

Safety and efficacy of long-acting somatostatin treatment in autosomal-dominant polycystic kidney disease

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Background. The fluid filling renal cysts in human polycystic kidneys is secreted chiefly by the tubular epithelium lining the cysts via secondary chloride transport. Inhibiting this process by somatostatin therapy should induce shrinking of renal cysts.

Methods. In this randomized, cross-over, placebo-controlled trial we compared the risk/benefit profile of 6-month treatment with long-acting somatostatin (octreotide-LAR, 40 mg intramuscularly every 28 days) or placebo in autosomal-dominant polycystic kidney disease (ADPKD) patients with mild-to-moderate renal insufficiency and no evidence of other kidney disease. Volumes of kidney structures were evaluated by a two-slice computed tomography (CT) scanner; while glomerular filtration rate (GFR) was estimated by iohexol plasma clearance.

Results. One patient on somatostatin and one on placebo were prematurely withdrawn because of nonsymptomatic, reversible cholelithiasis and asthenia, respectively. In the remaining 12 patients somatostatin was well tolerated. Kidney volume increased by 71 ± 107 mL ($P < 0.05$) on somatostatin and by 162 ± 114 mL ($P < 0.01$) on placebo. The percent increase was significantly lower on somatostatin ($2.2 \pm 3.7\%$ vs. $5.9 \pm 5.4\%$) ($P < 0.05$). Cystic volume tended to increase less on somatostatin than on placebo ($3.0 \pm 6.5\%$ vs. $5.6 \pm 5.8\%$). The “parenchymal” volume nonsignificantly increased by $2.5 \pm 8.4\%$ on placebo and slightly decreased by $4.4 \pm 8.9\%$ on somatostatin. The GFR did not change significantly during both treatment periods.

Conclusion. In ADPKD patients, 6-month somatostatin therapy is safe and may slow renal volume expansion. This may reflect an inhibited growth in particular of smallest cysts beyond the detection threshold of CT scan evaluation. Whether this effect may prove renoprotective in the long term should be tested in additional trials of longer duration.

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Autosomal-dominant polycystic kidney disease (ADPKD) is the most common hereditary renal disease, responsible for 8% to 10% of end-stage renal disease (ESRD) in Western countries [1]. ADPKD shows genetic heterogeneity, with at least three different genes implicated: the *PKD1* gene (85% of the cases), the *PKD2* gene (15% of the cases), and probably a *PKD3* gene not yet identified. *PKD1* is a more severe condition with an average age of ESRD at about 54 years compared to 73 years for *PKD2* [1]. Moreover, patients with ADPKD have a faster decline in glomerular filtration rate (GFR) than patients with other renal diseases, at comparable levels of blood pressure control and proteinuria, and do not seem to benefit to the same extent from angiotensin-converting enzyme (ACE) inhibitor therapy [2–4]. A reasonable explanation for these findings is that progression in ADPKD is largely related to the development and growth of cysts and concomitant disruption of normal renal tissue [5]. Thus, renal protective interventions in ADPKD, in addition to achieving maximal reduction of arterial blood pressure and proteinuria, and limiting the effects of other potential promoters of disease progression such as dyslipidemia, chronic hyperglycemia, or smoking, should also be specifically aimed to correct the dysregulation of epithelial cell growth, secretion, and matrix deposition that is characteristic of the disease [5]. Current therapies are inefficient in arresting or even in slowing the rate of progressive loss of renal function. As a result, approximately 50% of these patients will need renal replacement therapy by 60 years of age [6].

The fluid filling renal cysts in human polycystic kidneys, as well as in many forms of experimental cystic disease in rats, is formed chiefly by a process of secretion by the tubular epithelium lining the cysts [7, 8]. Secretion and reabsorption take place at approximately the same rate, with secretion slightly higher, so that the amount of fluid in the cysts increases slowly over time. This process of active secretion, via the molecular mechanism of

secondary active chloride transport [9], is also responsible for secretion of fluid into the lumen by proximal renal tubules in teleost and elasmobranch fishes [10, 11] and in the rectal (salt-excreting) gland of elasmobranchs [12]. In the shark, rectal gland chloride secretion is markedly inhibited by somatostatin in a way suggesting inhibition of adenylcyclase and of post-cyclic adenosine monophosphate (cAMP) events as well as an inhibition of secretion stimulated by agents that do not generate cAMP [13, 14]. Evidence that specific receptors for somatostatin are present in human kidneys [15] suggests the possibility that somatostatin treatment of patients with ADPKD might inhibit fluid formation and eventually induce shrinking of renal cysts.

Somatostatin is a cyclic 14 aminoacid peptide secreted by pancreatic islets (D cells), gastrointestinal tract, nervous system, and thyroid gland [16]. There are two native biologically active forms of somatostatin, and a number of synthetic analogues have been described [17]. Genes for five somatostatin receptor subtypes have been cloned and are named *sst1* to *sst5*. All receptors bind molecular forms of somatostatin as well as somatostatin analogues with varying affinity for the agonists. The *sst2* receptor is present in kidney tissue, and shows a high affinity for the somatostatin analogue octreotide [15]. Effector systems of *sst2* receptors are inhibitors of adenylate cyclase and stimulators of phosphatase and phospholipase C [16]. Recently somatostatin analogues have become available and have been used with negligible side effects for long-term treatment (up to 8 to 12 months) of multiple endocrine tumors [18].

We suspected a potentially beneficial effect of somatostatin in patients with ADPKD from observing a female patient on continued treatment with the somatostatin analogue octreotide for about 2 years to prevent uncontrolled growth hormone secretion from an adenoma of the pituitary gland. A comparative analysis of two computed tomography (CT) scans taken at the time octreotide treatment was started and 2 years later failed to detect any appreciable change in cyst areas (Fig. 1). This finding, combined with a stable serum creatinine concentration, suggested possible inhibition of the growth of renal cysts that might have prevented further damage to the residual functioning kidney parenchyma. We therefore designed a pilot study to assess the safety-profile and the structural and functional effects of a long-acting somatostatin in patients with ADPKD and varying degrees of renal insufficiency. The results of this clinical study form the basis of the present report.

