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Metformin reduces decline in the estimated glomerular filtration rate during progression of autosomal dominant polycystic kidney disease: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: A meta-analysis (MA) was carried out to examine the influence of metformin on autosomal dominant polycystic kidney disease (ADPKD) patient prognosis.

MATERIALS AND METHODS: We reviewed and examined scientific articles from PubMed, Clinicalkey, Google Scholar, Medline, Embase, and Cochrane from the initiation date till June 2023 to identify investigations that examined metformin performance in managing ADPKD. Among the employed search terminology, we searched for terms such as "metformin" and "ADPKD". MA was conducted using the Cochrane Collaboration's RevMan version 5.3.0 (The Cochrane Collaboration, Oxford, UK).

RESULTS: We identified 4 investigations, with 164 total subjects who fulfilled our inclusion criteria. The experimental cohort displayed a marked reduction in the decline of estimated glomerular filtration rate (eGFR) relative to controls [mean difference (MD) = 2.31, 95% confidence interval (CI) = 0.82-3.79, $p = 0.002$]. We observed no obvious difference in the height-adjusted total kidney volume alteration, gastrointestinal side effects, and hypoglycemia between the two cohorts.

CONCLUSIONS: Metformin was easily tolerable and safe and substantially reduced the eGFR decline among ADPKD patients. Moreover, although metformin-treated patients were more likely to suffer gastrointestinal adverse events, we observed no discernible difference between the two cohorts.

Key Words:
Metformin, ADPKD, AMP-activated protein kinase.

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is a highly prevalent hereditary kidney disease marked by several bilateral renal cysts, which increases kidney volume and induces a gradual decline of kidney function. The vesicles diffuse and distribute in both kidneys in varied dimensions, often involving tissue and organs, such as the liver, spleen, and cerebral arteries[1]. It has a predicted incidence of 1 in 100 to 1 in 2,500 individuals[2,3]. The synergistic occurrence of enlarged kidneys and/or reduced glomerular filtration rate and progressive kidney function decline occur over several decades and often result in end-stage renal disease (ESRD) either during or after the sixth decade of life[4]. With the emergence of abundant nephron epithelial cell-derived fluid-filled cysts, whose expansion compresses and damages the surrounding normal parenchyma, 50% of ADPKD patients ultimately develop ESRD[5]. Additionally, ADPKD accounts for 8-10% of the global ESRD patient population[6]. Among diseases that necessitate renal replacement therapy (RRT), ADPKD ranks fourth in terms of incidence and prevalence[7]. Moreover, 1 in 10 patients requiring RRT have ADPKD[8].

ADPKD is typically brought on by pathogenic variants in the *PKD1* (78%) and *PKD2* (15%) and other minor genes: *GANAB*, *DNAJB11*, *ALG9*, *ALG5*, and *IFT140*[9-11]. Until a few decades ago, ADPKD was considered an untreatable disease, which relentlessly progresses towards ESRD owing to a lack of specific interventions. However, recent data[12] from the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) Registry suggested that conventional chronic kidney disease treatments do not minimize RRT requirement in ADPKD.

Over the past decade, enhancements in the genetic and molecular pathobiological knowledge of ADPKD focused on certain abnormal signaling networks that relate to disease pathology in an attempt to delay disease progression[13]. The vaso-

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pressin V2 receptor antagonists tolvaptan[14] and somatostatin octreotide[15] are the only ADPKD drugs approved by the Food and Drug Association. However, among the tolvaptan side effects is nephrogenic diabetes insipidus[16], which results from polyuria (average 6-8 L/d)[17], which restricts its usage in the clinics. Somatostatin octreotide[18] had been observed as evidence of efficacy in reducing renal function decline only in the early period. Hence, it is both critical and urgent to establish novel efficacious drugs that delay ADPKD development, and/or reverse its progression to ESRD.

Emerging reports revealed that metformin, a frequently used drug for treating type 2 diabetes, also potentially treats ADPKD *via* activation of the metabolic sensor AMP-activated protein kinase (AMPK)[19]. Moreover, certain studies[20-23] also reported that metformin delays ADPKD progression. However, the available data regarding this remains controversial.

