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Effect of lipid reduction on the progression of renal disease: A meta-analysis

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Background. It has been proposed that hyperlipidemia contributes to the progression of renal disease. A large trial has not been performed; however, a number of small, controlled trials have been reported. We examined the effects of antilipemic agents on glomerular filtration rate and proteinuria or albuminuria in patients with renal disease.

Methods. We used Medline, abstracts from scientific meetings, and bibliographies from recent reviews and scientific reports to locate pertinent studies. Thirteen prospective controlled trials examining the effects of antilipemic agents on renal function, proteinuria, or albuminuria were included. Studies were published as full reports or abstracts and were at least three months in duration. For five of the studies, individual patient data were obtained. Other summary data were independently extracted from the published reports by two investigators and included study quality, subject characteristics, cause of renal disease, change in serum cholesterol, blood pressure, glomerular filtration rate, proteinuria, and albuminuria.

Results. There was a lower rate of decline in glomerular filtration rate with treatment compared with controls (treated controls, 0.156 mL/min/month; 95% CI, 0.026 to 0.285 mL/min/month, $P = 0.008$). The study results were statistically homogeneous, and in a regression analysis, the effect of treatment on glomerular filtration rate did not correlate with study quality, the percentage change in cholesterol, the type of lipid-lowering agent, or the cause of renal disease. However, longer follow-up correlated with the amount of improvement in glomerular filtration rate from treatment ($P = 0.007$). There was a tendency for a favorable effect of treatment on protein or albumin excretion [Ln (treatment) − Ln (control) = −0.248, 95% CI, −0.562 to 0.064, $P = 0.077$]. However, these results were statistically heterogeneous between studies ($P < 0.001$). No obvious explanation for this heterogeneity was apparent in a regression analysis examining potential reasons for differences in study results.

Conclusions. Lipid reduction may preserve glomerular filtration rate and may decrease proteinuria in patients with renal disease.

Key words: hyperlipidemia, nephropathy, progressive renal disease, proteinuria, albuminuria, glomerular filtration rate.

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Hyperlipidemia is a common complication of nephrotic syndrome and renal insufficiency. Patients with nephrotic syndrome invariably have elevated total and low-density lipoprotein (LDL) cholesterol. Often, triglycerides are increased as well, and high-density lipoprotein (HDL) cholesterol may be low [1]. Patients with progressive renal failure, but without significant proteinuria, often have abnormalities in circulating lipoproteins as well. Hypertriglyceridemia, for example, is evident when the glomerular filtration rate (GFR) is less than 30 mL/min. However, elevations of apoC-III and a reduction in the apoA-1/ApoC-III ratio occur earlier in renal disease [2]. The apoA-1/apoC-III ratio is a marker of the efficiency of removal of triglyceride-rich lipoproteins [2].

For almost 100 years, it has been suggested that hyperlipidemia could cause renal injury. More recently, Moorhead et al proposed that lipid abnormalities might contribute to the progression of renal disease [3]. In a number of animal models, lipogenic diets worsen, while cholesterol-lowering medications ameliorate renal injury [4–8]. Epidemiological studies also suggest a role for hyperlipidemia in the progression of diabetic nephropathy [9, 10]. Although there have been no large investigations examining the effects of cholesterol reduction on nephropathy, several small, controlled trials have recently been reported. We performed a meta-analysis of these trials to assess the effect of antilipemic agents on nephropathy.

METHODS

Study selection

We searched Medline to July 1, 1999, to locate trials examining the effects of lipid-lowering therapy on renal

disease progression, using the key words hyperlipidemia, cholesterol, diabetes, diabetic nephropathy, progression, kidney disease, and nephrotic syndrome. The bibliographies of these and other recent articles were reviewed to locate additional studies. We also searched abstracts from major nephrology meetings that occurred in the past 10 years, including the American Society of Nephrology and the International Congress of Nephrology. We included studies that were published as full reports in peer-reviewed journals or as abstracts. We included only studies that were prospective and were controlled with a parallel or crossover design control group. Studies that were uncontrolled, or used historical controls, were not included. We excluded studies that treated subjects for less than three months and studies that examined the effects of only diet or dietary supplements on renal function or proteinuria. In particular, we excluded studies that examined the effects of fish oil or other dietary fatty acid supplements.

Data extraction

Authors were asked to provide patient-specific data (without unique identifiers). Despite our best efforts, only the authors from 5 of the 12 studies that were ultimately included in the analysis provided individual patient data [11–15]. These individual data were used in the calculation of endpoints and variances. In addition, the individual patient data were used to calculate the covariance of end-point values before and after intervention or placebo, and the means of these covariances were used to estimate the covariance (and thereby calculate variance) for studies where the covariance was not known (discussed later in this article). Further data on studies presented as abstracts were obtained from data presented at the scientific meeting.