METHODS

This randomized, longitudinal, cross-over study compared the safety and efficacy of treatment for 6 months with long-acting somatostatin or placebo in adult patients

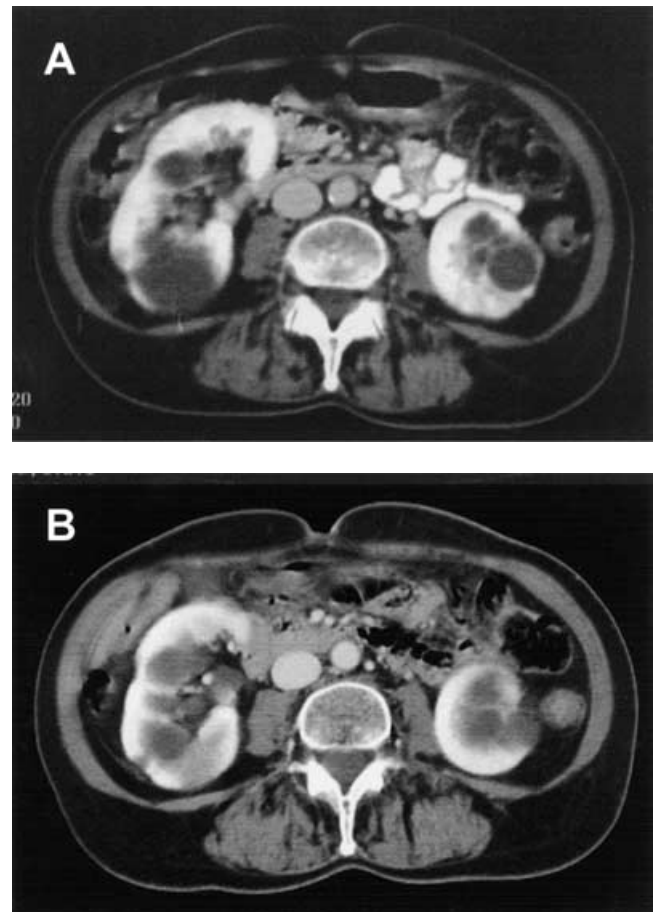


Fig. 1. Representative images of abdominal computed tomography (CT) scans of a patient with autosomal-dominant polycystic kidney disease (ADPKD), before (A) and after 2-year treatment (B) with the somatostatin analogue octreotide for an adenoma of the pituitary gland.

with ADPKD. The safety and tolerability of somatostatin treatment was assessed by comparing the incidence of serious and nonserious adverse events as well as of clinically relevant changes in several laboratory parameters throughout both treatment periods. The efficacy profile was assessed by comparing the effects of the two study treatments on kidney structure and functional determinations. The main efficacy variable was total kidney volume. Secondary efficacy variables were cystic and parenchyma volumes, determined by spiral CT scan evaluations, and GFR, as determined by iohexol plasma clearance [19], recorded at baseline and at the end of each treatment period. The morpho-functional relations between concomitant changes in kidney volumes and GFR during treatment period and during placebo were also evaluated. The study protocol was approved by the Ethical Committees of the Clinical Research Center for Rare Diseases of the Mario Negri Institute and of the Azienda Ospedaliera Ospedali Riuniti di Bergamo. Before inclusion, eligible

patients provided their written informed consent according to the Declaration of Helsinki guidelines.

Patient selection

Patients aged 18 years or older, with a clinical and echographic diagnosis of ADPKD and a serum creatinine concentration <3.0 mg/dL, but >1.2 mg/dL (males) or >1.0 mg/dL (females) were selected for study participation. Patients with concomitant systemic, renal parenchymal or urinary tract disease, diabetes, overt proteinuria (urinary protein excretion rate >1 g/24 hours), or abnormal urinalysis suggestive of concomitant, clinically significant glomerular disease, urinary tract lithiasis, infection or obstruction, biliary tract lithiasis or obstruction, more than two hemorrhagic or complicated cysts, cancer and major systemic diseases that could prevent completion of the planned follow-up or interfere with data collection or interpretation, psychiatric disorders, and any condition that could prevent full comprehension of the purposes and risks of the study were not considered eligible for study participation. Pregnant or lactating women or fertile women without effective contraception were also excluded from the study.

Study design

At a screening visit, potentially eligible patients had an ultrasound evaluation of the kidneys and liver. Those with no evidence of urinary tract or gallbladder lithiasis and satisfying all the other inclusion/exclusion criteria entered the study. After 5 minutes rest in sitting position, they had three blood pressure measurements (Korotkoff phase I and V) taken by a standard sphygmomanometer 2 minutes apart at the dominant arm, and the mean of the three readings was recorded for statistical analyses. Blood and urine samples were taken in the morning with the patient fasting from the evening before, for routine laboratory evaluations, including routine hematochemistry, renal and liver function tests, and coagulation tests. The GFR was measured by the iohexol plasma clearance technique, as described in details previously [19]. Parenchymal resistive indexes of both kidneys were evaluated by Doppler ultrasounds. Total kidney, cysts, and parenchymal volume were evaluated by spiral CT and morphometric analysis as described below.

