indicated by its phosphorylated state (P). AMPK in turn phosphorylates TSC2 and CFTR leading to their functional inhibition.