Herein, we conducted an extensive review and meta-analysis (MA) of randomized controlled trials (RCTs) that examined the influence of metformin on ADPKD progression. Our findings can potentially assist clinical decisions for metformin usage against ADPKD.

Materials and Methods

Research Design

Data reporting utilized the preferred reporting items for systematic reviews and meta-analyses (PRISMA)[24] guidelines.

Screening Criteria

We systematically screened multiple databases, namely, PubMed, Clinicalkey, Google Scholar, Medline, Embase, and Cochrane, from the initiation date till June 2023, for articles on ADPKD, either with metformin (experimental) or placebo (control). The employed search terminology is as follows: metformin and ADPKD. Our literature screening was restricted to 'human studies' and 'English' and was not limited based on the publication year.

Inclusion/Exclusion Guidelines

Only studies that compared outcomes of metformin *vs.* treatment were eligible for our investigation. The following articles were selected for MA: (1) those examining patients who received ADPKD treatment; (2) clinical intervention with placebo or metformin; (3) complete manuscript and available unpublished information, and (4) studies disclosing the entire subject population and appropriate results. Reviews, single-arm studies, or studies with insufficient data were eliminated from the MA.

Data Retrieval

Two authors (FY and XLJ) performed separate data retrieval of the following parameters: study demographics (author name, nationality, calculus description, publication year, sample size, and detail methods), intervention [metformin], outcome [alteration in estimated glomerular filtration rate (eGFR) and height-adjusted total kidney volume (htTKV)], and complications. All disagreements in data extraction were settled *via* discussion and agreement.

Bias Risk Assessment

Calibration was done with the Cochrane Collaboration tool[25]. Two reviewers (XSC and XLJ) assessed and reported the bias risk and conducted separate evaluations of individual studies. The risk was categorized as 'No' if the reported data violated the standards and 'unclear' if the data was insufficient and an obvious conclusion could not be made. Any disagreements concerning screening, selection eligibility, or risk evaluations were resolved by reviewers *via* discussion and mutual agreement.

Statistical Analysis

All data analyses employed the RevMan v5.3.0 (The Cochrane Collaboration, Oxford, UK). A p-value < 0.05 was set as the significance threshold. Categorical outcomes and risk ratios (RRs) with 95% confidence interval [CI] were assessed using the Mantel-Haenszel method. We assessed continuous outcomes and mean difference (MD) with 95% CI using the inverse variance method. Heterogeneity evaluation among publications was assessed using the Chi-square test and I^2 statistic. A random-effects model was used for data with heterogeneity ($I^2 > 50\%$), and the fixed-effects model was used for data without heterogeneity. Sensitivity analysis was used to evaluate the influence of a single investigation on the overall estimation. In this analysis, 1 study was sequentially eliminated, or subgroup analysis was performed. Lastly, since our eligible study quantity was relatively low (< 10), we did not evaluate publication bias.

Results

Study Demographics

Out of the 903 eligible articles, 895 were eliminated following title and abstract screening. In addition, 4 articles were excluded owing to their study design and lack of available data. Ultimately, we selected 1 retrospective study[20] and 3 RCTs[21-23] that assessed metformin-mediated alleviation of ADPKD symptoms. Figure 1 details our strict inclusion and exclusion process, and the 4 selected article demographics are summarized in Table I.

Study Quality

Out of the 4 articles, 1 was not randomized[20]; 1 did not report the allocation concealment, as well as the participant and personnel blinding protocols[20]; 2 had unclear detection bias risk[20,21], and all were free of other biases (Table I). We did not employ study quality as a selection criterion in this study. Additionally, using a funnel plot, we demonstrated a qualitative estimation of publication bias. The plot was very symmetric, with four squares well-contained within the large triangle, and no obvious bias evidence (Figure 2).