After baseline evaluations, patients were randomly allocated to start a 6-month treatment period with the long-acting somatostatin octreotide-LAR (Sandostatin-LAR[®] Depot; Novartis Pharma AG, Basel, Switzerland) or with placebo (40 mg intramuscularly for 28 days, given as two intragluteal 20 mg injections). Every 2 months blood pressure and routine laboratory tests, including blood glucose, serum creatinine, creatinine clearance, complete blood cell count, and 24-hour urinary protein excretion rate, were evaluated and a kidney and liver ul-

trasound evaluation was repeated. At 6 months, all the measurements performed at baseline evaluation (including CT and GFR evaluations) were repeated. Then, each patient crossed over to the other treatment arm. The same measurements performed during the first treatment period were repeated every 2 months and at completion of the second treatment period, all baseline evaluations were repeated before patients were discharged from the study.

No specific change in diet and pharmacologic treatment was introduced throughout the study period, unless deemed clinically appropriate to control blood pressure or limit the signs of renal or liver dysfunction. In particular only adjustments in the doses of the ongoing antihypertensive treatments were recommended in order to maintain the same level of blood pressure control (target systolic/diastolic blood pressure $<130/80$ mm Hg) throughout the whole study period. Concomitant changes in blood glucose levels and need for antidiabetic therapy throughout the study period were carefully monitored since they could be taken as indirect evidence of an untoward effect of somatostatin therapy on insulin sensitivity and glucose metabolism.

Spiral CT scanning and volumetric analyses

Volumes of kidney structures were evaluated by a two-slice CT scanner (CT-Twin) (Elscent, Haifa, Israel). A single breath-hold CT scan was used to eliminate artifacts due to respiratory motion. CT acquisitions were started 90 seconds after start of an intravenous injection of 170 mL of nonionic contrast agent (Iopamiro) (Bracco, Milano, Italy) at a rate of 2.5 mL/second. Main scanning parameters were maintained constant for all acquisitions (voltage 120 kV, current 230 mA, field-of-view 43 cm, matrix 512×512 , collimation 5 mm, pitch 1, increment 3 mm, and overlap $>50\%$). Digital CT images were transferred to a PC workstation in Dicom format and used for digital morphometry, using in-house developed software (C++ and Insight Toolkit, ITK) [www.itk.org] [20]. Briefly, kidneys were initially outlined by a trained radiologist (G.F.) with manual operation on digital images. The operator was not required to identify precisely the kidney boundary where a fat region surrounded the organ, but to place the outline at the organ interface when other tissues, such as the liver, were in contact with the kidney. The total volume of the right and left kidney, of the parenchyma and of the cysts was evaluated by automatic segmentation of kidney images. To obtain this result images were initially enhanced by anisotropic diffusion filtering [21] whose implementation is available in the ITK library. After smoothing image segmentation was performed by a histogram-based statistical approach known as Otsu's thresholding [22]. Briefly, in this method the image intensity histogram is

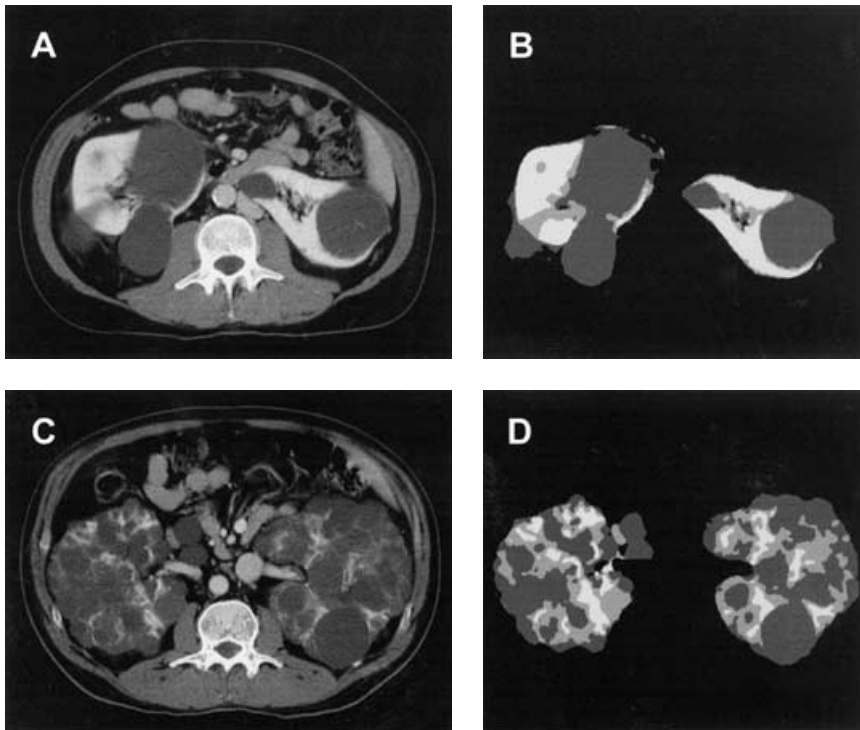


Fig. 2. Two representative images of kidney segmentation in two different patients with cyst different morphology of cyst and parenchymal volumes. Original images (A and C) are compared with corresponding pixel identification (B and D). In segmented images white pixels represent parenchymal volume, dark gray pixels represent cyst area, while light gray pixels represent transitional area between parenchyma and cyst volume.

partitioned in a previously assumed number of classes ($N = 3$) as to minimize the between-class variance. Intensity of image pixels of the kidney were then assigned automatically to one of these areas, respectively, the parenchyma, the cysts, and an intermediate area that we considered to be a transition from parenchyma to cyst area likely deriving from the partial volume effect. A representative example of this image segmentation is reported in Figure 2. The number of pixels of the parenchyma and cysts areas was used to calculate total volume of these structures in left and right kidney, taking into account pixel dimensions as contained in Dicom images and the distance between two slices. Thus, two volumes were identified, a cystic volume and parenchymal volume. The cystic volume included cysts of approximately 3 mm in diameter or larger, the parenchymal volume included apparently normal parenchyma as well as parenchyma with early changes consisting of initial tubular dilatation and small cysts below the detection threshold of the CT scans. To account for this approximation, this volume was identified by the term parenchymal volume inserted between inverted commas. The residual kidney tissue, accounting for about 20% of the total kidney volume, could not be unequivocally assigned to either cystic or parenchyma volume and was not considered in the analyses. A three-dimensional representation of these kidney volumes is reported in Figure 3. The results of image segmentation were verified by an expert radiologist. Finally, the accuracy of volume measurements was evaluated as previously described by King et al [5] using a

phantom. This validation permitted to estimate a mean error between calculated and actual volumes of the phantom to be less than 0.7%.

