Effect of Statins on Renal Function and Total Kidney Volume in Autosomal Dominant Polycystic Kidney Disease

Cheng Xue^a Li-Ming Zhang^b Chenchen Zhou^c Chang-Lin Mei^a
Sheng-Qiang Yu^a

^aDepartment of Nephrology, Changzheng Hospital, Second Military Medical University, Shanghai, China;

^bDepartment of Nephrology, Zhabei Central Hospital of Jing'an District, Shanghai, China; ^cOutpatient Department, Yangpu Third Military Retreat, Shanghai, China

Keywords

Polycystic kidney disease · Autosomal dominant · Statins · Glomerular filtration rate · Proteinuria · Meta-analysis

Abstract

Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary nephropathy with few treatments to slow renal progression. The evidence on the effect of lipid-lowering agents (statins) on ADPKD progression remains inconclusive. **Methods:** We performed a systematic review and meta-analysis by searching the PubMed, Embase, Web of Science, and Cochrane databases (up to November 2019). Changes in estimated glomerular filtration rate (eGFR) and total kidney volume (TKV) were the primary outcomes. Mean differences (MDs) for continuous outcomes and 95% confidence intervals (CIs) were calculated by a random-effects model. **Results:** Five clinical studies with 648 participants were included. Statins did not show significant benefits in the yearly change in eGFR (4 studies, MD = -0.13 mL/min/m², 95% CI: -0.78 to 0.52 , $p = 0.70$) and the yearly change in TKV (3 studies, MD = -1.17% , 95% CI: -3.40 to 1.05 , $p = 0.30$) compared with the control group. However, statins significantly decreased uri-

nary protein excretion (-0.10 g/day, 95% CI: -0.16 to -0.03 , $p = 0.004$) and serum low-density lipoprotein level (-0.34 mmol/L, 95% CI: -0.58 to -0.10 , $p = 0.006$). **Conclusion:** Despite these proteinuria and lipid-lowering benefits, the effect of statins on ADPKD progression was uncertain.

© 2020 The Author(s)

Published by S. Karger AG, Basel

Introduction

Autosomal dominant polycystic kidney disease (ADPKD), characterized by progressive growth of cysts from renal tubules, affects approximately 1–2% people worldwide [1]. ADPKD is the 4th pathogenesis of renal replacement therapy [1]. Increased enlargement of cysts, abnormal fluid secretion, and inflammation play important roles in ADPKD progression [2]. Estimated glomerular filtration rate (eGFR), proteinuria, and total kidney volume (TKV) are the most commonly used indicators to monitor ADPKD progression [3].

Cheng Xue and Li-Ming Zhang contributed equally.

Table 1. Characteristics of included trials

Studies	Year	Country	Rando- mization setting	Setting	Duration, months	Groups	N	Male/ female, n	Age, years	Dose, m/d	eGFR, mL/ min/1.73 m ²	HtTKV	UPE, g/d	Outcomes
van Dijk et al. [8]	2001	Netherlands	RCT, DB, cross-over	SC	1	Simvastatin	10	6/4	35±4	40	124±4	NA	NA	①④⑤⑥⑦
						Placebo	10	6/4	35±4		124±4	NA	NA	
Fassett et al. [14]	2010	Australia	RCT, open-label	SC	24	Pravastatin	29	12/17	53±15	20	58.5±18.2	NA	0.37±0.49	①②④⑤⑥⑦
						No treatment	20	7/13	49±12		49.9±23.2	NA	0.22±0.23	
Cadnapaphornchai et al. [7]	2014	USA	RCT, DB	SC	36	Pravastatin	56	NA	16±4	20/40	135±28	336±187	0.1±0.1	①②③④⑤⑥⑦
						Placebo	54	NA	16±4		138±27	315±175	0.2±0.2	
Zhou and Mei [15]	2016	China	RC	SC	24	Statin	16	8/8	41±4	NA	86±27	827.5±375.3	NA	①②
						No treatment	15	7/8	38±3	NA	89±26	759.1±342.8	NA	
Brosnahan et al. [9]	2017	USA	RC	Multi- center	36	Statin	56	24/32	35±3	NA	94.9±7.2	703±65	NA	①②
						No treatment	382	190/192	37±1	NA	91.4±0.9	702±21	NA	

