Diverse Effects of Increasing Lisinopril Doses on Lipid Abnormalities in Chronic Nephropathies

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Background—Dyslipidemia frequently complicates chronic nephropathies and increases the risk of renal and cardiovascular events. This might be ameliorated by drugs, such as angiotensin-converting enzyme inhibitors, which effectively reduce proteinuria.

Methods and Results—In this longitudinal study, we evaluated the extent to which uptitration of the ACE inhibitor lisinopril to maximum tolerated doses (median [range]: 30 [10 to 40] mg/d) ameliorated proteinuria and dyslipidemia in 28 patients with nondiabetic chronic nephropathies. Maximum lisinopril doses significantly and safely reduced proteinuria, serum total, LDL cholesterol, and triglycerides without substantially affecting serum HDL and renal hemodynamics. Proteinuria already decreased at 10 mg/d. Serum lipids progressively and dose-dependently decreased during uptitration to maximum doses. Reduction in total and LDL cholesterol correlated with increases in serum albumin/total protein concentration and oncotic pressure, peaked at lisinopril maximum doses, and persisted after treatment withdrawal. Despite less proteinuria reduction, hypercholesterolemia decreased more (and reflected the increase in serum albumin) in hypoalbuminemic than in normoalbuminemic patients who, despite more proteinuria reduction, had less decrease in cholesterol and no changes in serum albumin. Changes in serum triglycerides were independent of changes in serum proteins, were strongly correlated with lisinopril doses ($r = -0.89$, $P = 0.003$) and recovered promptly after treatment withdrawal. Lisinopril was well tolerated, did not affect renal hemodynamics, and caused symptomatic, reversible hypotension in only two patients.

Conclusions—In chronic nephropathies, angiotensin converting enzyme inhibitor uptitration to maximum tolerated doses safely ameliorated hypertriglyceridemia by a direct, dose-dependent effect, and hypercholesterolemia through amelioration of the nephrotic syndrome, particularly in patients with more severe hypoalbuminemia. (Circulation. 2003; 107:586-592.)

Key Words: inhibitors, angiotensin-converting enzyme ▪ nephropathies ▪ proteinuria ▪ dyslipidemia ▪ nephrotic syndrome

Proteinuria of chronic renal disease is associated with dyslipidemia, which manifests with high total and low-density lipoprotein (LDL) cholesterol, increased serum triglycerides, and decreased high-density lipoproteins (HDL).1–2 Lipid abnormalities are of major clinical concern in this setting because in patients with nephrotic-range proteinuric nephropathies, the relative risk of myocardial infarction is 5.5 and the relative risk of coronary death is 2.8 as compared with controls.3 Animal and human data are also available that suggest that dyslipidemia of nephritics is also a causative factor for the progression of chronic renal disease to end-stage renal failure (ESRF).4–8

Inhibitors of the renin angiotensin system, such as angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists, reduce urinary proteins by 20% to 50% but seldom ameliorate the lipid abnormalities to a substantial extent.9–12 Notably, studies have thus far used conventional doses of ACE inhibitors or angiotensin II receptor antagonists, ie, doses recommended by the manufacturer to maintain blood pressure. One open question here is whether dyslipidemia of chronic nephropathies might be ameliorated by the use of higher than usual doses. The present study was therefore aimed to evaluate whether, in proteinuric chronic nephropathies, uptitration of an ACE inhibitor to maximum tolerated doses, besides reducing proteinuria, could also ameliorate dyslipidemia to a clinically significant extent.

Methods

Patient Selection and Basal Evaluation

Patients of both sexes who had nondiabetic chronic nephropathies, urinary protein excretion rate persistently >2 g/24 hours, and no
concomitant treatment with statins or other lipid-lowering agents for ≥6 months were selected for study participation and referred to the Bergamo Renal Unit. They gave written informed consent according to the Declaration of Helsinki guidelines. Patients with severe renal insufficiency (creatinine clearance <30 mL · min⁻¹ · 1.73 m⁻²), rapidly worsening renal function (serum creatinine increase >30% over the last 6 months), evidence or suspicion of renovascular disease, obstructive uropathy, urinary tract infection, heart failure (NYHA class III-IV), atrioventricular block grade 2 to 3, hyper- or hypokalemia (serum potassium concentration >5.0 mmol/L or <3.5 mmol/L), stroke or acute myocardial infarction in the last 3 months, known or suspected intolerance to ACE inhibitor therapy, and any condition that could affect study conduct or data interpretation were excluded. Pregnant or potentially childbearing women and nursing women were not included.

