Renal hemodynamic effects of the HMG-CoA reductase inhibitors in autosomal dominant polycystic kidney disease

Ladan Zand¹, Vicente E. Torres¹, Timothy S. Larson¹, Bernard F. King², Sanjeev Sethi³, Eric J. Bergstralh⁴, Andrea Angioi¹ and Fernando C. Fervenza¹

¹Department of Medicine, Division of Nephrology and Hypertension, Mayo Clinic College of Medicine, Rochester, MN, USA, ²Department of Radiology, Mayo Clinic College of Medicine, Rochester, MN, USA, ³Division of Anatomic Pathology, Department of Laboratory Medicine and Pathology, Mayo Clinic College of Medicine, Rochester, MN, USA and ⁴Department of Statistics, Mayo Clinic College of Medicine, Rochester, MN, USA

Correspondence and offprint requests to: Fernando C. Fervenza; E-mail fervenza.fernando@mayo.edu

ABSTRACT

Background. To determine the effect of statins on renal hemodynamics in normal volunteers and those with autosomal dominant polycystic kidney disease either with mild or moderate renal dysfunction.

Methods. Thirty-two study subjects were enrolled in this study: 11 normal volunteers, 11 study subjects with autosomal dominant polycystic kidney disease (ADPKD) and mild kidney disease and 10 study subjects with ADPKD and moderate kidney disease. Subjects in each group received simvastatin 40 mg once daily for a period of 4 weeks. Renal blood flow was measured based on para-amino-hippurate (PAH) clearance and with the use of a magnetic resonance (MR) scanner at the beginning and following 4 weeks of therapy with statins.

Results. At the end of the study, except for the lipid profile, which was significantly lower in all groups, other laboratory results showed no change. Four weeks of therapy with simvastatin resulted in no change in serum creatinine, 24-h urinary protein, sodium, iothalamate clearance, PAH clearance or renal blood flow as measured by MRI or based on PAH clearance.

Conclusions. Four weeks of therapy with simvastatin did not change renal blood flow in the study subjects with ADPKD with mild-to-moderate renal dysfunction or in healthy volunteers.

Clinical Trial Registration Number. NCT02511418.

Keywords: ADPKD, HMG-CoA reductase inhibitor, renal blood flow, statins

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic kidney disease, with a progressive course leading to end-stage renal disease [1]. Renin-angiotensin system activation, hypertension and vasoconstriction occur early in the course of ADPKD. Endothelial dysfunction plays a major role [2, 3]. Decreased nitric oxide (NO) levels [4–6], increased asymmetric dimethylarginine (ADMA) levels and increased oxidative stress [5, 7–10] are the main causes of endothelial dysfunction in patients with ADPKD. The endothelial dysfunction can in turn impair renal blood flow (RBF) [11]. Reduced RBF in ADPKD patients has been associated with a decline in renal function [12]. Abnormal lipid metabolism has also been implicated in the progression of ADPKD and loss of renal function [13–15]. It is conceivable that improving lipid metabolism and RBF by improving NO bioavailability and reducing oxidative stress would help slow down the progression of ADPKD and improve renal function. Statins, in addition to improving lipid metabolism, have been shown to reduce ADMA levels, increase NO bioavailability and improve endothelial function and flow-mediated dilatation [16–18]. The beneficial effect of statins on RBF and renal function in ADPKD patients is less clear. In a small number of ADPKD patients, simvastatin was shown to improve RBF and function [19]. In this study, we aimed to further evaluate the effect of simvastatin on RBF in ADPKD patients with either mild or moderate renal dysfunction, as well as normal volunteers.
Statin effects on RBF in ADPKD

Methods

Study population

The study was approved by the Institutional Review Board and informed consents were obtained from all patients. A total of 32 patients (≥18 years of age) were enrolled in this study. Patients were divided into three groups: (i) healthy volunteers (n = 11), (ii) study subjects with ADPKD and mild renal dysfunction (n = 11) and (iii) study subjects with ADPKD and moderate renal dysfunction (n = 10). Healthy volunteers were those with no known history of renal disease, a serum creatinine ≤1.3 mg/dL and an iothalamate clearance ≥75 mL/min/1.73 m². Study subjects with ADPKD and mild renal dysfunction had a serum creatinine ≤1.6 mg/dL and an iothalamate clearance ≥65 mL/min/1.73 m². Renal function had to be stable for 3 months preceding the study and blood pressure had to be adequately controlled (<140/90 mmHg), with or without the use of antihypertensive agents. If angiotensin-converting enzyme inhibitors or AT1 receptor blockers were used, they were not to be initiated or their dose increased during the study period. Patients with ADPKD and moderate renal dysfunction had a serum creatinine ≥1.4 but ≤2.0 mg/dL and an iothalamate clearance between 30 and 64 mL/min/1.73 m². The rest of the inclusion criteria were the same as the ADPKD patients with mild renal dysfunction.