Two investigators independently extracted data. Differences were resolved by conferencing. We extracted data on study quality. To assess possible effects of study quality on results, we defined a study quality index in which two points were assigned if patients were allocated to treatment and control groups randomly. Two points were assigned if a parallel group design was used. One point was assigned if a crossover design was used. One point was assigned if the inclusion and exclusion criteria were clearly delineated. One point was assigned if subjects were masked, and one point was assigned if investigators were masked. We also extracted data on the age of subjects, their gender, the cause of renal disease (diabetes, glomerulonephritis, or other/unknown), the change in serum cholesterol, and the change in blood pressure in treatment and control groups.

Renal function and urine protein excretion

The major endpoint of interest was change in estimated GFR (mL/min). In most studies, this was measured in both treatment and control groups as the difference in GFR before and after treatment and control. We divided this difference by the duration of follow-up (in months) to determine the rate of change in GFR (mL/min/month). The second end point that we examined was change in proteinuria or urine albumin excretion. We used the natural logarithm of the values for proteinuria or urine albumin excretion to calculate this endpoint, that is, $\text{Ln}(\text{UP}_{\text{After}}) - \text{Ln}(\text{UP}_{\text{Before}})$, where UP_{After} was the urine protein or albumin excretion measured after completing the treatment or control period and $\text{UP}_{\text{Before}}$ was the urine protein or albumin excretion measure before initiating treatment or control. The natural logarithm was used to transform these data, since protein and albumin excretion data are usually not normally distributed [16–18]. In addition, the logarithmic transformation enabled us to combine different measures of protein or albumin excretion as a single endpoint (as the logarithm of the difference would be without units). The studies used several different methods for measuring this end point, including (*1*) timed urine collections to measure protein, (*2*) timed urine collections to measure albumin, (*3*) protein to creatinine ratios on untimed urine collections, or (*4*) albumin to creatinine ratios on untimed urine collections. There is a direct relationship between protein excretion rates determined on timed and untimed collections [19, 20]. For example, $\text{UP} = \text{PCR} \times \text{C}$, where UP is 24-hour urine protein, PCR is protein creatinine ratio, and C is a constant. Therefore,

$$\begin{aligned}\text{Ln}(\text{UP}_{\text{After}}) - \text{Ln}(\text{UP}_{\text{Before}}) &= \text{Ln}(\text{PCR}_{\text{After}} \times \text{C}) - (\text{PCR}_{\text{Before}} \times \text{C}) \\ &= \text{Ln}[(\text{PCR}_{\text{After}} \times \text{C})/(\text{PCR}_{\text{Before}} \times \text{C})] \\ &= \text{Ln}(\text{PCR}_{\text{After}}/\text{PCR}_{\text{Before}}) \\ &= \text{Ln}(\text{PCR}_{\text{After}}) - \text{Ln}(\text{PCR}_{\text{Before}})\end{aligned}$$

The same is true for timed and untimed urine albumin excretion [21]. In addition, at a given level of protein excretion, the proportion of protein that is albumin is relatively constant [21]. Since in most studies subjects had approximately the same level of protein excretion, a similar crude equivalence of the logarithmically transformed albumin and protein excretion differences can be assumed. Several of the studies included in the analysis had either individual patient data on albumin or protein excretion [11–15] or published logarithmically transformed geometric means with the antilog values of their standard errors [22, 23]. These allowed calculation of the difference in protein or albumin excretion between treatment and controls, as well as its variance (discussed later in this article). However, in the other six studies, this was estimated as the logarithm of the mean of untransformed data [abstracts; Scanferla et al, *Am J Hypertens* 4:868, 1991; Olbricht et al, *International Symposium on Lipids and Renal Disease*, 1999, Kashikojima, Japan

(October 8–11, 1998), p 29; Nishimura et al, *Am Soc Nephrol* 10:131A, 1999; Buemi et al, *J Am Soc Nephrol* 10:69A, 1999] [24, 25]. In these cases, the variance of the change in proteinuria or albuminuria was imputed as the mean variance across studies that allowed us to calculate this variance accurately.