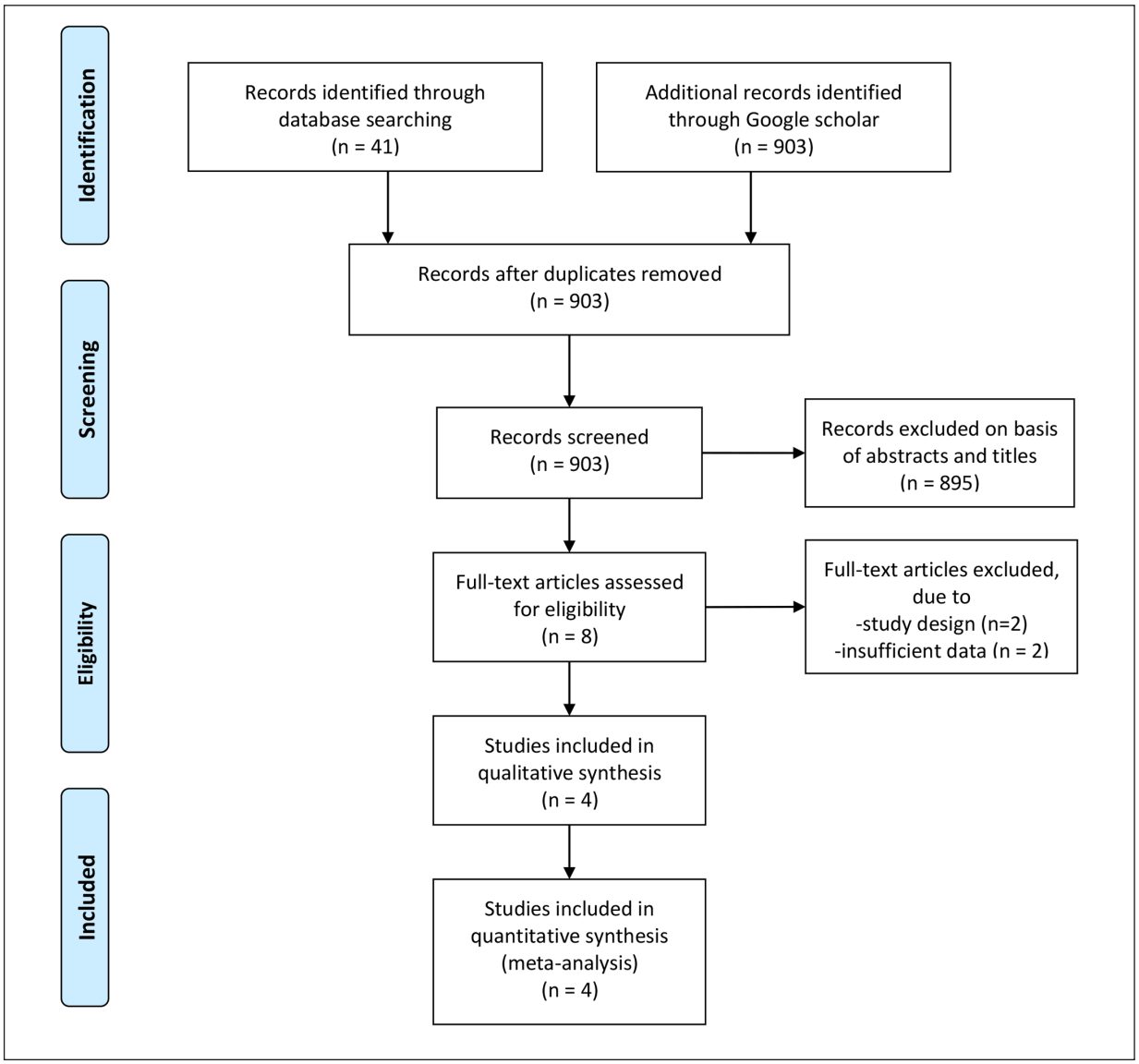

Figure 1. PRISMA Flow diagram.

Table I. Characteristics of the included studied and quality assessment.