All patients were on a stable low-sodium (50 to 100 mEq Na+/d) and controlled protein content (0.8 mg per kg body weight/d) diet. After submitting three consecutive 24-hour urine collections (the last one to be completed the morning of the visit), they had a prestudy evaluation of arterial blood pressure (mean of three consecutive measurements 2 min apart after 5 min rest in the sitting position), a blood sample collection for routine laboratory analyses, and an evaluation of 24-hour urinary protein excretion rate over the three consecutive urine collections. Samples of the last collection were also used to measure creatinine clearance and 24-hour urinary urea and sodium excretion.

Study Design
The study protocol was approved by the Ethics Committee of the Clinical Research Center. After screening evaluation, selected patients entered a 6-week washout, run-in period. No change in usual daily intake of calories, lipids, proteins, and sodium was introduced at inclusion or throughout the study. No lipid-lowering agents or antihypertensive treatments different from the study drug were allowed, with the only exception of diuretics and clonidine for the treatment of edema and to maintain systolic/diastolic blood pressure <150/90 mm Hg.9 At completion of the washout, run-in phase, patients with stable renal function (<15% increase in serum creatinine, confirmed in at least two separate measurements, as compared with inclusion) underwent renal clearance studies to evaluate pre-treatment renal hemodynamics (basal clearances). Then patients entered four 4-week lisinopril (Astra Zeneca) uptitration periods (from 10, to 20, 30, and 40 mg/d), followed by a 6-week backtitration period to lisinopril 10 mg/d and 4-week recovery period (lisinopril withdrawal). Basal evaluations were repeated at the end of each treatment period and after the recovery phase. The clearance studies were repeated at the end of the treatment period with maximum tolerated lisinopril doses (treatment clearances) and at the end of the recovery period (recovery clearances).

Blood pressure, serum potassium, and serum creatinine were measured within 7 days after screening evaluation, at completion of each study period, within 7 days after each study treatment uptitration or backtitration, and whenever deemed appropriate. When diastolic blood pressure decreased ≤70 mm Hg, the study drug was not further uptitrated to prevent symptomatic hypotension. Patients who, despite careful uptitration, had symptomatic hypotension, hyperkalemia (serum K⁺ >5.5 mEq/L) refractory to medical treatment (thiazidic or loop diuretics, sodium bicarbonate, and potassium binding resins), or serum creatinine increases ≥30% versus previous values, had the lisinopril dose downtitrated to previous step or withdrawn. All withdrawn patients were followed up to the end of the study.

Aim
The primary aim of the study was to evaluate the changes in total cholesterol induced by maximum tolerated doses of lisinopril versus basal or recovery evaluations.

Sample Size Estimation
Primary efficacy variable of the study was serum total cholesterol. A previous study in 16 patients with diabetic and nondiabetic, protein-uric, chronic nephropathies found that 6-month treatment with conventional, antihypertensive doses of an ACE inhibitor (fosinopril) achieved mean (95% CI) 0.84 (1.59 to 0.08) mmol/L reduction (from 6.37 to 5.54 mmol/L) in total serum cholesterol.12 Assuming, conservatively, that maximum tolerated doses of lisinopril achieved at least the same proteinuria reduction, we estimated that to give the study an 80% power to detect as statistically significant (P<0.05, two-sided test) such reduction in urinary protein excretion rate, ≥22 patients had to complete the study.

Clearance Studies
The routine patient treatment (including the maximum tolerated lisinopril dose for the day of the treatment clearances) was administered in the morning and blood and urine samples were collected before each clearance study to measure serum creatinine and total protein concentration. The glomerular filtration rate (GFR) and renal plasma flow (RPF) were measured, respectively, as inulin and para-aminohippuric acid (PAH) clearance, as previously described.13 The same protocol was exactly used for each patient during all the clearance studies.