Exclusion criteria included the following: use of corticosteroids, cytotoxic drugs (alkylating agents, chlorambucil, cyclophosphamide), mycophenolate mofetil or cyclosporin A therapy; positive hepatitis B surface antigen or hepatitis C antibody; serum transaminase levels [aspartate aminotransferase (AST), alanine aminotransferase (ALT)] ≥2 times the upper limit of normal; the presence of concomitant renal artery stenosis; pregnancy or breastfeeding, or women intending to conceive during the course of the study; the presence or suspicion of active infection, recent serious infection or chronic/recurrent viral or bacterial infection; clinically significant medical conditions that, in the opinion of the investigator, were likely to interfere with the patient’s participation in the study or evaluation of the study medication’s safety or if patients were unable to complete the required testing for magnetic resonance (MR) scanning, which included those with cardiac pacemakers, cerebral aneurysm clips and severe claustrophobia.

Study protocol

All study subjects were seen in the renal function laboratory at the beginning of the study and their iothalamate I¹²⁵ and para-amino-hippurate (PAH) clearance were determined. During the same visit, fasting blood samples were drawn for measurement of complete blood count, serum sodium, potassium, chloride, bicarbonate, serum creatinine, glucose level, AST, alkaline phosphatase and lipid panel [total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglyceride levels. A 24-h urine collection for measurement of sodium, protein and microalbumin was also obtained in all participants. Prior to initiation of therapy, blood pressure was measured in an upright position using a manual cuff. The study subjects then underwent RBF measurements using an MR scanner. Subsequently, study subjects received simvastatin at a dose of 40 mg by mouth once daily at night for a total of 4 weeks. At the end of 4 weeks, the measurements noted above were repeated. The subjects did not undergo dietary modification during the study.

Measurement of GFR, ERPF and renal blood flow

Glomerular filtration rate (GFR) and estimated renal plasma flow (ERPF) were determined by standard iothalamate I¹²⁵ and PAH clearance methods as previously described [20]. RBF was determined in two ways: (i) calculated using the hematocrit (Hct) and ERPF [RBF (mL/min) = 1.1 (ERPF/1 − Hct)] [20] and (ii) measured in each renal artery by breath-hold phase-contrast MRI as previously described [21]. The total RBF was the sum of right and left renal artery blood flow.

Statistical analysis

Power calculation was based on the results of the study by van Dijk et al. [19]. In this study, 10 patients received 40 mg of simvastatin and their renal plasma flow increased from 494 ± 30 to 619 ± 60 mL/min (P < 0.05). Based on these results, it was calculated that a sample size of 20 will have 99% power to detect a difference of 125.0 by means of the RBF, assuming a standard deviation of differences of 65.0 using a paired t-test with a 0.05 one-sided significance level.

Differences between mean values for lipid profile, serum creatinine, GFR and RBF at baseline versus mean values after 4 weeks of therapy were analyzed using two-tailed paired t-test. Between-group differences as measured by absolute differences after 4 weeks of therapy were compared between groups using analysis of variance. Analysis of variance was used when comparing baseline characteristics with normal distribution and results expressed as mean ± standard deviation. Nonparametric Wilcoxon test was used when comparing patient’s baseline characteristics that were not normally distributed and results reported as median with minimum and maximum. A P-value <0.05 was considered significant.