RCT, randomized controlled trial; RC, retrospective cohort study; SC, single center; DB, double-blind; eGFR, estimated glomerular filtration rate; HtTKV, height-adjusted total kidney volume; UPE, urinary protein excretion; NA, not available. ① eGFR; ② HtTKV; ③ UPE; ④ total cholesterol; ⑤ triglycerides; ⑥ low-density lipoprotein; ⑦ high-density lipoprotein.

Treatments for ADPKD mainly include diet and lifestyle management, hypertension interventions, and tolvaptan for high-risk ADPKD patients [4]. In recent years, hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) were found to have anti-inflammatory, antiproliferative, and antioxidant effects in addition to lipid-lowering effects in ADPKD from experimental and human data [5, 6]. However, the evidence of statin treatment in ADPKD patients remains controversial.

Cadnapaphornchai et al. [7] performed a randomized controlled trial (RCT) to investigate the effects of pravastatin in children and young adults with ADPKD. They found that pravastatin could decrease TKV but had no significant effect on eGFR. However, van Dijk et al. [8] suggested that simvastatin may have an ameliorative effect on renal function decrease in a small cohort study of 10 ADPKD patients. A post hoc analysis of the HALT-PKD trial [9] showed that statin treatment did not reduce the TKV change compared with the nonuse group. Therefore, we performed this systemic review and meta-analysis to summarize present studies evaluating statins on ADPKD progression for a better understanding of statins in ADPKD.

Materials and Methods

This systemic review was performed following the PRISMA guideline and the standard PICOS strategy [10]. The authors (X.C. and Z.C.) performed a literature search using the PubMed, Embase, Web of Science, and Cochrane databases (up to November 2019). The PubMed search terms (both as medical subject headings and free-text terms) were as follows: (polycystic kidney or polycystic kidney disease or PKD or ADPKD) and (statins or hydroxymethylglutaryl-CoA reductase inhibitors or HMG CoA or hypolipidemic agents) and (humans). The search terms were adapted for the other electronic data source. Google scholar and Baidu scholar (Chinese) were searched to find additional relevant studies.

The literature was evaluated by 2 authors (X.C. and Z.C.) independently with the following eligibility criteria: (1) RCT or cohort study (retrospective or prospective); (2) patients with ADPKD; (3) comparing the effects of statins with placebo or no-use; and (4) providing data on renal outcomes or TKV. When more than one publication of one cohort study was found, we used the latest publication. We excluded studies with the following properties: (1) patients received any other lipid-lowering interventions besides statins; (2) patients with autosomal recessive polycystic kidney disease; (3) and studies with no renal outcomes of eGFR, TKV, and proteinuria. We attempted to contact the original investigators to obtain additional information if necessary.

Studies estimating the effects of statins in ADPKD patients were selected. Mean difference (MD) and 95% confidence intervals (CI) were calculated in the random-effects model. We used the Cochrane tool to evaluate the quality of the included studies. Sta-

Fig. 1. Flow chart of study identification, inclusion, and exclusion.

tistical heterogeneity was assessed using Q and I^2 statistics [11]. The sensitivity analysis was conducted by excluding each study at a time to find whether the result was affected by a large study or an extreme result. Begg's test and Egger's test were used to investigate the publication bias [12, 13]. The primary outcomes were eGFR yearly changes and TKV yearly changes. Secondary outcomes were urinary protein excretion (UPE) and lipid levels. All analyses were assessed using Revman (version 5.3, Cochrane) and Stata (version 12, College Station, TX, USA). When $p < 0.1$, the heterogeneity was significant. Otherwise, the p value was 2-sided with a significance level of 0.05.

