Serum Cholesterol in Wisconsin Epidemiologic Study of Diabetic Retinopathy

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OBJECTIVE — To describe serum total and high-density lipoprotein (HDL) cholesterol in a sample of people with diabetes.

RESEARCH DESIGN AND METHODS — Subjects were those who participated in the 1984–1986 Wisconsin Epidemiologic Study of Diabetic Retinopathy. Data were from three groups of subjects: 304 younger-onset and 185 older-onset people taking insulin and 162 older-onset individuals not taking insulin. Serum lipids, duration of diabetes, glycosylated hemoglobin, diastolic blood pressure, sex, age, serum creatinine, units of insulin per kiliogram per day, smoking status, serum C-peptide level, and alcohol use were analyzed statistically.

RESULTS — In subjects taking insulin, glycosylated hemoglobin was correlated most strongly with total cholesterol. In those not taking insulin, C-peptide was correlated most strongly. In subjects taking insulin, the units used per day (fewer) and sex (female) were significantly associated with higher HDL cholesterol, and in both older-onset groups, serum C-peptide was significantly associated with lower HDL cholesterol. Mean total cholesterol levels were generally higher and mean HDL cholesterol levels were generally lower than those found in a nondiabetic comparison group.

CONCLUSIONS — By the National Cholesterol Education Program guidelines, 17% of younger-onset and 30% of older-onset insulin users and 32% of older-onset subjects not taking insulin were in the high-risk range for total cholesterol. Lower levels of glycosylated hemoglobin might result in lower cholesterol levels.

People with diabetes mellitus are at increased risk of coronary heart disease, and elevated cholesterol concentrations are a known risk factor for that disease as well (1–4). Because the level of cholesterol may be influenced by the presence of diabetes, we studied this factor in data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR; 5).

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RESEARCH DESIGN AND METHODS

— The study subjects were identified in 1979–1980 and seen in 1980–1982 and again in 1984–1986. The specifics of identification, sampling, and participation were described previously (5–9). In brief, 891 people who were diagnosed with diabetes before 30 yr of age and who were taking insulin (younger onset) and 987 who were ≥30 yr of age at the time of diagnosis (older onset) were seen during the follow-up examination in 1984–1986. Data in this report are based only on a sample of the subjects participating in that evaluation. Spouses of study subjects and a group of children attending a well-child practice, none of whom had diabetes, were evaluated. These people are called the nondiabetic comparison group.

The specifics of the examinations and laboratory studies have been reported elsewhere (10–16). The determination of cholesterol values began late in the study because of administrative considerations. Of those subjects who were seen after July 1985, 92% were tested. Data from one subject whose total cholesterol level was 35.6 mM are excluded from the older-onset insulin-using group because that value has an inordinate effect on the analyses.

Cholesterol levels were measured when the subjects presented for the study examination, and most were not fasting. However, neither total cholesterol nor high-density lipoprotein (HDL) cholesterol is significantly associated with time since the last meal in any group. Use of cholesterol-lowering agents occurred in a few subjects and was not considered in the following analyses.

Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared (kg/m^2). Proteinuria in a casual urine specimen was defined as values ≥0.30 g/L found with Labstix (Miles, Elkhart, IN). Some people who were diagnosed at