Results

Study subject’s baseline characteristics and laboratory profile

Thirty-two study subjects were enrolled in this study. Eleven were healthy volunteers (6 females and 5 males) with a mean serum creatinine of 1.0 ± 0.2 mg/dL, 11 (8 females and 3 males) had ADPKD with mild renal dysfunction with mean serum creatinine of 1.1 ± 0.3 mg/dL and 10 (6 females and 4 males) had ADPKD with moderate renal dysfunction with mean serum creatinine of 1.8 ± 0.3 mg/dL (Table 1). There were no statistically significant differences in study subjects’ baseline profile, including age, sex, baseline blood pressure and lipid profile (Table 1). In addition, there were no statistically significant differences among three groups when comparing baseline serum sodium, potassium, chloride, bicarbonate, fasting glucose, hemoglobin and AST (data not shown). As expected, 24-h urinary protein and microalbuminuria were significantly different among the three groups, consistent with the presence of renal disease in the ADPKD group (Table 1).
Renal hemodynamics prior to statin therapy

ADPKD patients with moderate renal dysfunction had an iothalamate clearance and PAH clearance that was significantly lower than in ADPKD patients with mild renal dysfunction and normal volunteers (P < 0.0001) (Table 2). There was no statistically significant difference between ADPKD patients with mild renal dysfunction and normal volunteers when comparing iothalamate or PAH clearance.

RBF measured based on PAH clearance and MR scanning was significantly lower in patients with ADPKD and moderate renal dysfunction (369.5 ± 88.5 and 408.7 ± 155.6 mL/min) compared with those with ADPKD and mild renal dysfunction (717.2 ± 189.9 and 582.1 ± 139.9 mL/min) and normal volunteers (820.7 ± 202.8 and 757.3 ± 259.4 mL/min) (P < 0.0001 and P = 0.007) (Table 2). There were no significant differences when comparing the RBF between patients with ADPKD and mild renal dysfunction and normal volunteers using either method (Table 2).

Laboratory profile after simvastatin therapy

Following simvastatin therapy, total cholesterol, LDL and triglyceride were significantly reduced in each group (Table 3). There was, however, no significant difference in total cholesterol, LDL or triglyceride levels among the three groups following therapy (Table 3). There was a statistically significant increase in HDL in the ADPKD patients with moderate renal dysfunction after treatment with statins but no significant change in the other two groups (Table 3).

There was no significant difference among the three groups posttreatment in any of the basic laboratory profiles, including sodium, potassium, bicarbonate, chloride, hemoglobin, AST, fasting glucose and urinary sodium (data not shown). There was no significant reduction in the degree of proteinuria or microalbuminuria or 24-h urinary sodium in patients with ADPKD with mild or moderate renal dysfunction or in normal volunteers following simvastatin therapy (data not shown).

Renal hemodynamics after simvastatin therapy

There was no significant change in creatinine level, iothalamate clearance or PAH clearance after simvastatin therapy in any of the groups (Table 4). Patients with ADPKD and moderate renal dysfunction had an iothalamate clearance of 46.4 ± 11.1 mL/min/1.73 m² after simvastatin therapy compared with 47.1 ± 11.7 mL/min/1.73 m² prior to simvastatin (P = 0.6),...
while patients with ADPKD and mild renal dysfunction had an iothalamate clearance of 82.3 ± 16.7 mL/min/1.73 m² after simvastatin compared with 86.4 ± 15.8 mL/min/1.73 m² prior to simvastatin (P = 0.3). Normal volunteers had an iothalamate clearance of 91.4 ± 15.3 mL/min/1.73 m² after simvastatin therapy compared with 100.3 ± 15.1 mL/min/1.73 m² prior to simvastatin (P = 0.1). The results for serum creatinine and PAH clearance are shown in Table 4.

In addition, there was no significant change in RBF measured via PAH clearance after receiving simvastatin therapy; specifically, 378.2 ± 94.2 mL/min in patients with ADPKD and moderate renal dysfunction compared with 369.5 ± 88.5 mL/min prior to simvastatin (P = 0.05) and 809.2 ± 216.6 mL/min in normal volunteers compared with 820.7 ± 202.8 mL/min prior to simvastatin (P = 0.8) (Table 4).

When using the MR scanner for measurements of RBF, 2 of the 11 normal volunteers, 2 of the 11 patients with ADPKD and mild kidney disease and 3 of 10 patients with ADPKD and moderate kidney disease were excluded because of a technical inability to measure RBF. In those who were included, following simvastatin therapy, there was no significant change in RBF; specifically 431.0 ± 196.2 mL/min in patients with ADPKD and moderate renal dysfunction compared with 408.7 ± 194.4 mL/min in patients with ADPKD and mild renal dysfunction compared with 820.7 ± 202.8 mL/min prior to simvastatin (P = 0.8) (Table 4).