Statistical analysis

For the *i*-th study, the difference in GFR caused by treatment (t) was calculated as:

$$\Delta GFR_{ti} = GFR_{ti2} - GFR_{ti1}$$

where GFR_{ti1} was the mean GFR before treatment, and GFR_{ti2} was the mean GFR after treatment. The variance of ΔGFR_{ti} caused by treatment in the *i*-th study was estimated as follows:

$$S_{ti}^2 = SD_{ti1}^2 + SD_{ti2}^2 - 2\gamma \cdot SD_{ti1} \cdot SD_{ti2}$$

where SD_{ti1} is the standard deviation of GFR_{ti1}, SD_{ti2} is the standard deviation of GFR_{ti2}, and γ is the covariance between GFR_{ti1} and GFR_{ti2}. The γ was calculated from individual patient data, and a mean of γs was used in cases in which no individual patient data were available. In the same manner, we also calculated ΔGFR_c and S_{ci}^2 for the placebo control group (c). We then calculated the difference between treatment and control, $y_i = \Delta GFR_{ti} - \Delta GFR_{ci}$ and the variance of the difference (y_i) was calculated as:

$$S_i^2 = \left(\frac{1}{n_{ti}} + \frac{1}{n_{ci}}\right) \cdot \frac{(n_{ti} - 1) \cdot S_{ti}^2 + (n_{ci} - 1) \cdot S_{ci}^2}{n_{ti} + n_{ci} - 2},$$

where n_{ti} and n_{ci} were the numbers of patients in the treatment and control groups, respectively. We calculated 95% confidence intervals for each study y_i as follows:

$$y_i \pm S_i \cdot t_{df}^{(i)}$$

where $t_{df}^{(i)}$ is the 97.5th percentile of the t-distribution with degrees of freedom $= n_{ti} + n_{ci} - 1$. The differences between treatment and control for proteinuria (logarithmically transformed) were calculated in an analogous manner.

Weighted means and confidence intervals were then calculated for the combined differences between treatment and control groups using a fixed-effects model. The weighted mean treatment effect was calculated as:

$$\bar{y}_w = \Sigma w_i y_i / \Sigma w_i$$

where y_i is the difference between treatment and control for the i^{th} study, and $w_i = 1/S_i^2$ is the inverse of the variance of y_i. The 95% confidence interval of this weighted mean treatment effect was calculated as:

$$\bar{y}_w \pm \sqrt{1/\Sigma w_i} \times t_{df}$$

where t_{df} is the 97.5th percentile of the t-distribution for degrees of freedom $= k - 1$, and k is the number of studies. This is a conservative choice for the number of degrees of freedom, since the actual number of degrees of freedom lies between $k - 1$ and $n - 1$, where n is the total number of patients included in the combined trials. Had we selected n for the degrees of freedom, t would have approximated 1.96, and the confidence intervals would have been narrower.

We looked for homogeneity of treatment effects with the test statistic:

$$Q = \sum_i w_i (y_i - \bar{y}_w)^2$$

where Q is approximately a χ^2 statistic with $k - 1$ degrees of freedom [26]. Q was used to test whether the variance of the treatment effect from the population mean of treatment effects was significantly different from 0 (the null hypothesis). To address the possible effects of heterogeneity of treatment effects, we also combined the results of trials using a random effects model as described by DerSimonian and Laird [27].

Analysis was carried out using a Microsoft Excel© spreadsheet and the Statistical Package for the Social Sciences (SPSS)© software package. Results were considered significant for two-tail $P < 0.05$. Values are expressed as means and 95% confidence intervals unless indicated otherwise.

RESULTS

Thirteen studies met the inclusion and exclusion criteria (Table 1). For the remainder of the results, the studies will be referred to by letter designation in Table 1. One study did not have sufficient data to calculate renal function (G), and two did not have data on protein excretion or albuminuria (A, L). Thus, 12 studies were combined in an analysis of the effects of treatment on change in GFR. In these 12 studies, 362 of 384 (94%) of patients completed the follow-up. In 11 studies with data on proteinuria, 246 of 262 (94%) patients completed follow-up. Reasons that some patients in five of the trials did not complete the follow-up varied (B–D, H, and J). In the remainder of the studies, there was no mention of enrolled subjects being dropped or excluded.

The percentage of patients in each study who were male varied from 25 to 80% (mean of study proportions was 61%). The mean age of patients in each study ranged from 36 to 65 years (mean of study means was 49 years). In seven studies, all patients had diabetes. In three studies, all had glomerulonephritis. In two trials, 76 to 81% had glomerulonephritis, and in one study, the cause of renal disease was not indicated (Table 1). Ten trials were randomized and controlled (Table 1). One trial assigned every other patient to treatment or control (H). Two