Inulin and PAH concentrations in plasma and urine samples were determined with methods previously described.13 Total protein concentration in plasma and urine samples was measured by an automatic analyzer (Synchron CX5, Beckman). Albumin concentration in plasma and urine samples collected during the clearance studies was determined by nephelometric technique (Beckman). Other laboratory measurements were done by routine laboratory techniques. Mean GFR, RPF, filtration fraction (FF), and albumin fractional clearance were calculated with a standard formula normalized for body surface area. To take into account incomplete renal extraction of PAH, an assumed renal extraction coefficient equal to 0.7 and 0.8 was adopted for corresponding mean GFR ±80 mL · min⁻¹ · 1.73 m⁻², respectively.14

Statistical Analysis
Data were expressed as mean ± SD or median and range, as specified. Data were subjected to a repeated-measures analysis of variance (ANOVA) to test the following: between-subject effect (status of normo- versus hypoalbuminemia), within-subject effect (dose as the level of the repeated measure), and the interaction between the two types of effects. Because of the nature of the repeated-measures effect (ie, different doses of a drug), the polynomial transformation of the general linear model procedure in the SAS software (release 8.2) was applied. The significance of multiple pairwise comparisons was determined by paired Student’s r tests with the Bonferroni correction for a preplanned number of comparisons.19 Correlation analyses were done with Pearson’s r correlation coefficient. Nonnormally distributed parameters were log-transformed before the statistical analysis.

Results
Patient Characteristics
Twenty-eight patients were identified for study participation. Four patients, however, did not enter the treatment phase because of consent withdrawal (n=1) or serum creatinine increase >15% during the washout, observational period (n=3). Two other patients were withdrawn because of symptomatic hypotension. Both patients had systolic/diastolic blood pressure <130/90 mm Hg before study entry. The remaining 22 patients (males/females: 20/2; age [range]: 43 [17–66] years) completed the study (Table 1). Nine patients had biopsy-proven idiopathic membranous nephropathy, 6 had IgA nephropathy, one had type 2 membranoproliferative glomerulonephritis, one had focal and segmental glomerulosclerosis, and one had an aspecific pattern of chronic glomerulonephritis. Of the remaining 4 patients, one had adult polycystic kidney disease, one reflux nephropathy, and two a
TABLE 2. GFR, RPF, and FF at Basal Evaluation, at Completion of the Treatment Period With Lisinopril Maximum Doses (Lis 40) and After Lisinopril Withdrawal (Recovery) in the Whole Study Group and in the 2 Subgroups of Normo- and Hypoalbuminemic Patients With Chronic, Proteinuric Nephropathies

<table>
<thead>
<tr>
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<th>Overall</th>
<th>Normoalbuminemic Patients</th>
<th>Hypoalbuminemic Patients</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Basal</td>
<td>Lis 40</td>
<td>Recovery</td>
</tr>
<tr>
<td>GFR, mL·min⁻¹·1·73 m²⁻¹</td>
<td>35.1±10.4</td>
<td>33.2±9.3</td>
<td>35.6±14.7</td>
</tr>
<tr>
<td>RPF, mL·min⁻¹·1·73 m²⁻¹</td>
<td>218±120</td>
<td>203±80</td>
<td>188±70</td>
</tr>
<tr>
<td>FF</td>
<td>0.19±0.08</td>
<td>0.18±0.07</td>
<td>0.19±0.05</td>
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chronic disease of unknown origin. Nine patients were hypoalbuminemic (serum albumin <3.2 g/dL) at study entry. Three patients were normotensive and were not receiving any antihypertensive drug. Of the remaining patients, seven were on concomitant treatment with ACE inhibitors alone and eight with ACE inhibitors and diuretics. Ten patients achieved the maximum planned doses of 40 mg of lisinopril/d (6 with serum albumin <3.2 mg/dL and 4 with serum albumin ≥3.2 mg/dL). Four, 3, and 5 patients achieved the maximum dose of 30, 20, and 10 mg/d, respectively. Decrease of diastolic blood pressure to ≤70 mm Hg and a reversible increase in serum creatinine were the primary causes of discontinuation of lisinopril up titration in 11 and one cases, respectively. Patient baseline characteristics and actual lisinopril doses received throughout the different treatment periods are given in Tables 1, 3, and 4.

Blood Pressure, 24-Hour Urinary Protein Excretion Rate, and Urine P/C Ratio

Arterial blood pressure, 24-hour urinary protein excretion rate, and urine P/C ratio significantly decreased throughout each treatment period, compared with baseline, and increased again to pretreatment levels at the end of the recovery period (Table 1). Although a trend to more reduction in the above parameters was observed at maximum tolerated lisinopril doses (40 mg/d), most of the reduction was already appreciable at lisinopril lowest doses (10 mg/d) and differences between blood pressure, proteinuria, and P/C ratio reductions with different lisinopril doses never achieved statistical significance. Percent changes (versus baseline) in mean arterial pressure (MAP) and 24-hour urinary protein excretion rate are shown in Figure 1.