In this study, we evaluated the effect of 4 weeks of therapy with simvastatin 40 mg daily on RBF measured by PAH clearance or MRI in patients with ADPKD with mild and moderate renal dysfunction as well as healthy volunteers. The use of statins resulted in a significant reduction in total cholesterol, triglyceride and LDL levels in all three groups as expected. But we found no change in RBF in any of the groups after treatment with statins despite using two different methods to measure RBF. Similarly there was no change in urinary sodium or urinary microalbumin after treatment with statins. This was in contrast to the study by van Dijk et al. [19] who showed a significant improvement in RBF as measured by PAH clearance in 10 adult ADPKD patients after treatment with 4 weeks of simvastatin 40 mg daily. The reason for this difference is not entirely clear, but the younger age (35 years) and higher GFR (124 mL/min/BSA) in the ADPKD population in the van Dijk et al. study may account for this difference. The average age in our study was 47 years and the average GFR for all ADPKD patients combined was 68 mL/min/BSA.

More recently, a study of 110 children with ADPKD treated with pravastatin for 3 years showed that those in the statin group had a lower percent change in their kidney volume, suggesting that statins may slow the progression of structural kidney disease in this population [27]. Similar to the van Dijk et al. study, patients were much younger (mean age of 16 years) and had an average creatinine clearance of 135 mL/min [27]. It is possible that the beneficial effects of statins can be seen when they are used in young population with high GFR and low kidney volume.

Additionally, in the above study, patients were treated with pravastatin, which is a hydrophilic statin (compared with simvastatin, which is lipophilic) [28]. Hydrophilic statins are more hepatoselective and less dependent on the cytochrome P450 enzyme [28, 29]. Hydrophilic statins have been shown to be superior to lipophilic statins in certain clinical trials [30, 31]. It is conceivable that the difference in the type of statin and the duration of therapy may have accounted for the difference in the outcomes.

It should also be noted that many of the previous animal and human studies that have evaluated the effects of statins on renal hemodynamics have relied primarily on the use of surrogate markers for endothelial function, such as increased basal nitroglycerin oxide synthase (NOS) activity [32], decreased monomeric endothelial NOS renal expression [33], renal vasoconstrictor response to norepinephrine and vasopressin [34] and a change in vessel diameter in response to L-NMMA [19]. We did not

| Table 4. Renal measurements before and after statin therapy |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                | Normal subjects | PKD–mild renal dysfunction | PKD–moderate renal dysfunction | P-value |
|                                | Before tx | After tx | P-value | Before tx | After tx | P-value | Before tx | After tx | P-value |
| Creatinine (mg/dL)             |          |          |          |          |          |          |          |          |          |
|                                 | 1.0 ± 0.2 | 1.05 ± 0.2 | 0.05 | 1.1 ± 0.3 | 1.1 ± 0.3 | 0.7 | 1.8 ± 0.3 | 1.71 ± 0.3 | 0.2 | <0.0001 |
| Iothalamate clearance (mL/min) |          |          |          |          |          |          |          |          |          |
| (mL/min/BSA)                    |          |          |          |          |          |          |          |          |          |
| PAH clearance (mL/min/BSA)      | 462.0 ± 32.32 | 454.8 ± 125.5 | 0.8 | 393.6 ± 28.38 | 372.3 ± 103.8 | 0.1 | 209.8 ± 16.31 | 214.1 ± 53.1 | 0.5 | <0.0001 |
| RBF based on PAH (mL/min)      | 820.7 ± 202.8 | 809.2 ± 216.6 | 0.8 | 717.2 ± 189.9 | 668.7 ± 194.4 | 0.05 | 369.5 ± 88.5 | 378.2 ± 94.2 | 0.4 | <0.0001 |
| RBF based on MRI (mL/min)      | 757.3 ± 259.4 | 726.0 ± 235.3 | 0.4 | 582.1 ± 139.9 | 561.0 ± 139.9 | 0.4 | 408.7 ± 153.6 | 413.0 ± 196.2 | 0.5 | 0.01 |

BSA, body surface area; MRI, magnetic resonance imaging; PAH, para-amino-hippurate; RBF, renal blood flow; tx, treatment. Values are mean ± standard deviation.