Table 1. Study characteristics

Study	First author [Reference]	Year	Study design	*N*	Duration *months*	Renal disease %	Treatment	End point studied		Baseline GFR *mL/min*		Baseline total cholesterol *mmol/L (mg/dL)*	
								GFR	Proteinuria	Treated	Control	Treated	Control
A	Scanferla[a]	91	RCT	24	12	Not stated 100	Simva/Prava	Yes (24)	No	44 ± 8[f]		6.8 ± 0.6 (263 ± 22)	6.9 ± 0.5 (268 ± 21)
B	Hommel [22]	92	RCT	26	3	Diabetes 100	Simvastatin	Yes (21)	Yes (21)	64 ± 30	72 ± 23	6.4 ± 0.9 (247 ± 35)	6.8 ± 1.0 (263 ± 39)
C	Nielsen [23]	93	RCT	20	9	Diabetes 100	Simvastatin	Yes (18)	Yes (18)	97 ± 23	97 ± 21	6.7 ± 0.8 (259 ± 31)	6.7 ± 0.9 (259 ± 35)
D	Thomas [24]	93	RCT	30	6	GN 76	Simvastatin	Yes (17)	Yes (23)	77 ± 37	75 ± 40	9.2 ± 1.3 (355 ± 50)	9.5 ± 2.4 (367 ± 93)
E	Aranda [11]	94	RCT	16	6	GN 81	Pravastatin	Yes (16)	Yes (16)	73 ± 17	57 ± 7	11.0 ± 4.8 (425 ± 185)	8.9 ± 3.7 (344 ± 143)
F	Lam [12]	95	RCT	34	26	Diabetes 100	Lovastatin	Yes (34)	Yes (34)	83 ± 38	84 ± 22	6.6 ± 0.4 (255 ± 15)	6.3 ± 0.4 (243 ± 15)
G	Zhang [25]	95	RXO	20	3	Diabetes 100	Pravastatin	No	Yes (20)	Not provided		5.4 ± 0.8 (210 ± 33)	5.4 ± 0.8 (210 ± 33)
H	Rayner [13]	96	RCT[e]	17	17	GN 100	Simvastatin	Yes (16)	Yes (16)	84 ± 31	74 ± 33	10.0 ± 2.8 (386 ± 108)	10.5 ± 2.8 (405 ± 108)
I	Smulders [14]	97	RCT	15	12	Diabetes 100	Gemfibrozil	Yes (15)	Yes (15)	73 ± 30	97 ± 31	6.9 ± 1.0 (266 ± 39)	6.6 ± 1.1 (255 ± 42)
J	Tonolo [15]	97	RXO	20	12	Diabetes 100	Simvastatin	Yes (19)	Yes (19)	96 ± 8	97 ± 7	6.7 ± 0.4 (259 ± 15)	6.0 ± 0.3 (232 ± 12)
K	Olbricht[b] [27]	98	RCT	43	24	GN 100	Simvastatin	Yes (43)	Yes (43)	77 ± 29	91 ± 43	9.4 ± 3.4 (364 ± 130)	8.7 ± 1.9 (334 ± 74)
L	Nishimura[c]	99	RCT	118	24	Diabetes 100	Probucol	Yes (118)	No	119 (93,138)	122[g] (100,165)	5.3 ± 0.9 (203 ± 35)	5.2 ± 0.8 (199 ± 30)
M	Buemi[d]	99	RCT	21	6	GN 100	Fluvastatin	Yes (21)	Yes (21)	90 (54–108)	90[h] (47–92)	Not provided	

Abbreviations are: RCT, randomized controlled trial; RXO, randomized crossover trial; GN, glomerulonephritis; Simva, simvastatin; Prava, pravastatin.

[a] Abstract; Scanferla F, et al, *Am J Hypertens* 4:868, 1991

[b] Olbricht CJ, for the Simvastatin in Nephrotic Syndrome Study Group: International Symposium on Lipids and Renal Disease 1999; Kashikojima, Japan (October 8–11, 1998), page 29

[c] Abstract; Nishimura M, et al., *J Am Soc Nephrol* 10:131A, 1999

[d] Abstract; Buemi M, et al., *J Am Soc Nephrol* 10:69A, 1999

[e] Although included as a randomized controlled trial, subjects in this study were alternately allocated to treatment and control

[f] Only the pooled baseline GFR was given

[g] Data are median and interquartile range

[h] Data are mean and range

trials used a randomized, crossover design (G, J). In six trials, both the investigators and subjects were masked (B–D, I–K). In four trials, neither investigators nor subjects were masked (A, E, G, H). In one trial, the subjects, but not the investigators, were masked (F). In two trials, information on masking was not available (L, M). Four of the studies have appeared only in abstract form, while the remainder were published in peer-reviewed journals.

In all but two studies (K, M), data on the change in total cholesterol were available. The difference between treatment and control in the percentage change in total cholesterol was −10.1% for gemfibrozil (I). For probucol, the difference between treatment and control in the percentage change in total cholesterol was −11.2% (L). Among the nine studies that reported the effects of an HMG-CoA reductase inhibitor on the change in total cholesterol, the difference between treatment and control in the percentage reduction in total cholesterol was −25.5% (mean of the study means), range −16.2% to −35.3%. In six studies that examined the effects of HMG-CoA reductase inhibitors, we were able to calculate that the difference between treatment and control in percentage change in mean arterial blood pressure was −2.8% (range of −8.9 to 2.6%). In Rayner, Byrne, and van Zyl Smit (H), one patient on simvastatin had a rise in creatinine phosphokinase (CPK) to 761 [13]. In Zhang et al (G), simvastatin was associated with a statistically significant, but clinically insignificant change in CPK (49 ± 23 to 68 ± 49) [25]. No other serious adverse events were reported.