Characteristic	[20]	[21]	[22]	[23]
Country	Italy	USA	USA	Netherlands
Author	Pisani	Brosnahan	Perrone	Kramers
Year	2018	2021	2021	2022
Patients, n (in/co)	7/7	21/22	37/44	13/13
Design	Retrospective	RCT	RCT	RCT
Experimental time	36 months	12 months	12 months	2 months
Treatment (in/co)	Me/no	Me/pl	Me/pl	Me/pl
Dosage of Me at the start	500 mg bid	500 mg bid	500 mg qd	500 mg bid
The maximum dosage of Me	500 mg bid	1,000 mg bid	1,000 mg bid	1,000 mg bid
Results				
Change in eGFR, mL/min/1.73 m^2 (mean ± SD)				
Me group	-0.9 ± 2.43	-0.41 ± 8.29	-1.71 ± 4.59	-1.1 ± 2.94
Control group	-5 ± 2.43	-3.35 ± 7.97	-3.07 ± 4.91	0 ± 11.53
Change in htTKV, mL/m (mean ± SD)				
Me group	NR	3.45 ± 5.96	3.87 ± 8.66	NR
Control group	NR	3.15 ± 7.55	2.16 ± 8.65	NR
Complication and Adverse events				
Hypoglycemia/patients, n				
Me group	1/7	1/26	4/49	NR
Control group	0/7	1/25	4/48	NR
Gastrointestinal side effects/Adverse events, n				
Me group	NR	40/69	1/8	9/24
Control group	NR	18/41	0/5	2/10
Quality assessment				
Random sequence generation	No	Yes	Yes	Yes
Allocation concealment	Unclear	Yes	Yes	Yes
Blinding of participants and personnel	Unclear	Yes	Yes	Yes
Blinding of outcome assessment	Unclear	Unclear	Yes	Yes
Complete outcome data	Yes	Yes	Yes	Yes
No selective reporting	Yes	Yes	Yes	Yes
No other bias	Yes	Yes	Yes	Yes

Me, metformin; Pl, placebo; RCT, randomized controlled trials; in, intervention; co, control; eGFR, estimated glomerular filtration rate; htTKV, height-adjusted total kidney volume; SD, Standard Deviation; bid, bis in die; NR, not reported.

In all[20-23], we analyzed studies for alterations in eGFR. The studies exhibited insignificant heterogeneity. Thus, we utilized the fixed-effects model (p = 0.28; I^2 = 22%). We revealed considerable protection against eGFR decline after metformin treatment (MD = 3.05, 95% CI = 0.82-3.79; p = 0.002), as opposed to controls (Figure 3).

Considering that one of the included studies did not undergo randomized controlled allocation, we excluded this study and conducted a subgroup analysis. In terms of subgroup analysis, we revealed inconsistencies between the subgroup and overall analysis results, with an MD value of 1.39 (95% CI = - 0.44–3.21; p = 0.14) (Figure 4).

We examined 2 studies[21,22] for htTKV alterations, as they presented corresponding results. We noted insignificant heterogeneity among the 2 studies; thus, we utilized the fixed-effects model (p = 0.63; I^2 = 0%). We revealed insignificant al-

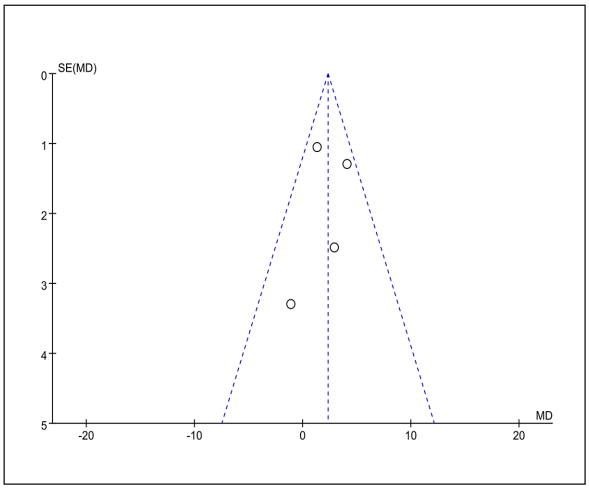

Figure 2. Funnel plot of the studies presented in our study. SE standard error, MD mean difference. Primary outcome: Alterations in eGFR and htTKV.