DISCUSSION

There is growing evidence that statins may have renal protective effects independent of their ability to lower plasma lipids [22]. This protective effect may be mediated by improvement in RBF through improving endothelial function by reducing oxidative stress and ADMA levels and increasing NO synthesis [16–18]. Experimental animal models of chronic kidney disease (CKD) have suggested that statins indeed enhance RBF, improve GFR and delay the progression of renal disease [23–25]. More specifically in an animal model of ADPKD, losartan was shown to reduce kidney size and volume and reduce serum urea nitrogen level [26]. These results imply that there may be a possible role for statins in improving renal hemodynamics in ADPKD patients.

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assess the renal vasculature response to L-NMMA or the NOS activity in the presence of statins, which perhaps may be the main effect of statins in renal vasculature as suggested by multiple studies, but rather we studied the effect of statins on overall RBF. In addition, the dose of statins that has been shown to improve RBF in animal studies is significantly higher than what was used in this study (moderate intensity). The majority of animal studies have used lovastatin at a dose of 15 mg/kg/day [23–25], which would translate to >1000 mg in a patient who weighs 70 kg. Additionally, in a meta-analysis that evaluated the effect of statins on estimated GFR (eGFR) in patients with CKD, only high-intensity statins were shown to improve eGFR and low- and moderate-intensity statins had no effect [35]. It is possible that the beneficial effect of statins on renal hemodynamics is seen only at high or even supratherapeutic doses.

Our results are in keeping with the study by Fassett et al. [36] that found no change in eGFR or urinary albumin excretion in ADPKD patients with mild- to-moderate renal dysfunction despite treatment with pravastatin 20 mg daily for 2 years. Similarly, other studies have shown no beneficial effect from statins on renal hemodynamics in patients with hypercholesterolemia [37] or in healthy normocholesteremic patients [38]. Studies that have evaluated the effect of statins on GFR in the general population [39] or in CKD patients with diabetes [40, 41] also did not find any beneficial effects from the statin therapy.

The small number of patients, the fact that the short duration of therapy with statins, and the fact that not all study subjects had repeat MRI RBF measurements are major limitations of our study. It is possible that a longer duration of therapy with statins in a larger population may result in an improvement in renal hemodynamics, although the absence of short-term trends makes this less likely. In addition, whether this improvement in renal hemodynamics translates into an improvement in GFR is to be determined. It should be noted that in the study by Cadnapaphornchai et al. [27], who evaluated the effect of statins in children with ADPKD, despite the beneficial effect of statins in decreasing the percent change in kidney volume, the use of statins did not result in a change in GFR or urinary albumin excretion.

In conclusion, short-term statins have no effect on GFR or RBF in normal volunteers or in mild or moderate kidney disease secondary to ADPKD. Whether more sustained therapy with statins, larger doses of statins or a different type of statin results in a change in these parameters remains to be investigated.

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### CONFLICT OF INTEREST STATEMENT

None declared.


### REFERENCES


L. Zand et al.
Increased risk of glomerular hyperfiltration in subjects with impaired glucose tolerance and newly diagnosed diabetes

Zih-Jie Sun1,2,3,4, Yi-Ching Yang1,3, Jin-Shang Wu1,3, Ming-Cheng Wang5, Chih-Jen Chang1,3 and Feng-Hwa Lu1,2,4

1Department of Family Medicine, National Cheng Kung University Hospital, Tainan, Taiwan, Republic of China, 2Department of Family Medicine, National Cheng Kung University Hospital Dou-Liou Branch, Yunlin, Taiwan, Republic of China, 3Department of Family Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan, Republic of China, 4Institute of Gerontology, College of Medicine, National Cheng Kung University, Tainan, Taiwan, Republic of China, 5Division of Nephrology, Department of Internal Medicine, National Cheng Kung University Hospital, Tainan, Taiwan, Republic of China

Correspondence and offprint requests to: Feng-Hwa Lu; E-mail: fhlu@mail.ncku.edu.tw

ABSTRACT

Background. Glomerular hyperfiltration is closely related to diabetes and may lead to subsequent nephropathy, but the association between glomerular hyperfiltration and prediabetic state is unclear. We examined the relationship of different glycemic statuses, including normal glucose tolerance (NGT), isolated impaired fasting glucose (IFG), impaired glucose


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