Four studies measured GFR with plasma clearance of ^{51}Cr-EDTA (B, C, F, H). Two measured GFR with renal clearance of inulin (D, K), five with renal clearance of creatinine (E, I, J, L, M), and one with plasma clearance of ^{99m}Tc-DPTA (A). Five studies measured urine albumin excretion in timed 24-hour or overnight collections (B, C, G, J, M); three studies measured urine protein excretion in timed collections (D, E, F). Two measured protein:creatinine ratios (H, M), and one measured albumin:creatinine ratio (I).

The mean weighted effect of lipid-lowering treatment on the change in GFR was 0.156 (0.026 to 0.285) mL/min/month ($P = 0.008$), indicating that treatment with lipid-reducing agents had a favorable effect on GFR, that is, less decline (Fig. 1). A chi-square test for heterogeneity between the studies was not statistically significant, supporting the validity of pooling these trial results. Indeed, the combined treatment effect and confidence intervals were the same for the random effects model. When the trial that was not truly random (it assigned treatment to every other patient) was excluded, [13], the resulting effect of treatment remained at 0.156 (0.025 to 0.289) mL/min/month ($P = 0.008$). A funnel plot failed to suggest that there was publication bias (Fig. 2). A L'Abbé plot failed to reveal any marked heterogeneity between the trials (Fig. 3) [28].

In a regression analysis (using the difference in GFR between treatment and control as the dependent variable and weighting by least squares with inverse variance), the only statistically significant correlate with the effect of treatment was the duration of follow-up [effect of lipid lowering on change in GFR = 0.036 × (follow-up in months) − 0.323; $P = 0.007$]. There was a trend for a more beneficial effect of treatment in studies of better quality ($r = 0.563$, $P = 0.057$), and there was a similar trend for a more beneficial effect in larger studies ($r = 0.547$, $P = 0.066$). There was no relationship between the effect of treatment and age, gender, cause of renal disease, type of lipid lowering agent used, percentage change in cholesterol, the method for measuring GFR, or the difference in treatment and control in the (logarithmically transformed) urine protein/albumin excretion change. In a multivariate model, only duration of follow-up independently correlated with the effect of treatment on the change in GFR. To examine the effects of duration of follow-up further, we combined the eight trials of greater than six months duration (fixed effects model) and found that the effect of treatment was 0.157 (0.024 to 0.290, $P = 0.008$). In contrast, the effect of treatment in the four trials with follow-up of six months or less was −0.200 (−2.838 to 2.439, $P = 0.810$).

Using the fixed effects method for combining trials, the mean weighted effect of treatment on change in urine protein or albumin excretion was −0.283 (−0.427 to −0.139, $P < 0.001$). However, the chi-square test for heterogeneity between the studies was statistically significant ($P < 0.001$), questioning the validity of combining the results for proteinuria. Indeed, the results were not statistically significant using the random effects method for combining trials, where the mean weighted mean was −0.249 (−0.562 to 0.064, $P = 0.077$; Fig. 4). A funnel plot failed to suggest that there was publication bias (Fig. 5). In a regression analysis (using the difference in logarithmically transformed proteinuria or albuminuria between treatment and control as the dependent variable and weighting by least squares with inverse variance), there were no statistically significant correlations between reductions in proteinuria and the study quality index, sample size, age, gender, cause of renal disease, percentage change in cholesterol, or difference between treatment and control in GFR. There was possibly a trend for an effect of duration of follow-up on the effect of treatment on proteinuria ($r = -0.453$, $P = 0.162$). To examine further the effects of duration of follow-up on heterogeneity in protein excretion results, we combined the six trials of greater than six months duration and found that the (random effects model) effect of treatment was −0.450 (−0.783 to −0.116, $P < 0.001$). In contrast, the effect of treatment in the five trials with