Serum Lipids, Albumin, and Total Protein Concentrations and Oncotic Pressure

Serum total and LDL cholesterol and triglycerides decreased in a dose-dependent manner throughout each treatment period (with maximum reductions achieved with maximum tolerated doses of lisinopril) and only partially increased toward pretreatment values after lisinopril backtitration and withdrawal (Table 1). Serum HDL cholesterol also decreased, but with smaller variations versus baseline values. As a consequence, total/HDL cholesterol ratios dose-dependently decreased throughout each treatment period, reached maximum reductions at lisinopril maximum doses and partially increased toward baseline after treatment backtitration and withdrawal. Notably, as compared with lipid changes, post-treatment serum albumin, total proteins, and oncotic pressure changes followed a parallel but specular trend with a progressive increase throughout each treatment up titration that peaked at maximum lisinopril doses and did not recover after lisinopril backtitration and withdrawal. Percent changes (versus baseline) in serum albumin are shown in Figure 1 and those in serum total and LDL cholesterol and triglycerides are shown in Figure 2.
Clearance Studies

GFR, RPF and FF did not change significantly during the whole study period (Table 2).

Correlation Analyses

Serum Cholesterol

Throughout the whole study period, changes (versus baseline) in total cholesterol levels were negatively correlated with concomitant changes in total proteins ($r = -0.59$, $P = 0.03$). At maximum lisinopril doses, changes (versus basal) in both total ($r = -0.44$, $P = 0.04$) and LDL ($r = -0.52$, $P = 0.02$) cholesterol levels were negatively correlated with concomitant changes in serum albumin concentration.

Serum Triglycerides

During each treatment period, changes (versus baseline) in serum triglyceride levels were strongly correlated with lisinopril doses in the study group as a whole ($r = 0.89$, $P = 0.003$) and in the subgroup of normoalbuminemic patients ($r = 0.99$, $P = 0.01$), but not with concomitant changes in serum albumin or urinary protein excretion rate.

Safety and Compliance Parameters

Serum creatinine, serum potassium, and creatinine clearance did not change significantly during the whole study period. Hemoglobin concentration significantly decreased by about 1 g/dL throughout the different treatment periods and fully recovered after treatment backtitration and withdrawal. Changes in hemoglobin were not associated with symptoms of anemia and did not require therapy.

Comparisons Between Normo- and Hypoalbuminemic Patients

Clinical and laboratory parameters throughout the study period are given in Tables 3 and 4 and in Figure 3. Changes in MAP were comparable in the two groups. Twenty-four-
hour proteinuria and P/C ratio decreased more in patients with normoalbuminemia; total and LDL cholesterol and total/HDL cholesterol ratio decreased more in those with hypoalbuminemia. In hypoalbuminemic patients, body weight decreased by ≈1 kg during the treatment period, whereas serum albumin, total proteins, and oncotic pressure increased through each period with a dose-dependent effect that peaked at lisinopril maximum doses (serum albumin increase versus basal: 21%).

Posttreatment changes in serum triglycerides were comparable and dose dependent in both groups, with a maximum increase versus basal: 21%.

Analyses of Variance ANOVA
At analysis of variance ANOVA, there was a highly significant, within-subject effect of the dose on proteinuria \((P=0.0099)\), serum albumin \((P=0.004)\), and triglycerides \((P=0.005)\), and a weak and marginal effect on total \((P=0.028)\) and LDL \((0.06)\) cholesterol, respectively. On the contrary, the status of normo- or hypoalbuminemia had a significant effect on the response to lisinopril treatment for proteinuria \((P=0.015)\), serum albumin \((<0.0001)\), and total \((P=0.017)\) and LDL \((P=0.005)\) cholesterol, but not for serum triglycerides \((P=0.16)\).

Discussion
The main finding of the present study is that, in proteinuric chronic nephropathies, high (ie, maximum tolerated) doses of lisinopril decreased total and LDL cholesterol and triglycerides without substantially affecting serum HDL concentrations. Serum lipids—unlike blood pressure and urinary proteins that already decreased substantially at a low \((10 \, \text{mg/d})\) lisinopril dose—were only marginally affected by such a dose, but progressively and dose-dependently decreased during uptitration \((30\text{ to }40 \, \text{mg/d})\). Notably, cholesterol reduction combined to only marginal changes in serum HDL concentrations, resulting in a significant decrease in total/HDL cholesterol ratio that was more consistent at lisinopril maximum doses.