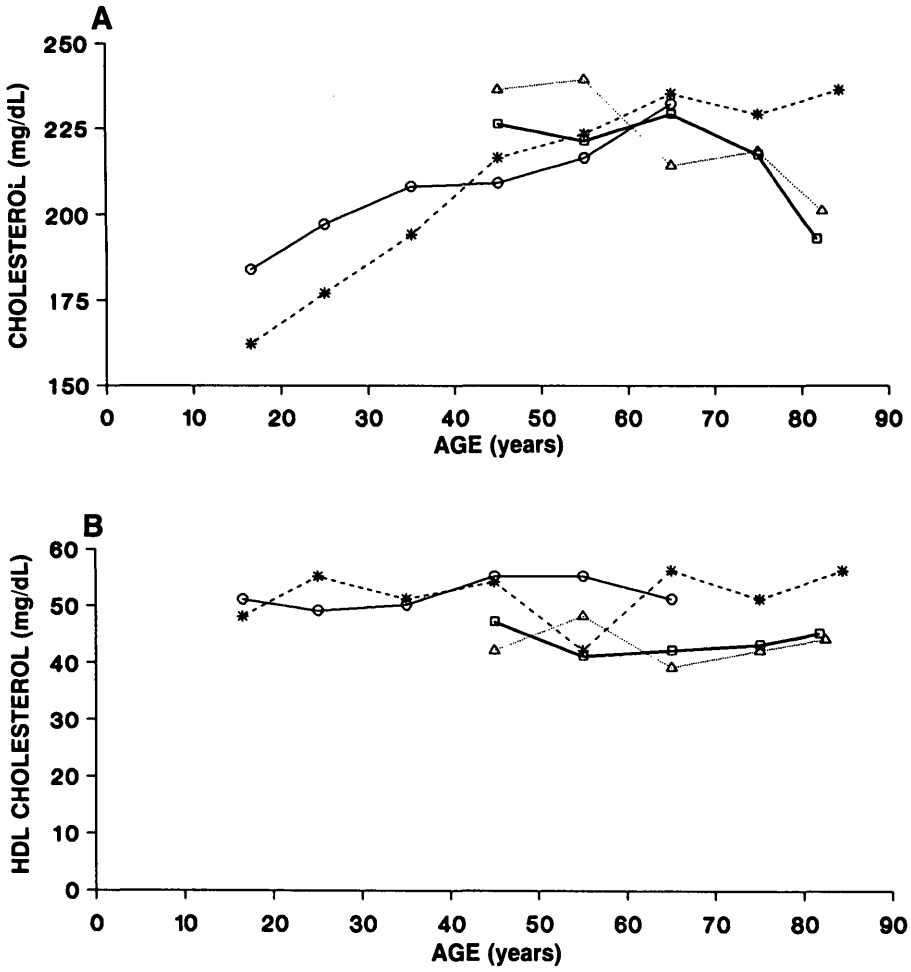

Figure 1—*Mean serum cholesterol (A) and mean high-density lipoprotein (HDL) cholesterol (B) by age for 4 study groups: younger-onset patients (circles), older-onset patients using insulin (squares), older-onset patients not using insulin (triangles), and nondiabetic subjects (stars).*

≥30 yr of age were taking insulin and some were not. Thus, data are presented for the two older-onset subgroups.

RESULTS — Figure 1 shows the mean total and HDL cholesterol by age. In both the younger-onset and nondiabetic groups, total cholesterol tended to increase with increasing age. In both older-onset groups, total cholesterol tended to decrease at older ages. For HDL cholesterol, the mean values in all groups varied little with age. The younger-onset and nondiabetic groups tended to have higher mean values than both older-onset groups.

Table 1 lists the mean total and HDL cholesterol by different characteristics for the three diabetic groups. Total cholesterol is not significantly different between the sexes in any group, but HDL cholesterol is (levels in females are 0.15–0.20 mM higher in each group) for both insulin-using groups; the difference is of borderline significance in those not using insulin (perhaps a result of the small sample size).

Other characteristics vary in their association with total and HDL cholesterol among the groups. Duration of diabetes is significantly related to increased total and HDL cholesterol in the younger-onset group; diastolic blood pressure is related to total cholesterol in all groups (borderline in older-onset insulin users); BMI, to lower HDL cholesterol in all groups; amount of insulin to lower HDL cholesterol in insulin users; C-peptide to lower total and HDL cholesterols in both older-onset groups; glycosylated hemoglobin to higher total cholesterol in insulin users; creatinine inconsistently related to total cholesterol but consistently related to lower HDL cholesterol in all groups; and urinary protein to higher total cholesterol in younger-onset subjects and to lower HDL cholesterol in both insulin-using groups.

CONCLUSIONS — The characteristics that may influence cholesterol levels differ among the three groups of subjects. In both insulin-using groups, glycosylated hemoglobin was strongly associated with total cholesterol. This cross-sectional finding is consistent with the longitudinal findings of Ostlund et al. (17) who showed that therapeutically decreasing glycosylated hemoglobin in people with IDDM is associated with decreased levels of cholesterol.

Age at examination is positively associated with total cholesterol in the younger-onset group only. It is possible in this study cohort that those people with more elevated levels (and older age) were more likely to have died. We cannot assess this hypothesis because cholesterol levels were not evaluated at the baseline examination.