Statistical analysis

This was an exploratory study aiming to have at least ten patients available for full-set analyses, a figure considered a priori to provide a reasonable sample size for a preliminary evaluation of the efficacy and safety profile of the study drug. Two factors—the availability of a sensitive and reproducible technique such as spiral CT allowing for precise volumetric evaluations, and the cross-sectional design preventing the confounding effect of between-patients variability—were expected to permit powerful analyses with a relatively small sample size. Data are given as mean \pm standard deviation (SD) or median and range as specified.

RESULTS

Baseline characteristics

Fourteen patients entered the study. A positive family history for ADPKD was obtained for each subject. On the basis of the history, nine patients had the PKD1 form and one the PKD2 form (as suggested also by the linkage analysis). In the remaining four subjects the differential diagnosis between PKD1 and PKD2 was uncertain. One patient was withdrawn after 5 months of somatostatin therapy because of the detection at routine ultrasound

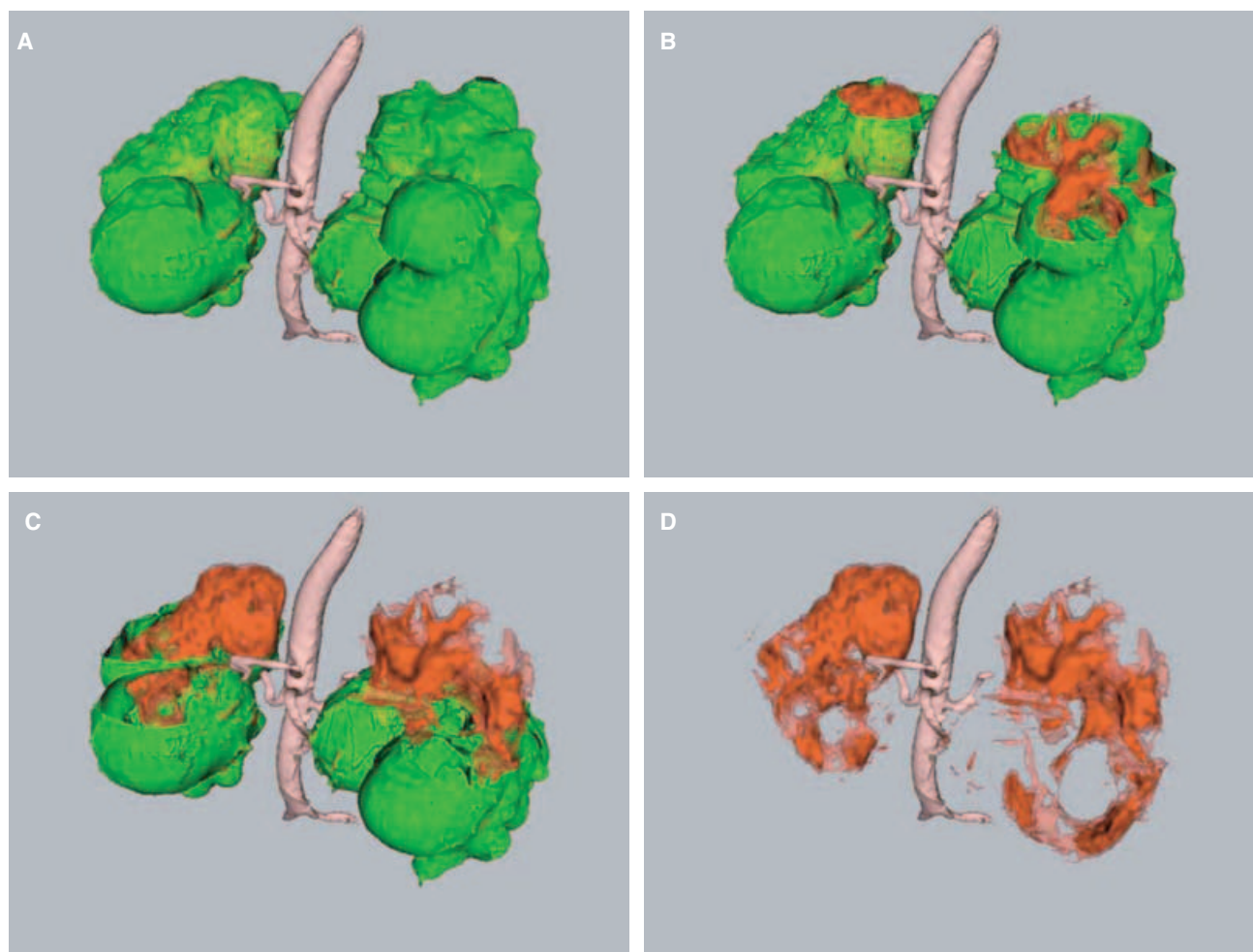


Fig. 3. Three-dimensional representation of the outer surface of renal cyst (in green) and parenchymal volume (in red). A numeric model of the abdominal aorta was digitally embedded in the three-dimensional representation. (A) Outer view of cyst volume. (B and C) Contemporary view of residual parenchymal volume and portions of the cyst volume. (D) Volume occupied by parenchymal tissue.

evaluation of two, nonsymptomatic, small gallstones that dissolved after 2 months' treatment with ursodeoxycholate acid. Another patient was withdrawn after 3 months of placebo treatment because of asthenia. Thus, 12 patients (nine males and three females) completed the study. Their main characteristics at study entry are summarized in Table 1. Two patients were normotensive. The remaining ten patients were on renin-angiotensin system (RAS) inhibition therapy, with ACE inhibitors ($N = 9$) or an angiotensin II receptor blocker ($N = 1$). In five patients the RAS inhibitor was a component of a multidrug regimen that included a beta blocker ($N = 1$), a beta blocker and a calcium channel blocker ($N = 1$), a diuretic and a calcium channel blocker ($N = 2$), or a diuretic and a beta blocker ($N = 1$). Nine patients had a serum creatinine equal to or greater than 1.3 mg/dL. In four patients urinary albumin was within normal limits; seven were microalbuminuric and one was macrolbuminuric.