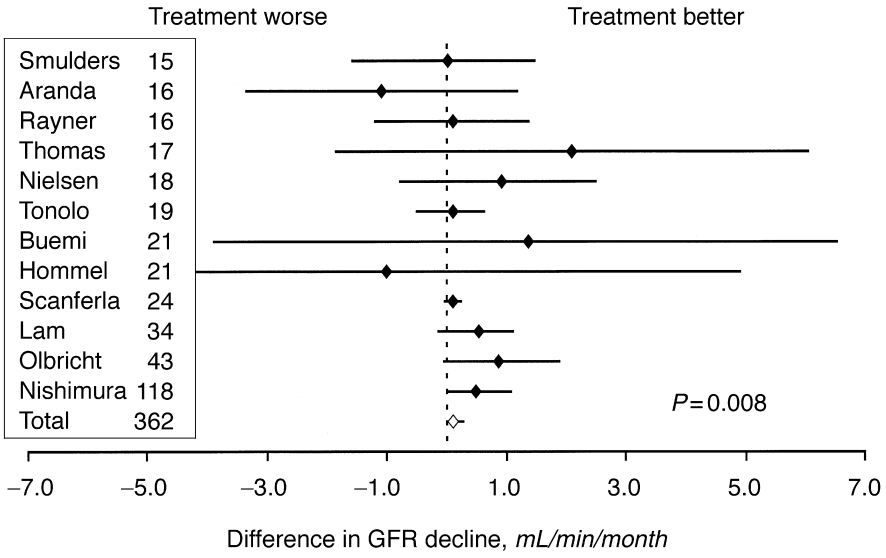

Fig. 1. Difference in change in the glomerular filtration rate (GFR) for each individual study (◆) and the combined results using a random effects model (◇). Horizontal lines indicate 95% confidence intervals. The number in parentheses is the number of patients who completed each study.

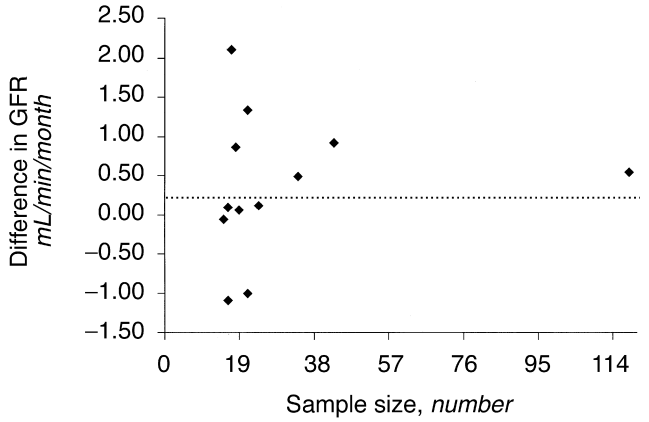

Fig. 2. Funnel plot for the included studies shows the sample size versus the difference in GFR.

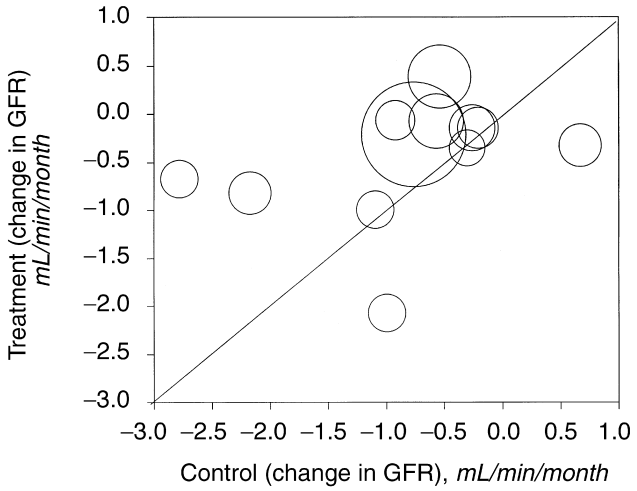

Fig. 3. L'Abbé plot of differences in GFR between treatment and control, with the area of the circle corresponding to the number of patients included in each study. Circles above the diagonal line indicate a beneficial effect of lipid-lowering agents on GFR compared with control.

follow-up of six months or less was −0.017 (−0.804 to 0.570, $P = 0.936$).

DISCUSSION

Although studies in animal models have found a favorable effect of lipid reduction on the progression of renal disease, the results of trials in humans are less clear. Most controlled trials have been too small to make a definitive conclusion. We used meta-analysis to pool the results of controlled clinical trials examining the effects of lipid-lowering therapy on renal function and proteinuria. We found that lipid reduction had a beneficial effect on the decline of GFR (Fig. 1). In only one trial (the largest) was there a statistically significant effect of lipid lowering on GFR (abstract; Nishimura et al, *Am Soc Nephrol* 10:131A, 1999). There was little evidence for publication bias (Fig. 2) or for heterogeneity in the results of the trials (Fig. 3). To our knowledge, this is the first reported meta-analysis examining the effects of lipid-lowering therapy on renal function. A previous meta-analysis that examined the effects of lipid-lowering therapy on lipoproteins did not investigate its effects on renal function or proteinuria in patients with renal disease [29].