Results

Literature Search and Study Characteristics

The process of selecting relevant studies initially found 69 publications from the databases (Fig. 1). After exclusion of irrelevant studies and duplicates, 16 potentially eligible studies were deeply screened. Eventually, 5 studies were included for the final meta-analysis [7–9, 14, 15]. Characteristics of the included studies are listed in Table 1. Three RCTs and 2 retrospective cohort studies with 648 patients were included to investigate the effects of statins in ADPKD [7–9, 14, 15]. Four studies [7–9, 14]

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Brosnahan, 2017	+	+	+	+	+	?	?
Cadnapaphornchai, 2014	+	+	+	+	?	+	?
Fassett, 2010	+	?	+	+	?	?	?
van Dijk, 2001	+	?	+	+	?	?	?
Zhou, 2017	+	+	+	+	+	+	?

Fig. 2. The risk of bias summary of the included studies.

Fig. 3. Effects of statins on eGFR change in ADPKD. eGFR, estimated glomerular filtration rate; ADPKD, Autosomal dominant polycystic kidney disease.

Fig. 4. Effects of statins on TKV change in ADPKD. TKV, total kidney volume; ADPKD, Autosomal dominant polycystic kidney disease.

were performed in Caucasians and 1 study [15] in Asians. Most of the participants were at CKD stage 1–3. The follow-up times ranged from 1 to 36 months. The bias risk of the studies is shown in Figure 2. Random sequence was reported in 3 RCTs [7, 8, 14]. Allocation concealment was not reported in any of the studies except the study by Cadnapaphornchai et al. [7].

Primary Outcomes

The yearly change of eGFR did not differ significantly between the statin group and the control group (4 studies, 602 patients, MD = -0.13 mL/min/m², 95% CI: -0.78 to 0.52 , $p = 0.70$; $I^2 = 0\%$, $p = 0.90$, Fig. 3). Sensitivity analysis by excluding one study each time found consistent results. Publication bias was not found (Begg's test $p = 0.60$; Egger's test, $p = 0.30$). Although van Dijk et al. [8] found an ameliorative effect of simvastatin on renal dysfunction, the number of ADPKD patients was few, and the follow-up time was too short (2 months).

There was also not a significant difference in the yearly rate of height-adjusted TKV between the statins group and the control group (3 studies, 560 patients, MD = -1.17% , 95% CI -3.40 to 1.05 , $p = 0.30$, Fig. 4). There was moderate heterogeneity ($I^2 = 70\%$, $p = 0.03$). In the subgroup analysis by age, the pediatric study of 110 ADPKD patients treated with lisinopril and randomized to pravastatin or placebo for 3 years demonstrated a benefit in TKV expansion associated with pravastatin.

Secondary Outcomes

Statins significantly decreased UPE compared with the control group (2 studies, MD = -0.10 g/day, 95% CI: -0.16 to -0.03 , $p = 0.004$; $I^2 = 0\%$, $p = 0.43$, Fig. 5). On the lipid-lowering effect, statins reduced the low-density lipoprotein level (MD = -0.34 mmol/L, 95% CI: -0.58 to -0.10 , $p = 0.006$). However, there were no significant differences in total cholesterol, high-density lipoprotein, and triglycerides (Fig. 5).

Fig. 5. Effects of statins on proteinuria and lipids in ADPKD. ADPKD, Autosomal dominant polycystic kidney disease; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Discussion

Statins have been widely used for reducing lipids and preventing cardiovascular events. Statins exert pleiotropic effects besides reducing serum lipid levels [16]. Statins could inhibit the mevalonate pathway which plays important roles in not only cholesterol synthesis but also cell signaling processes, such as the cell cycle and apoptosis

[16]. In ADPKD, statins could inhibit the cell proliferation of cystic cells in vivo and vitro [17]. Lovastatin was found to significantly reduce the cyst volume and serum urea nitrogen level in Han:SPRD rats [17, 18]. In recent years, several clinical studies confirmed that statins could enhance endothelial function and renal blood flow and attenuate vascular inflammation in patients with ADPKD [5, 6].