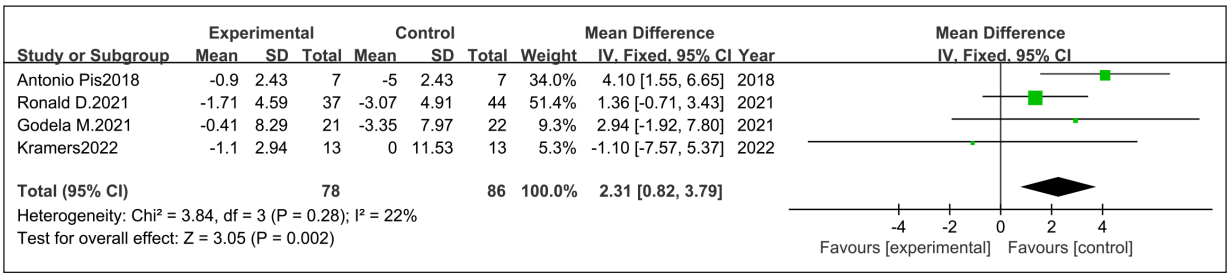

Figure 3. Forest plot of change in eGFR.

teration in htKTV reduction following metformin usage (RR = 0.7, 95% CI = -1.82-3.86; $p = 0.48$), as opposed to controls (Figure 5).

Metformin-induced gastrointestinal adverse events were reported in 3 out of 4 studies[21-23]. We noted insignificant heterogeneity among studies; thus, the fixed-effects model was used ($p = 0.85$; $I^2 = 0\%$). Based on our analysis, the gastrointestinal side effects were elevated among the metformin-treated patients *vs.* control; however, it was not significant (RR = 1.40, 95% CI = 0.95-2.06, $p = 0.09$) (Figure 6).

Only 1 investigation did not report hypoglycemia complication[23]. Hence, we assessed the reported complications of 3 remaining studies[20-22]. Owing to the presence of insignificant heterogeneity among studies, we used the fixed-effects model for complication analysis ($p = 0.73$; $I^2 = 0\%$). We revealed no significant difference between the metformin-treated and control patients (RR = 0.98, 95% CI = 0.35-2.77, $p = 0.97$) (Figure 7).

Sensitivity Analysis

We determined insignificant heterogeneity among all outcomes. Thus, we did not perform sensitivity analysis for result stability evaluation.

Discussion

At present, it is well established that ADPKD with progressive multiple, bilateral renal cysts development includes both fluid release

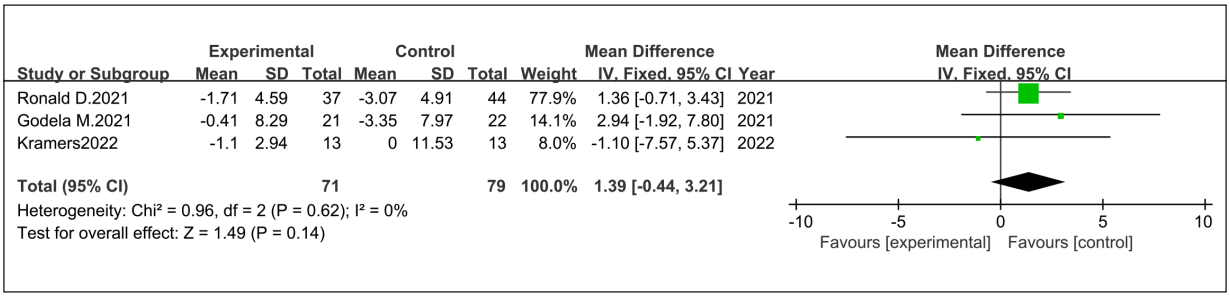

Figure 4. Forest plot of subgroup analysis depicting the change in eGFR of studies with randomized controlled allocation.

