Higher Levels of HDL Cholesterol Are Associated With a Decreased Likelihood of Albuminuria in Patients With Long-Standing Type 1 Diabetes

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OBJECTIVE — The objective of this study was to determine whether high levels of HDL cholesterol are associated with a lower prevalence of albuminuria.

RESEARCH DESIGN AND METHODS — We analyzed the lipid profiles of patients with type 1 diabetes of ≥20 years duration in 42 patients with albuminuria (28 microalbuminuria and 14 macroalbuminuria) and 65 patients without increased albumin excretion before any interventions with either statins or ACE inhibitors.

RESULTS — Several characteristics were similar in the two groups: sex, age, duration of diabetes, total cholesterol, LDL cholesterol, and triglycerides. By univariate analysis, significant differences (P < 0.01) were found in HDL cholesterol (albuminuria 1.42 mg/dl, no albuminuria 1.71 mg/dl, P < 0.01), HbA1c (A1C) (albuminuria 8.5%, no albuminuria 7.5%), and proportions with no, background, and proliferative retinopathy (albuminuria 2.4, 16.7, and 81%; no albuminuria 24.6, 52.3, and 23.1%, respectively). When adjusted for age and sex, a 0.26-mmol/l (10-ml/dl) increase in HDL cholesterol is associated with an odds ratio (OR) of 0.70 (95% CI 0.54–0.90) for having albuminuria. In a multivariate model that adjusted for age, sex, diabetes duration, and A1C, for every 0.54-mmol/l (21-ml/dl) increase in HDL cholesterol, patients are approximately half (OR 0.51 [95% CI 0.30–0.86]) as likely to have albuminuria, even after controlling for A1C.

CONCLUSIONS — Higher HDL cholesterol levels may be protective against the development of albuminuria in patients with type 1 diabetes. Whether this is due to the HDL cholesterol levels or whether they serve as a marker for some other mechanism remains to be determined.

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Diabetes is the most common cause of kidney failure in the U.S. (1) and is among the most common causes in the rest of the world. The natural history of diabetic kidney disease in individuals with type 1 diabetes is characterized by the onset of albuminuria, initially microalbuminuria (30–300 mg/g creatinine) and subsequently macroalbuminuria (≥300 mg/g creatinine), followed by a progressive decline in glomerular filtration rate (GFR). Many epidemiologic studies and controlled trials in type 1 diabetes have defined risk factors for progression of diabetic kidney disease and response to treatment (2,3). The most important of these risk factors is hyperglycemia, as shown by a number of observational and prospective studies (4,5) and then more definitively by the Diabetes Control and Complications Trial (6–8). However, glycemic control cannot be the only determinant of who develops diabetic nephropathy. As only about one-third of individuals with type 1 diabetes develop nephropathy, regardless of glycemic control, it is clear that other genetic, metabolic, and possibly environmental factors must be important.

Many studies have shown a strong link between nephropathy and atherosclerotic cardiovascular disease in patients with type 1 and type 2 diabetes (9–12). Both hypertension and dyslipidemias have been shown to be risk factors for both of these complications (3,13). In a number of studies, an increase in LDL cholesterol levels has been found to be a risk factor for nephropathy in type 1 diabetes (14–29). Although an elevated HDL cholesterol level has been shown to be protective for coronary artery disease in many studies (30,31), this parameter has not been evaluated as a potential protective factor against the development of nephropathy.

It was the purpose of this study to evaluate the hypothesis that high HDL cholesterol levels are associated with a lower prevalence of albuminuria, as a marker of nephropathy, in individuals with long-standing type 1 diabetes.

RESEARCH DESIGN AND METHODS — Data on the presence of diabetic nephropathy, lipid levels, and other characteristics were obtained by chart review of patients seen in the routine office practice of one of the authors (M.E.M.). Charts of all patients with type 1 diabetes were reviewed and selected solely on the basis of a self-reported duration of diabetes of ≥20 years. Patients were designated as having type 1 diabetes on the basis of a history of diabetic ketoacidosis or the need to begin insulin therapy within 1 year of diagnosis.