Table 1. Demographic, clinical, and kidney structural data at baseline

Age years	44.5 (35-58)
Systolic blood pressure mm Hg	144.1 \pm 11.6
Diastolic blood pressure mm Hg	94.2 \pm 11.9
Serum creatinine mg/dL	1.9 (1.0-3.4)
Glomerular filtration rate mL/min/1.73 m ²	57.1 (24.4-95.3)
Albuminuria μ g/min	27 (9-437)
Resistive index, left	0.61 \pm 0.07
Resistive index, right	0.63 \pm 0.06
Kidney volume mL	2435 \pm 966
Cyst volume mL	1631 \pm 838
Parenchymal volume mL	242 \pm 61
Residual volume mL	562 \pm 277

Data are mean \pm SD or median and (range).

Mean values of kidney volumes, as determined by CT investigation and digital image processing are reported in Table 1. Total (left + right) kidney volumes were quite heterogeneous within the study group, ranging from 1498 to 4294 mL. Five patients had a total kidney volume

Table 2. Main clinical and laboratory parameters at start and end of each treatment period with placebo or somatostatin

	Placebo		Somatostatin	
	Start	End	Start	End
Systolic blood pressure <i>mm Hg</i>	143 ± 12	143 ± 9	141 ± 8	143 ± 13
Diastolic blood pressure <i>mm Hg</i>	94 ± 12	91 ± 9	91 ± 12	94 ± 14
Creatinine <i>mg/dL</i>	1.8 ± 0.9	2.1 ± 1.0	2.1 ± 1.1	2.2 ± 1.1
Creatinine clearance <i>mL/min/1.73 m²</i>	54.9 ± 21.9	52.4 ± 25.0	56.7 ± 29.1	53.5 ± 28.9
Aspartate aminotransferase (AST) <i>U/L</i>	21.9 ± 6.2	22.5 ± 7.6	23.6 ± 5.6	25.0 ± 5.6
Alanine aminotransferase (ALT) <i>U/L</i>	23.5 ± 7.7	25.0 ± 11.8	30.2 ± 13.4	29.1 ± 13.8
Gamma glutaryl transaminase (GGT) <i>U/L</i>	17.3 ± 13.8	21.0 ± 14.5	19.5 ± 14.6	19.0 ± 15.2
Biliary acid <i>μmol/L</i>	3.3 ± 1.8	3.4 ± 1.3	4.1 ± 1.8	4.2 ± 1.9
Alkaline phosphatase <i>U/L</i>	60.8 ± 17.5	63.0 ± 19.4	62.5 ± 18.2	61.9 ± 18.8
Activated partial thromboplastin time (APTT) ratio	1.1 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1
Prothrombin time (PT) INR	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.1	1.0 ± 0.1
Calcium <i>mg/dL</i>	9.1 ± 0.3	9.2 ± 0.2	8.6 ± 1.7	8.6 ± 1.7
Phosphorus <i>mg/dL</i>	3.6 ± 0.7	3.7 ± 0.7	3.7 ± 0.8	3.6 ± 0.7
Sodium <i>mEq/L</i>	141.5 ± 2.1	142.1 ± 2.1	141.8 ± 2.5	142.2 ± 1.7
Potassium <i>mEq/L</i>	4.4 ± 0.4	4.3 ± 0.3	4.4 ± 0.4	4.4 ± 0.4
Blood glucose <i>mg/dL</i>	93.9 ± 12.0	93.5 ± 14.0	100.0 ± 16.0	102.8 ± 14.9
Uric acid <i>mg/dL</i>	6.7 ± 1.6	6.9 ± 1.3	7.2 ± 1.8	7.3 ± 1.8

Data are mean ± SD.

larger than 2 L. Most of the kidney volume was occupied by radiologically detectable cysts averaging 65% (range 52% to 86%). Ten patients had a GFR below the normal range (80 to 120 mL/min/1.73 m²). There was a marginally significant correlation between GFR and parenchymal volume ($r = 0.52$, $P = 0.08$). No correlation was found between GFR and total or cyst volume. The resistive index of both kidneys was below 0.80 in all patients.

Safety and tolerability

Somatostatin treatment was well tolerated in all patients who completed the study. Watery diarrhea was reported in three patients and spontaneously recovered in all within the first month of treatment. As shown in Table 2, blood pressure was relatively well controlled without significant changes throughout both treatment periods. No change in antihypertensive therapy was introduced throughout the study period. No clinically relevant or statistically significant change in the monitored laboratory parameters occurred throughout the two treatment periods (Table 2). In one patient the blood glucose increased above 125 mg/dL during placebo treatment. This mild increase did not require antidiabetic therapy and persisted after the study was ended. There was a transient and marginal increase in alanine aminotransferase levels in two patients on somatostatin and in one patient on placebo. These abnormalities disappeared spontaneously within 1 or 2 months.