In nephrotic syndrome, lipid abnormalities are considered the consequence of loss of urinary proteins, which reduces plasma oncotic pressure.\(^{16}\) Increase in LDL (cholesterol rich) fractions reflects at least in part an increased synthesis of cholesterol-rich lipoproteins, which serve to compensate for low serum proteins and oncotic pressure.\(^{17}\) Here we found that high-dose lisinopril—which effectively limited proteinuria—indeed increased serum total protein concentration, albumin, and oncotic pressure. Such changes paralleled the reduction in total and LDL cholesterol. The two variables were significantly correlated, correlations being even stronger in patients with low serum albumin to start with.

Of note, changes in serum albumin during lisinopril treatment did not depend on the extent of proteinuria reduction but rather on the severity of hypoalbuminemia at study entry. Actually, two patterns of response to ACE inhibitor therapy were observed. In patients already normoalbuminemic, serum albumin did not further increase despite proteinuria reduction; whereas in those with hypoalbuminemia, lisinopril induced a dose-dependent increase in serum albumin concentration up to normal ranges despite the fact that changes in urinary proteins were minimal. Conceivably, in the first setting, reduction in protein loss induced by the treatment limited the stimulus to enhanced liver synthesis that resulted in a new equilibrium in which a normal serum albumin level was maintained at lower rates of urinary loss and liver synthesis. At variance, in patients with hypoalbuminemia the initial decrease in urinary protein loss was not enough to offset the exuberant liver synthesis. The two together concurred to enhance serum albumin, which, however, served to augment glomerular protein load preventing further reduction in proteinuria despite restricted protein ultrafiltration. In this setting, a widespread amelioration of vascular permeability with less leakage of plasma albumin into the interstitium\(^{18}\) might have additionally contributed to augment serum albumin despite a modest reduction in urinary losses. This interpretation is in harmony with available data that children
with heavy proteinuria had their hypoalbuminemia corrected by ACE inhibitors even without appreciable changes in urinary proteins.\textsuperscript{19–20} Findings here that patients with hypoalbuminemia at study entry had their body weight reduced by high dose lisinopril also speak in favor of an effect of lisinopril on interstitial protein loss.

In the present study, amelioration of serum triglycerides was independent of serum and urinary proteins, but was strongly correlated with lisinopril dose, which suggests a direct effect of the drug. Actually evidence is available that vascular endothelium plays a crucial role in triglyceride rich, very low-density lipoprotein catabolism, a process that is inhibited in the nephrotic syndrome and that might be ameliorated by ACE inhibition therapy.\textsuperscript{21–22}

Finding that, at analysis of variance, reduction in serum triglycerides was strongly dependent on the dose of lisinopril regardless of serum albumin levels, whereas serum total and LDL cholesterol were influenced more by the status of normo- or hypoalbuminemia than by the dose of lisinopril, further reinforced the hypothesis that amelioration of hypertriglyceridemia was a direct effect of the drug, whereas amelioration of hypercholesterolemia was mostly a function of amelioration of the nephrotic syndrome.

Our present data suggest that, in nephrotics, lisinopril doses required to reduce lipids exceeded by about 2-fold the doses required to control blood pressure and could differ from patient to patient by a factor of four. Notably, lisinopril is cleared as the intact compound by the kidney and its bioavailability increases in patients with decreased GFR. If one considers that our patients had a GFR on average about 30% of normal and that on average they received a dose of lisinopril 2-fold the normal, their final exposure to the drug was even higher. Nevertheless, no patient had major side effects. Thus, our current practice is to find in each individual patient the highest tolerated dose by a gradual uptitration of the drug.

In conclusion, in chronic nephropathies, ACE inhibitor uptitration to maximum tolerated doses safely ameliorated hypertriglyceridemia by a direct, dose-dependent effect and hypercholesterolemia through amelioration of the nephrotic syndrome, particularly in patients with more severe hypoalbuminemia.

Hypertension and hypercholesterolemia are, along with smoking, the major acquired risk factors for atherosclerosis and their reversal decreases the risk of ischemic heart disease and other major clinical complications of atherosclerosis.\textsuperscript{23–26} Controlled trials have demonstrated that ACE inhibitors remarkably decrease cardiovascular mortality in patients with mild-to-moderate renal impairment.\textsuperscript{27} Further studies are needed to assess whether effective control of both hypertension and hypercholesterolemia by high-dose ACE inhibitors may in the long term further limit or prevent the excess cardiovascular risk associated with chronic renal disease.\textsuperscript{28}

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References


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