Patients had urine albumin levels assessed on an annual basis, initially as part of timed 24-h urine collections but since about 1990 by measurement of urine albumin-to-creatinine ratios, and these...
were not required to be first- or second-
voided morning specimens. Patients were
designated as having albuminuria if they had
a 24-h urine measurement >30 mg
or an albumin-to-creatinine ratio >30
mg/g creatinine on more than one occa-
sion (2). Lipid profiles were also generally
done yearly, including measurements of
total, HDL, and LDL cholesterol and tri-
glyceride levels. Unless the patient had el-
evated triglyceride levels, these blood
samples for lipid measurements were usu-
ally not fasting specimens. The levels of
these lipid parameters and HbA1c
(A1C) used in this study were obtained
before starting any hypolipidemic ther-
apy. Albuminuria characterization was
the last obtained before starting any hy-
polipidemic therapy or any ACE inhibitor
treatment and were within 1 year of the
lipid and A1C measurements. Angioten-
sin II receptor blockers were not used in
these patients. Urine albumin and cre-
atinine, serum lipids, and plasma A1C
were performed by routine assays in the
Northwestern Memorial Hospital Clinical
Pathology Laboratory. Assessments of di-
abetic retinopathy were performed at
least annually by ophthalmologists in
most patients and were reported in the
office records. The ophthalmic assess-
ments reported here were within 1 year of the
lipid, A1C, and urine microalbumin
assessments.

Statistical analysis
Descriptive data are reported as means ±
SD or proportions. For continuous and
categorical variables, statistical compari-
sions were made using t tests and \( \chi^2 \) tests,
respectively. A series of logistic regression
models with varying adjustment were used
to calculate the odds of having albumi-
numia per SD higher HDL: model 1, un-
adjusted; model 2, adjusted for age and
sex; and model 3, model 2 plus duration
of diabetes and A1C. HDL cholesterol lev-
els from this patient sample were also
compared against an external referent
population of people (with and without
diabetes) from the National Health and
Nutrition Examination Survey (NHANES)
1999–2002 (32). In a second set of logistic regression models, patients
with HDL cholesterol levels 1 SD above
the sex-specific NHANES population
mean (men 1.53 mmol/l, women 1.84
mmol/l) were classified as having high
HDL cholesterol. SAS version 9.0 (SAS In-
stitute, Cary, NC) was used for all analy-
ses. Statistical significance was denoted at
\( P < 0.05 \).

RESULTS — Chart review identified
107 patients with type 1 diabetes who had
diabetes of at least 20 years duration (Ta-
ble 1). Of this group, 42 were identified
who had increased urinary albumin excre-
tion (designated as albuminuria); 28
had microalbuminuria (30–300 mg/g
creatinine) and 14 had macroalbuminuria
(>300 mg/g creatinine). Nine with macro-
albuminuria had normal GFR and five
had decreased GFRs. Sixty-five patients
had normal urinary albumin excretion
and GFRs. The mean age of the patients
was 43.5 ± 10 years and the duration of
diabetes was 30.8 ± 7.1 years; the two
groups were virtually identical with re-
spect to age and duration of diabetes. Ap-
proximately two-thirds of the patients
were women, and this distribution did
not differ between the two groups. The
mean A1C was 7.9 ± 1.6% for the total
population, and the group with albumin-
uria had a significantly higher level than
those without albuminuria (8.5 ± 1.7 vs.
7.5 ± 1.4%, \( P < 0.01 \)). The proportions
with diabetic retinopathy also differed by
group. Proliferative retinopathy was more
common in individuals with albumin-
uria, whereas no or background retinop-
athy was more common in individuals
without albuminuria. Sixteen patients
(15%) had neither retinopathy nor albu-
minuria.

The total cholesterol level in these pa-
patients was 5.08 ± 1.07 mmol/l, with no
difference between the two groups. Al-
though LDL cholesterol and triglyceride
levels in those with albuminuria were
higher than those without albuminuria
(Fig. 1), these differences were not statis-
tically significant (LDL cholesterol, \( P =
0.26; \) triglycerides, \( P = 0.19 \)). In contrast,
A1C was higher and HDL cholesterol lev-
els were significantly lower in those who
had albuminuria compared with those
that did not have albuminuria (Fig. 1). By
univariate analysis, a 0.26-mmol/l (10-
mg/dl) increase in HDL cholesterol was
associated with an unadjusted odds ratio
(OR) of 0.74 (95% CI 0.59–0.93) for the
development of albuminuria and an OR
of 0.70 (0.54–0.90) after adjustment for
age and sex.