Kidney volumetric analysis

Total kidney, and cystic volumes before and after treatment with somatostatin or placebo in each individual patient are shown in Figure 4. On average, the volume of both kidneys significantly increased by 71 ± 107 mL (P

< 0.05) during somatostatin treatment and by 162 ± 114 mL ($P < 0.01$) during placebo (Table 3) (Fig. 5). Thus, on somatostatin the volume increase was about 60% less than on placebo. Total volume increase during placebo treatment was mainly due to a significant increase in the volume occupied by renal cysts (106 ± 105 mL) ($P < 0.01$) and was only marginally influenced by concomitant changes in the “parenchymal” volume, which increased by only 9 ± 22 mL (Table 3) (Fig. 5). The increase in kidney volume during treatment with somatostatin was entirely due to the concomitant increase in the volume identified as renal cysts (61 ± 106 mL), since the “parenchymal” volume actually numerically decreased by 10 ± 24 mL (Table 3) (Fig. 5).

As reported in Figure 5, on somatostatin treatment the percent change in total kidney volume was significantly lower than on placebo ($2.2 \pm 3.7\%$ vs. $5.9 \pm 5.4\%$, respectively) ($P < 0.01$). This difference was the result of a numerically lower growth of cyst volume on somatostatin than on placebo ($3.0 \pm 6.5\%$ vs. $5.6 \pm 5.8\%$) and of opposite changes in “parenchymal volume,” that non-significantly decreased by $4.4 \pm 8.9\%$ on somatostatin, but actually increased by $2.5 \pm 8.4\%$, on placebo (Fig. 5). There were no significant correlations between changes in total kidney, parenchymal or cyst volumes, and concomitant changes in GFR or serum creatinine, or resistive index throughout both treatment periods.

Renal functional analysis

As reported in Table 3, GFR did not change significantly on placebo or on somatostatin. Serum creatinine numerically increased both during placebo and treatment period, but these changes did not reach statistical significance. Albumin excretion rate did not change either during placebo or during treatment period. The resistive

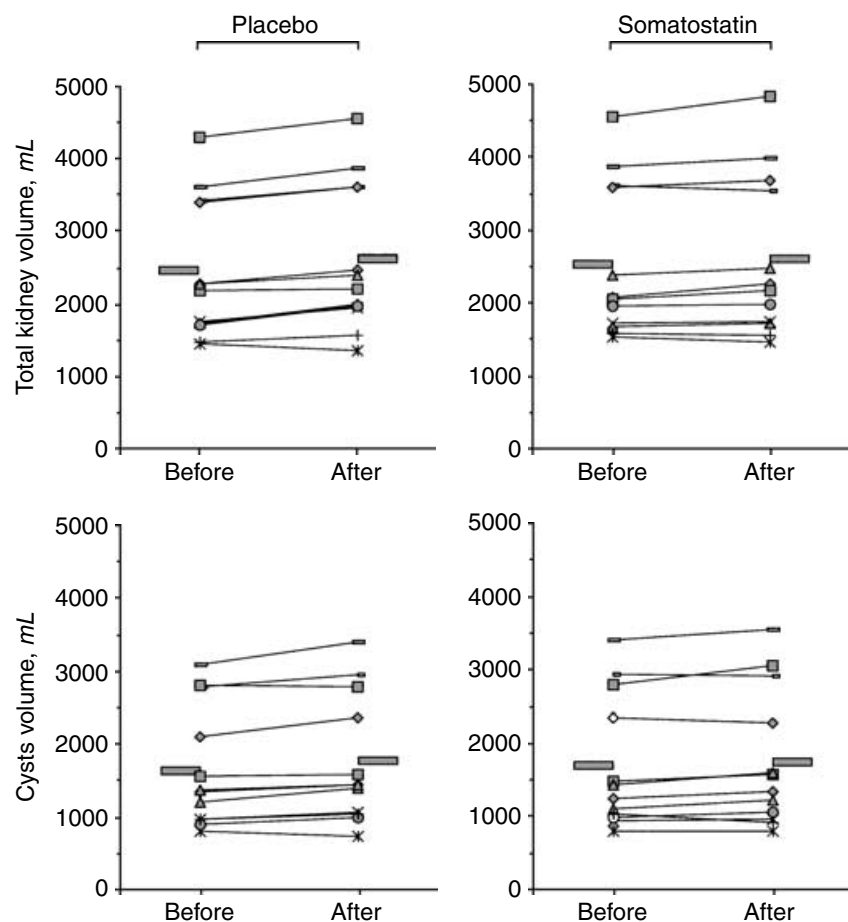


Fig. 4. Total kidney and cysts volumes in each individual patient before and after somatostatin or placebo treatment. Symbols represent individual patients.

Table 3. Kidney functional and structural parameters before and after 6-month treatment with placebo or somatostatin

	Placebo		Somatostatin	
	Before	After	Before	After
Serum creatinine mg/dL	2.0 ± 1.0	2.2 ± 1.1	1.9 ± 0.8	2.1 ± 1.1
Diuresis mL/24 hours	1954 ± 599	2054 ± 590	1979 ± 530	2046 ± 667
Glomerular filtration rate mL/min/1.73 m ²	57.9 ± 22.4	57.7 ± 25.7	59.5 ± 25.2	54.0 ± 23.6
Urinary albumin excretion µg/min	33 (9-543)	49 (8-595)	31 (13-437)	42 (7-543)
Resistive index, left	0.61 ± 0.07	0.64 ± 0.08	0.61 ± 0.08	0.64 ± 0.05
Resistive index, right	0.64 ± 0.06	0.65 ± 0.06	0.63 ± 0.07	0.66 ± 0.07
Total kidney volume mL	2461 ± 959	2623 ± 1021 ^a	2551 ± 1053	2622 ± 1111 ^b
Cyst volume mL	1656 ± 826	1762 ± 882	1709 ± 908	1770 ± 941
Parenchymal volume mL	242 ± 62	251 ± 72	247 ± 67	237 ± 65
Residual volume mL	562 ± 280	609 ± 325	595 ± 323	615 ± 347

Data are mean ± SD or median and (range). Student *t* test for paired data.