Our study summarized the evidence of statins on ADPKD progression based on existing clinical studies. The effects of statins on the eGFR change in ADPKD remain uncertain. A Cochrane systemic review [19] with 47 studies (39,820 participants) also found uncertain effects of statins on eGFR in CKD patients.

Statins were not associated with a lower rate of TKV change in our results. The RCT in pediatric ADPKD patients (mean age 16 ± 4 years) showed that treatment with pravastatin was associated with a slower increase in TKV, but the HALT study found no difference in TKV between the statin and nonuse groups [9]. The HALT study included older patients (mean age 36.2 ± 8.3 years), indicating that the antiproliferative effects of statins might work in the early stage of ADPKD [9]. This was consistent with the findings that statin benefits in renal plasma flow were limited to the early stages of ADPKD [20]. An ongoing RCT (NCT03273413) that uses statins in early stage ADPKD patients may give us an answer in the future.

According to our results, statins significantly reduced the proteinuria in ADPKD patients. This was consistent with a recent study that confirmed that statin therapy might modestly reduce proteinuria in patients with CKD [21].

This meta-analysis has a few limitations. First, the number of included studies is small. There may not be a sufficient statistical power to achieve robust conclusions. The outcomes still need more studies to prove the findings. Second, a meta-analysis illustrating statins on the progression of CKD found that the high-intensity statin group had a significantly slower decline of eGFR compared to the control group but did not find a benefit of eGFR in the low-intensity statin group [22]. Although subgroup analysis according to high and low intensities of statin could not be performed in this study, future studies could try a higher dose of statin to treat ADPKD.

Third, there is a moderate heterogeneity in the results of TKV. Differences in the follow-up time, the baseline renal function, and the age among the studies may lead to heterogeneity.

In summary, despite the proteinuria and lipid-lowering benefits, the effect of statins on ADPKD progression was uncertain. More RCTs with larger sample sizes and higher doses of statins are needed for validation.

Statement of Ethics

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Conflict of Interest Statement

All the authors declared no competing interests.

Funding Sources

This work was supported by the National Natural Science Foundation of China (81370784; 81770659, 81873595, 81670612, and 81700579), National Key Research and Development Program of China (2016YFC0901502), Shanghai Top Priority Key Clinical Disciplines Construction Project (2017ZZ02009), Shanghai Science and Technology Talents Program (19YF1450300), Research Projects of Shanghai Traditional Medicine (ZHYX-ZXYJHZZ-2-201713), and Research Projects of Shanghai Science and Technology Committee (17411972100).

Author Contributions

Y.S. was responsible for the study concept and design. Z.C., Z.L., and X.C. performed the literature search. Z.C., M.C., and X.C. analyzed and interpreted the data. X.C. drafted the manuscript.