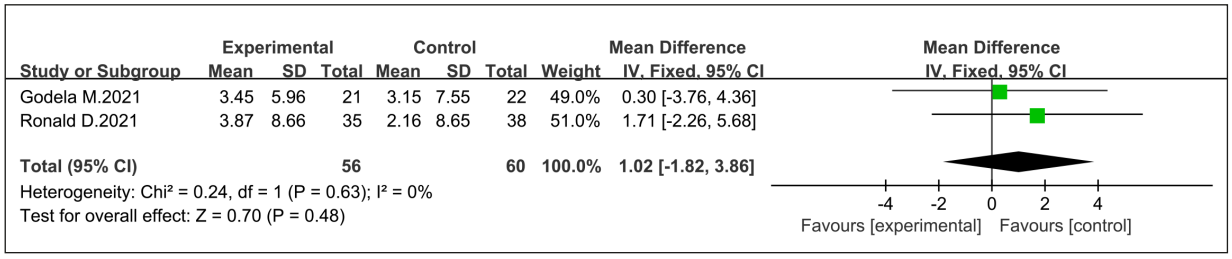

Figure 5. Forest plot of change in htTKV. Secondary outcomes: Hypoglycemia- and gastrointestinal-related adverse events.

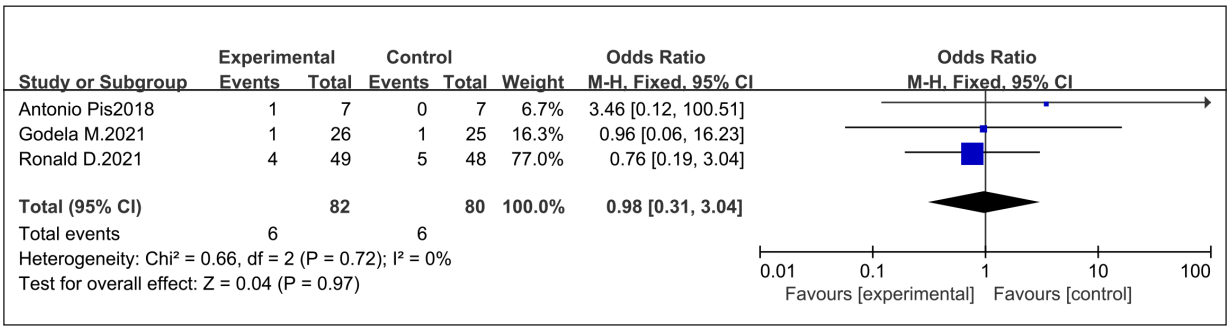

Figure 6. Forest plot of hypoglycemia.

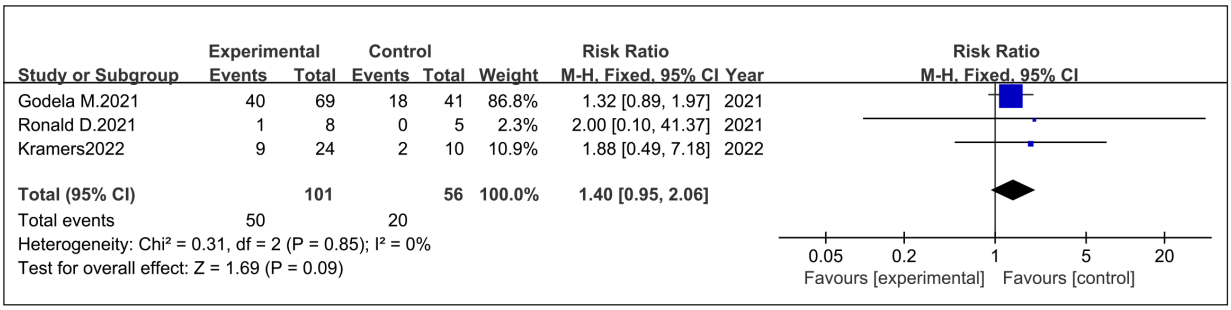

Figure 7. Forest plot of gastrointestinal related adverse events.

and aberrant cyst lining epithelial cell proliferation. The mammalian target of rapamycin (mTOR) axis modulates cyst epithelial cell hyperproliferation[26], while the cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel regulates cyst fluid release[27]. Of interest, AMPK activity and negatively modulates both mTOR and CFTR[28]. Consequently, metformin, a pharmacological AMPK activator, has potential beneficial effects on ADPKD, which is corroborated by emerging experimental and clinical data on ADPKD patients[21] and ADPKD animal models[29]. Using preclinical and extrapolating experimental data[30] in humans, it was revealed that AMPK must be activated among patients using metformin *via* a daily dose of 1,000-1,500 mg.