^a*P* < 0.05; ^b*P* < 0.01 vs. start.

index did not change significantly throughout either treatment periods (Table 2).

DISCUSSION

The hypotheses driving the present study were (1) that the growth of renal cysts in polycystic kidneys over time represents a slight cumulative excess of secretion over reabsorption and (2) that the process of secretion (via

secondary active transport of chloride) might be inhibited by somatostatin, as it is in the rectal gland of the shark [13, 14].

We found that in adult patients with ADPKD and different degrees of renal insufficiency, treatment for 6 months with the somatostatin analogue octreotide was safe and well tolerated. Moreover, octreotide, as compared to placebo, retarded the time-dependent increase in total kidney volume to a significant extent. The net

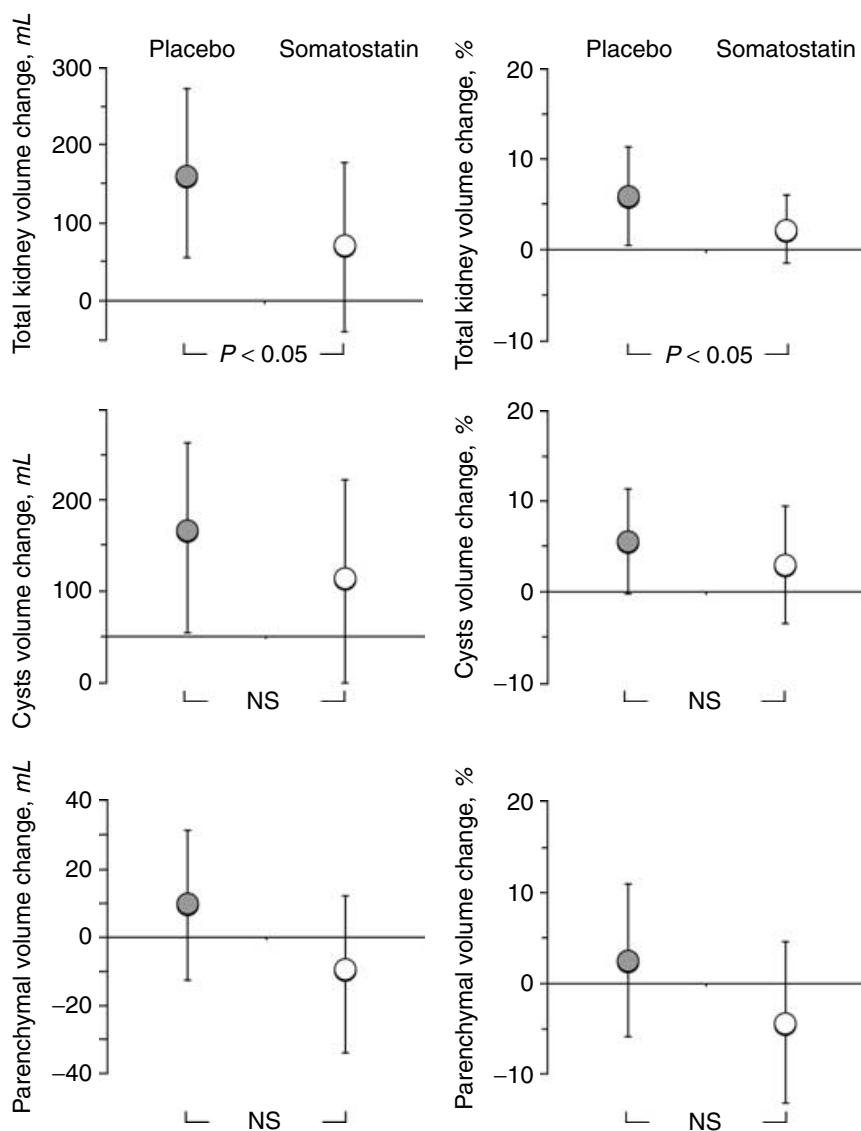


Fig. 5. Average changes in kidney volume, cyst volume, and “parenchymal” volume, and in the whole study group at the end of placebo and somatostatin treatment. Student *t* test for paired data.

effect on kidney volume resulted from an action of the drug on cyst volume and on parenchyma volume. While the volume of radiologically detectable cysts was not appreciably reduced by somatostatin treatment, average “parenchymal” volume was reduced while on active treatment, but increased on placebo. The GFR was marginally correlated with “parenchymal volume,” but not with total or cyst volumes, and tended to decrease on octreotide.

Of note, despite the different procedures used for the evaluation of kidney volumes and function [spiral CT scanning and iohexol plasma clearance versus magnetic resonance imaging (MRI) and iothalamate renal clearance, respectively] the morphologic and functional data in our present series were very well comparable with those in the remarkably larger series of patients with similar clinical characteristics included in the Consortium for

Radiologic Imaging Studies of Polycystic kidney disease (CRISP) [23].

Safety

Only one patient had to interrupt somatostatin therapy prematurely because of asymptomatic cholelithiasis that disappeared after a few months of treatment with ursodeoxycholate acid. Octreotide has occasionally been reported to favor the development of gallstones, that, however, promptly dissolved by ursodeoxycholic acid [24]. Three patients reported a watery diarrhea that spontaneously recovered during the first month of somatostatin therapy; this has also been occasionally reported as a side effect of octreotide treatment. No deleterious changes in laboratory parameters were observed during somatostatin therapy. In particular, in the study group as

a whole there were no significant changes in blood glucose and hemoglobin A_{1c} (HbA_{1c}) levels. In one patient on placebo, however, there was an increase in blood glucose above 125 mg/dL that did not require pharmacologic treatment. These reassuring findings are consistent with previous evidence that chronic treatment with somatostatin occasionally increased fasting blood glucose and HbA_{1c}, or reduced glucose tolerance, but never caused new onset diabetes [25]. Finally, we observed a marginal and transient increase in alanine aminotransferase levels, without any other change in liver function parameters, in two patients on somatostatin and in one on placebo. These abnormalities recovered spontaneously and may have been related to concomitant cystic disease of the liver.