The reduction in GFR from lipid-lowering agents in this study was 0.16 (0.03 to 0.27) mL/min/month or 1.9 (0.3 to 3.4) mL/min/year, and this compares favorably to the effect of converting enzyme inhibitors on the rate of change in renal function. Indeed, in a meta-analysis

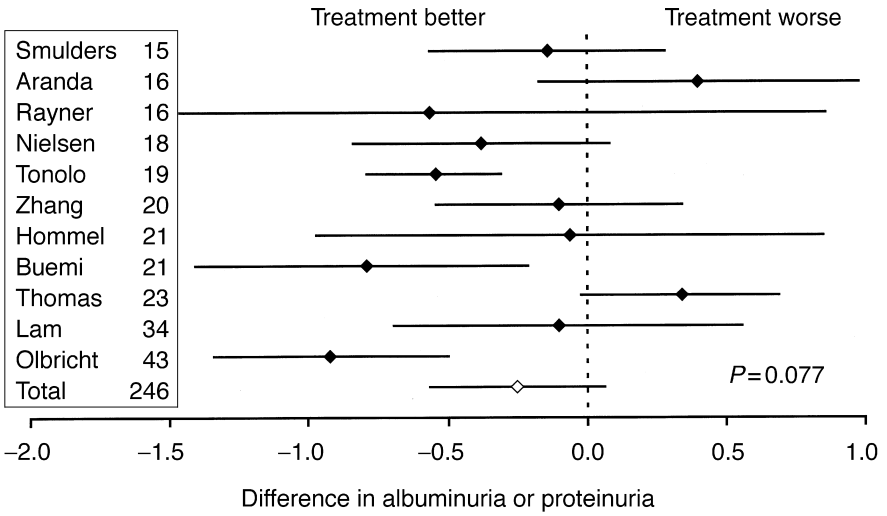

Fig. 4. Difference in change in albuminuria or proteinuria [Ln(treatment) − Ln(control)] for each individual study (◆) and the combined result using a random effects model (◇). Horizontal lines indicate 95% confidence intervals. The number in parentheses equals the sample size.

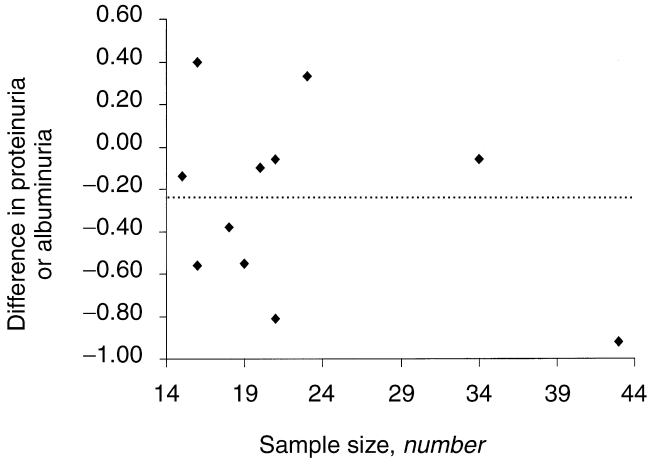

Fig. 5. Funnel plot for the included studies shows the sample size versus difference in proteinuria or albuminuria [Ln(treatment) − Ln(control)].

of randomized controlled trials employing statistical techniques similar to those used in the current study, the difference between patients treated with converting enzyme inhibitors compared with controls was 1.6 (1.2 to 1.9) mL/min/year [30]. In contrast, the effect on change in GFR of low protein diet was only 0.53 (0.08 to 0.98) mL/min/year in a similar meta-analysis [31].

We also examined the effects of lipid-lowering therapies on proteinuria. In this analysis, there appeared to be significant heterogeneity between the trial results (Fig. 4). Therefore, we attempted to combine these trials using a random effects model. There appeared to be a tendency for a reduction in protein excretion with lipid-lowering treatment; however, this result should be interpreted with caution.

There are several important limitations to this meta-analysis. The number of trials and the numbers of patients in the trials were relatively small. Moreover, there were many differences in the patients that were studied, the trial designs that were used, and the methods for measuring GFR and proteinuria. Particularly problematic is the interpretation of changes in proteinuria, given the heterogeneity in the results of the individual trials. It is not clear how to handle summary data when there is heterogeneity, and many believe that pooled results can be uninterpretable in the presence of heterogeneity [26, 32, 33]. Meta-analysis implies that a mean value estimating the effects of treatment can be determined by combining similar trials, and this is not the case when the outcome results of those trials are significantly heterogeneous [26]. We also performed regression analysis to identify patient or study characteristics associated with the change in GFR or proteinuria and thereby identify possible reasons for differences between studies. Only the duration of follow-up correlated with the effects of treatment on GFR. That the difference in change in GFR between treatment and control did not correlate with the difference in change in cholesterol probably reflects that the degree of change in cholesterol did not differ significantly across studies. It should not be taken to mean that the reduction in cholesterol was unimportant. There was a possible trend for study duration to correlate with changes in proteinuria. However, the statistical power of this analysis may be too low to determine whether the underlying disease process (for example, diabetic nephropathy) or other variables influence the response to lipid-lowering therapy. Had we been able to obtain individual patient data for more of the studies, we could have more fully examined the effect of other variables [34].