Based on our preliminary literature screening, this extensive review and MA is the first to examine the influence of metformin usage on ADPKD treatment outcomes. Herein, we demonstrated that metformin successfully delayed renal dysfunction progression among ADPKD patients. The findings of this study corroborate with the investigation by Pisani et al[20]. However, other studies[21-23] demonstrated insignificant eGFR alterations between metformin-treated and untreated patients, with a smaller decline in eGFR in the metformin-treated group. In subgroups analysis with RCTs[21-23], we observed no marked difference in metformin treatment of ADPKD. However, in the investigation by Brosnahan et al[21], it was revealed that although patients exhibited markedly larger kidneys and augmented hypertension, compared to the placebo group, the eGFR decline was much smaller among metformin-treated patients, thereby it was expected to have a larger eGFR decline in placebo group.

Throughout disease progression, the kidney volume becomes larger and larger. Herein, we did not detect marked differences in htTKV alterations between the patient groups. However, Brosnahan et al[21] further examined metformin efficacy on ADPKD patients. The repeated analyses were used for patients with htTKV > 600 mL/m, patients with htTKV > 800 mL/m, as well as for those in the more severe Mayo Imaging Classes 1C-E. Herein, it was revealed that htTKV alteration was not only numerically reduced among all 3 metformin *vs.* placebo subgroups. Meanwhile, studies observed a marked different in the subgroup with htTKV > 800 mL/m. This

discovery reminds us that metformin may be able to be used in rapidly progressive ADPKD, similar to tolvaptan[18], to slow down the course of the disease. Additional RCTs are warranted to elucidate the true nature of the metformin-mediated delay in ADPKD progression.

Over several years, metformin has been the go-to drug for treating diabetes and polycystic ovarian syndrome[31]. There is some concern that metformin usage may induce hypoglycemia among diabetic patients. Fortunately, this is not a prevalent complication, according to prior reports[20-22]. Herein, we observed no strong differences in hypoglycemia occurrence between the two patient cohorts. Despite reports[21] stating that gastrointestinal adverse events are the most prevalent (63.6%), such as nausea, vomiting, diarrhea, acid reflux and flatulence, following metformin treatment of ADPKD[32], the complication may resolve automatically or after dosage reduction of metformin. In this report, we observed a slight increase in the gastrointestinal adverse events among metformin-treated patients *vs.* controls. However, the values were not significant. Thus, additional explorations are warranted to verify the metformin-mediated regulation of the digestive tract during ADPKD treatment.

The selected studies had satisfactory methodological quality. However, our work still had certain potential limitations. We did not have enough metformin-related adverse effect information for extensive analyses. Moreover, unintended differences in patient age, kidney function, and metformin dosage may have introduced unpredictable bias. Likewise, unpublished and missing negative information may have introduced bias in metformin-induced results. Lastly, our sample article size was relatively small.

Conclusions

According to our findings, metformin was tolerable, safe, and successful in minimizing eGFR decline among ADPKD patients. However, it failed to delay the htTKV progressive enlargement. In the literature, it is reported that gastrointestinal side effects were the primary challenges of metformin usage among ADPKD patients. Herein, we demonstrated no evident difference in gastrointestinal side effects between the two patient cohorts. Our MA faced some limitations. In future investigations, we recommend examining additional high-quality RCTs to uncover the true effects of metformin usage among ADPKD patients.

Conflict of Interest

The authors declare that they have no conflict of interests.

Acknowledgements

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Ethics Approval

As this is a systematic review, the ethical approval was not required.

Informed Consent

As this is a systematic review, the informed consent was not required.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

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None.

Authors' Contribution

Feng Yao: Study design, Manuscript writing. ShiQuan Huang: Project development, Manuscript writing. XueSong Cheng: software. Ke Li: Data collection, Data management, Manuscript editing. XiaoLiang Jiang: Study design, software. All authors read and approved the final manuscript.

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