Efficacy

The heterogeneous effects on cystic and “parenchymal” volumes most likely reflected different effects of somatostatin therapy in modulating the development and growth of cysts at different stages of the disease. In early stages of ADPKD, cysts are generated from tubule segments that are perfused by glomerular filtrate [26]. These cysts have a diameter of a few millimeters, below the detection threshold of the present CT scan evaluation. Thus, the “normal” parenchyma identified by CT scan evaluation probably included not only normal nephrons but also nephrons with early cystic changes that precede the development of radiologically detectable cysts. As the cysts enlarge beyond a few millimeters in diameter, they are detected by CT scan. At this stage, about 75% of the cysts irreversibly lose their connections with the original tubule and become isolated sacs [1]. As a consequence, the normal architecture and function of the original tubules are irreversibly lost, with a consequent reduction in functioning nephron mass. At the same time, isolated cysts continue to grow in a process that may accelerate kidney damage through compression and ischemia of contiguous renal parenchyma [26, 27].

In evaluating the results of this short-term trial of somatostatin, the following facts should be kept in mind. First, somatostatin has been reported to depress GFR slightly and reversibly in human subjects [28–32]. Any tendency for improvement in GFR during treatment with somatostatin might be counteracted by this reversible functional effect. Second, the portion of polycystic kidneys identified radiologically as “parenchyma” probably contained many microscopic cysts, as deduced from the histologic examination of such kidneys at postmortem [33]. Third, the ratio of cyst surface to volume is much larger for small cysts than for bigger ones, so that the rates of secretion and reabsorption by the cyst epithelium may be expected to be proportionately greater per unit of cyst volume. It might be predicted, therefore, that

inhibition of secretion by cysts would have its first detectable effect on the volume of small cysts. Perhaps this is responsible for the diminution in the “parenchymal” segment of kidney volume in patients treated with octreotide as compared with placebo treatment. It is also possible that the reduction in parenchyma volume observed during somatostatin therapy reflects inhibition of the tubular cell proliferation that precedes cyst development and detachment from the tubuli of origin [34].

This interpretation is consistent with a possible effect of somatostatin on cAMP signaling that goes beyond an effect on fluid secretion. Indeed, evidence based on studies of cyst epithelial cells *in vitro* points strongly to a role for cAMP in determining the rate of cyst epithelial cell growth and fluid secretion [35], two biologic processes that are of fundamental importance in the expansion of renal cysts. Recent findings that in experimental models of human autosomal-recessive [36] or dominant [37] PKD these biological processes are effectively inhibited by agents that antagonize cAMP production and activity can be taken to suggest that somatostatin treatment may prevent cyst development and growth by directly affecting cell proliferation and apoptosis. Indeed, somatostatin is known to inhibit cAMP generation in Madin-Darby canine kidney (MDCK) cells [38] and in microdissected rat medullary and cortical collecting ducts [39] and to antagonize the effects of vasopressin in the toad urinary bladder [40] and dog collecting ducts [41] in a manner consistent with inhibition of basal and hormone-stimulated adenylyl cyclase. Data that cAMP and agonists of adenylyl cyclase stimulate the proliferation of epithelial cells derived from ADPKD kidneys provide convincing evidence that cAMP may have a cystogenetic role also in human disease [35] and can be taken to suggest that in our present study the effects of somatostatin therapy were at least in part mediated by the inhibition of cAMP-dependent polycystic kidney cell proliferation [42]. If early enough, these effects, in addition to preventing cyst formation and growth, might preserve the original tubular architecture, which in turn might prevent further loss of tissue and deterioration of renal function over time. The inhibition of compensatory hypertrophy and hyperplasia of residual glomerular/tubular units still not involved in cyst development and growth might also contribute to the reduction in “parenchyma” volume observed during somatostatin therapy and help to explain the slight GFR reduction observed during somatostatin therapy. Octreotide is known to decrease the GFR in healthy individuals [29, 30], as well as in patients with type 1 diabetes [29–31] or liver cirrhosis [32], perhaps by inhibiting the secretion of growth hormone. Such an effect might counteract the tendency to compensatory hyperfiltration that accompanies the glomerular and tubular hypertrophy/hyperplasia of residual functioning nephrons. In the long-term, glomerular hyperfiltration may cause

premature glomerular obsolescence with worsening proteinuria, declining filtration power, and eventual glomerulosclerosis. Total GFR is maintained until progressive parenchymal loss precludes complete compensation. At that point, total GFR begins to fall rapidly by mechanisms no longer dependent on cyst growth, resulting in irreversible kidney failure [33]. Thus, long-term somatostatin therapy might prove renoprotective in patients with ADPKD not only by preventing cyst development and inhibiting tubular secretion, but also by inhibiting the maladaptive events sustained by, and contributing to, progression to nephron loss.

The good safety profile and the marginal reduction in renal growth demonstrated in this short-term study suggest the feasibility of a randomized trial in larger series of ADPKD patients to verify whether long-term somatostatin treatment may eventually provide effective renoprotection. At the present time no treatment that may appreciably affect the relentless progression of the disease to end-stage has been identified. Studies are also needed to assess the effects of somatostatin therapy in the liver cystic disease that so often accompanies ADPKD.

CONCLUSION

In patients with ADPKD somatostatin therapy given for 6 months is safe and may slow renal volume expansion, largely by preventing the growth of the “parenchymal” volume. Whether this effect may prove renoprotective in the long term should be tested in additional trials of larger duration.

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