With any meta-analysis, publication bias and "file-drawer" bias may significantly influence the results. Pub-

lication bias results when small trials showing weak or negative effects are less often published [35]. We tried to avoid this potential source of bias by including both published and unpublished (abstracts to meetings) trials. However, it is possible that a number of trials that failed to show a beneficial effect of lipid-lowering therapy on renal function or proteinuria were never submitted for presentation at meetings and were never published, and thus were subject to "file-drawer bias." To screen for both publication and "file-drawer bias," we constructed funnel plots. These plots did not suggest that publication bias was present (Figs. 2 and 5). Had there been publication bias, we may have expected to find fewer studies appearing on the "negative result" side of the pooled treatment effect line toward the left side of the graph, suggesting the selective exclusion of smaller studies that reported negative results [26]. Of course, this and other tests of publication bias do not exclude the possibility that significant publication bias in fact exists.

The exact mechanism by which hyperlipidemia worsens renal disease is not known. Hyperlipidemia alone does not appear to cause renal disease, although patients with hereditary lipid disorder, such as lecithin-cholesterol acyltransferase deficiency, develop proteinuria and renal failure [36]. Biopsy of patients with this disorder reveal foam cells in the glomeruli with lipid deposition in the glomerular basement membrane and mesangium. Glomerulosclerosis is correlated with the presence of atherosclerosis, leading investigators to suggest similar pathologic mechanisms [37, 38]. Mesangial cells resemble vascular smooth muscle cells and respond to many of the same stimuli [38]. In tissue culture assays, mesangial cells express receptors for LDL cholesterol and LDL or very LDL promotes mesangial cell proliferation [39, 40]. LDL stimulates fibronectin and chemoattractant production, which could lead to increased mesangial matrix and recruitment of inflammatory cells [41]. This response could then worsen the renal disease and set up a vicious circle in which the worsening renal disease then worsens the hyperlipidemia.

Reduction of lipid levels may also have hemodynamic effects that could be relevant to the mechanism of improvement of GFR. Treatment with lipid-lowering medications has been shown to lower peripheral vascular resistance, raise cardiac output, and improve endothelial function in some [42–45], but not all studies [46, 47]. The improvement in endothelial function can develop rapidly. O'Driscoll, Green, and Taylor, in a study of 10 subjects treated with simvastatin, found improvement after only four weeks [44]. The majority of these studies have been performed using statins, but the effect has also been seen with cholestyramine, which suggests that it is due to the cholesterol lowering and not an effect of statins per se [43].

The present meta-analysis may have important implications for therapy of patients with renal disease, because large, multicenter, randomized, controlled trials to determine definitively whether lipid-lowering agents slow the rate of renal disease progression may never be carried out. If a randomized trial was to be planned, we estimated that it would need to have 2600 subjects to have sufficient power (80%) to examine the impact of lipid reduction on progression of renal disease (assuming that the difference in GFR was the same as the aggregate value in our study and using the median variance across the studies that we found). However, there is growing evidence that cardiovascular disease is prevalent in patients with renal disease and that hyperlipidemia may play an important role in its pathogenesis [48]. Therefore, it may be unethical to include an untreated control group of hyperlipidemic patients with renal disease in a clinical trial requiring long-term follow-up. Indeed, the majority of patients with renal disease have hyperlipidemia as well as other cardiovascular disease risk factors that would make lipid-lowering therapy difficult to withhold in a placebo control group. Indeed, the American Diabetes Association and the National Kidney Foundation now recommend strict control of lipoprotein levels for diabetics and those with chronic renal failure, respectively (greater than half of the studies in this meta-analysis were in diabetics) [48, 49]. These groups recommend starting pharmacological therapy for a LDL >130 mg/dL (3.37 mmol/L) and targeting LDL <100 mg/dL (2.59 mmol/L) for those without a history of cardiovascular disease.

In conclusion, the results of this meta-analysis suggest that lipid-lowering therapy in patients with renal insufficiency may help slow the rate of renal disease progression. It is clear that therapy with newer lipid-lowering agents is relatively safe in patients with nephrotic syndrome and renal insufficiency [29]. It is also increasingly apparent that hyperlipidemia may contribute to the cardiovascular disease that is so prevalent in this patient population. This meta-analysis lends further support to the argument that hyperlipidemia should be treated in patients with nephrotic syndrome and/or renal insufficiency.

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