In a multivariable model that in-
cluded HDL cholesterol, A1C, age, sex,
and diabetes duration, both A1C and
HDL cholesterol were associated with a
lower likelihood of having albuminuria
(Table 2). For every 0.54-mmol/l (21-
mg/dl) increase in HDL cholesterol, pa-
tients are half as likely to have albuminuria,
even after controlling for A1C.

Categorical analysis showed that pa-
ients with HDL cholesterol levels >1 SD
above the NHANES population mean are
74% less likely (OR 0.26 [95% CI 0.10–
0.72]) to have albuminuria independent of
the A1C levels. Sixteen percent of those
with albuminuria and 46% of those with-
out albuminuria had HDL cholesterol
values >1 SD above the NHANES popu-
lation mean.

CONCLUSIONS — Microalbumin-
uria is the earliest clinical indicator of di-
abetic nephropathy, and 25–80% of
those with type 1 diabetes and microalbu-
minuria go on to progress to higher rates of urinary albumin excretion associated with progressive kidney disease (33). Most long-term epidemiologic studies have shown that generally only \(\sim 30–40\%\) of patients with type 1 diabetes will ever develop diabetic kidney disease even with poor diabetes control (8,34,35), with the peak incidence being reached by \(\sim 20\) years duration of diabetes. This information, along with the known familial clustering of diabetic kidney disease in those with type 1 diabetes (36–38), suggests that there must be some additional genetic or other factor(s) that either predispose individuals to this complication or, alternatively, protect some individuals from this complication (39–42).

In this study, we selected a time point of 20 years duration of diabetes for inclusion of patients in this analysis, a time at which the annual incidence of new development of microalbuminuria has already decreased markedly, and those who do not have microalbuminuria by this point are unlikely to ever develop it (8,34,35). In fact, the mean duration of diabetes in the two groups was 30 years. We have shown that elevated HDL cholesterol levels may indicate a partial protection from the development of nephropathy.

Our patients with long-term disease and no microalbuminuria also had less severe retinopathy, only 23% of them having proliferative disease compared with 81% of those with albuminuria. This clustering of microvascular complications has been demonstrated by a number of studies previously (6,7).

As indicated above, clustering of coronary artery disease with nephropathy has been shown previously in patients with type 1 and type 2 diabetes (9–12). Furthermore, a protective effect of HDL cholesterol levels on coronary artery disease has been known for many years (30,31), but its protective effect on other complications of diabetes has not been remarked upon previously. Whether protective effects of high HDL cholesterol levels on coronary artery disease and nephropathy will correlate with each other can only be determined by long-term studies. It is thought that HDL is not only involved in reverse cholesterol transport but also may have a number of other beneficial effects on the vascular endothelium (31). Therefore, it is possible these additional mechanisms may be the means by which high HDL levels may have a salutary effect on the glomerulus.

We have shown in this study that higher HDL cholesterol levels may be protective against the development of albuminuria in patients with type 1 diabetes. Whether this is due to the HDL cholesterol levels or whether they serve as a

![Figure 1](image)

**Table 2—ORs of the association between HDL (per SD) and microalbuminuria**

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL (per 0.54 mmol/l)</td>
<td>0.54 (0.34–0.86)</td>
<td>0.48 (0.28–0.80)</td>
<td>0.51 (0.30–0.86)</td>
</tr>
<tr>
<td>Age</td>
<td>1.02 (0.98–1.06)</td>
<td>1.04 (0.98–1.10)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>0.71 (0.29–1.72)</td>
<td>0.76 (0.29–1.96)</td>
<td></td>
</tr>
<tr>
<td>Diabetes duration</td>
<td>0.98 (0.90–1.07)</td>
<td></td>
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<tr>
<td>A1C</td>
<td>1.45 (1.08–1.93)</td>
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<td></td>
</tr>
</tbody>
</table>

Data are OR (95% CI).
marker for some other mechanism remains to be determined.

Acknowledgments — This study was presented in part at the Scientific Sessions of the 65th Annual Meeting of the American Diabetes Association, San Diego, California, 10–14 June 2005 (44).

References


HDL cholesterol levels and albuminuria

44. Molitch ME, Rupp D, Carnethon M: Higher levels of HDL cholesterol (HDL cholesterol) are associated with a decreased likelihood of diabetic nephropathy (DN) in patients with long-standing type 1 diabetes (Abstract). *Diabetes* 54 (Suppl. 1):A198, 2005