References

- 1 Xue C, Zhou CC, Wu M, Mei CL. The clinical manifestation and management of autosomal dominant polycystic kidney disease in China. *Kidney Dis*. 2016;2:111–9.
- 2 Xue C, Zhou CC, Sun LJ, He LL, Xu CG, Dai B, et al. Effects of endothelial nitric oxide synthase gene on end-stage renal disease progression in autosomal dominant polycystic kidney disease. *Nephrology*. 2014;19:630–7.
- 3 Kline TL, Korfiatis P, Edwards ME, Warner JD, Irazabal MV, King BF, et al. Automatic total kidney volume measurement on follow-up magnetic resonance images to facilitate monitoring of autosomal dominant polycystic kidney disease progression. *Nephrol Dial Transplant*. 2016;31:241–8.
- 4 Xue C, Zhou C, Dai B, Yu S, Xu C, Mao Z, et al. Antihypertensive treatments in adult autosomal dominant polycystic kidney disease: network meta-analysis of the randomized controlled trials. *Oncotarget*. 2015;6:42515–29.
- 5 Epstein M, Campese VM. Pleiotropic effects of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors on renal function. *Am J Kidney Dis*. 2005;45:2–14.
- 6 Namli S, Oflaz H, Turgut F, Alisir S, Tufan F, Ucar A, et al. Improvement of endothelial dysfunction with simvastatin in patients with autosomal dominant polycystic kidney disease. *Ren Fail*. 2007;29:55–9.
- 7 Cadnapaphornchai MA, George DM, McFann K, Wang W, Gitomer B, Strain JD, et al. Effect of pravastatin on total kidney volume, left ventricular mass index, and microalbuminuria in pediatric autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol*. 2014;9:889–96.
- 8 van Dijk MA, Kamper AM, van Veen S, Souverijn JH, Blauw GJ. Effect of simvastatin on renal function in autosomal dominant polycystic kidney disease. *Nephrol Dial Transplant*. 2001;16:2152–7.

- 9 Brosnahan G, Abebe KZ, Rahbari-Oskoui FF, Patterson CG, Bae KT, Schrier RW, et al. Effect of statin therapy on the progression of autosomal dominant polycystic kidney disease. A secondary analysis of the HALT PKD trials. *Curr Hypertens Rev*. 2017;13:109–120.
- 10 Xue C, Yang B, Zhou C, Dai B, Liu Y, Mao Z, et al. Fibroblast growth factor 23 predicts all-cause mortality in a dose-response fashion in pre-dialysis patients with chronic kidney disease. *Am J Nephrol*. 2016;45:149–59.
- 11 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–60.
- 12 Egger M, Davey Smith G, Schneider M, Mindes C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629–34.
- 13 Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994;50:1088–101.
- 14 Fassett RG, Coombes JS, Packham D, Fairley KF, Kincaid-Smith P. Effect of pravastatin on kidney function and urinary protein excretion in autosomal dominant polycystic kidney disease. *Scand J Urol Nephrol*. 2010;44:56–61.
- 15 Zhou J, Mei C. Statin use in autosomal dominant polycystic kidney disease. *Medres of Nephrolog*. 2016;4:5–9.
- 16 Marz W, Koenig W. HMG-CoA reductase inhibition: anti-inflammatory effects beyond lipid lowering? *J Cardiovasc Risk*. 2003;10:169–79.
- 17 Klawitter J, Zafar I, Pennington AT, Klepacki J, Gitomer BY, Schrier RW, et al. Effects of lovastatin treatment on the metabolic distributions in the Han:SPRD rat model of polycystic kidney disease. *BMC Nephrol*. 2013;14:165.
- 18 Gile RD, Cowley BD Jr, Gattone VH 2nd, O'Donnell MP, Swan SK, Grantham JJ. Effect of lovastatin on the development of polycystic kidney disease in the Han:SPRD rat. *Am J Kidney Dis*. 1995;26:501–7.
- 19 Palmer SC, Navaneethan SD, Craig JC, Johnson DW, Perkovic V, Hegbrant J, et al. HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis. *Cochrane Database Syst Rev*. 2014; CD007784.
- 20 Zand L, Torres VE, Larson TS, King BF, Sethi S, Bergstralh EJ, et al. Renal hemodynamic effects of the HMG-CoA reductase inhibitors in autosomal dominant polycystic kidney disease. *Nephrol Dial Transplant*. 2016;31:1290–5.
- 21 Su X, Zhang L, Lv J, Wang J, Hou W, Xie X, et al. Effect of statins on kidney disease outcomes: a systematic review and meta-analysis. *Am J Kidney Dis*. 2016;67:881–92.
- 22 Sanguankeo A, Upala S, Cheungpasitporn W, Ungprasert P, Knight EL. Effects of statins on renal outcome in chronic kidney disease patients: a systematic review and meta-analysis. *PLoS One*. 2015;10:e0132970.