Diastolic blood pressure is correlated with total cholesterol in all groups, although in the older-onset insulin users, the relationship is not statistically significant. This nonsignificance may be due to an association of nephropathy with cholesterol. In the younger-onset group, there is evidence

Table 1—*Mean total and high-density lipoprotein (HDL) cholesterols by subject characteristics*

	Total cholesterol (mM)			HDL cholesterol (mM)		
	N	Mean ± SD	*P*	*N*	Mean ± SD	*P*
YOUNGER ONSET						
Sex						
Women	143	5.40 ± 1.30	0.06	143	1.40 ± 0.40	<0.005
Men	161	5.10 ± 1.30		159	1.25 ± 0.35	
Duration (yr)						
5–9	70	4.80 ± 1.15		68	1.30 ± 0.35	
10–14	86	5.15 ± 1.30	<0.0001	86	1.30 ± 0.40	0.05
15–24	76	5.20 ± 1.20		76	1.30 ± 0.40	
≥25	72	5.70 ± 1.45		72	1.40 ± 0.45	
Diastolic blood pressure (mmHg)						
≤69	75	4.85 ± 1.10		75	1.35 ± 0.40	
70–77	69	5.10 ± 1.35	<0.005	68	1.25 ± 0.35	0.41
78–84	79	5.45 ± 1.40		79	1.35 ± 0.45	
≥85	77	5.40 ± 1.30		77	1.30 ± 0.40	
Body mass (kg/m^2)						
≤22.1	75	5.30 ± 1.40		75	1.35 ± 0.40	
22.2–24.1	69	5.05 ± 1.25	0.09	68	1.35 ± 0.35	<0.001
24.2–26.4	75	4.95 ± 1.10		75	1.30 ± 0.45	
≥26.5	71	5.40 ± 1.40		71	1.25 ± 0.40	
Insulin ($U \cdot kg^{-1} \cdot day^{-1}$)						
0.1–0.5	72	5.20 ± 1.05		72	1.45 ± 0.40	
0.6–0.9	157	5.05 ± 1.30	0.27	156	1.25 ± 0.40	<0.05
≥1.0	61	5.40 ± 1.55		61	1.25 ± 0.40	
C-peptide (nM)						
0–0.03	262	5.25 ± 1.35		262	1.30 ± 0.40	
0.04–0.29	31	5.15 ± 1.25	0.99	31	1.20 ± 0.35	0.40
≥0.30	9	5.05 ± 1.20		9	1.20 ± 0.40	
Glycosylated hemoglobin (%)						
≤8.6	74	4.80 ± 1.10		73	1.30 ± 0.45	
8.7–10.0	77	4.90 ± 1.10	<0.0001	77	1.30 ± 0.35	0.81
10.1–11.3	74	5.20 ± 1.10		73	1.30 ± 0.35	
≥11.4	76	5.95 ± 1.60		76	1.30 ± 0.45	
Creatinine (μM)						
≤0.7	65	5.10 ± 1.05		65	1.45 ± 0.40	
0.8–1.0	174	5.10 ± 1.35	<0.05	173	1.30 ± 0.40	<0.01
≥1.1	64	5.65 ± 1.30		63	1.20 ± 0.40	
Urine protein						
Absent	239	5.05 ± 1.20	<0.0001	237	1.35 ± 0.40	<0.05
Present	60	5.85 ± 1.40		60	1.20 ± 0.40	
OLDER ONSET (INSULIN)						
Sex						
Women	115	5.70 ± 1.20	0.30	115	1.20 ± 0.45	0.005
Men	69	5.55 ± 1.10		69	1.00 ± 0.40	

Table 1—*Continued*

	Total cholesterol (mM)			HDL cholesterol (mM)		
	N	Mean ± SD	*P*	*N*	Mean ± SD	*P*
Duration (yr)						
5–9	35	5.55 ± 1.40		35	1.05 ± 0.35	
10–14	42	5.50 ± 1.00	0.19	42	1.15 ± 0.45	0.30
15–24	68	5.70 ± 1.15		68	1.05 ± 0.40	
≥25	39	5.75 ± 1.15		39	1.20 ± 0.50	
Diastolic blood pressure (mmHg)						
≤64	46	5.35 ± 1.30		46	1.05 ± 0.35	
65–72	47	5.70 ± 1.10	0.06	47	1.15 ± 0.40	0.28
73–81	42	5.80 ± 1.15		42	1.20 ± 0.50	
≥82	46	5.80 ± 1.15		46	1.10 ± 0.40	
Body mass (kg/m^2)						
≤24.8	35	5.55 ± 1.10		35	1.40 ± 0.55	
24.9–28.5	35	5.85 ± 1.50	0.36	35	1.10 ± 0.35	<0.005
28.6–33.7	36	5.90 ± 0.95		36	0.95 ± 0.30	
≥33.8	36	5.70 ± 1.00		36	1.10 ± 0.35	
Insulin ($U \cdot kg^{-1} \cdot day^{-1}$)						
0.1–0.4	34	5.40 ± 1.10		34	1.25 ± 0.45	
0.5–0.8	80	5.95 ± 1.20	0.85	80	1.15 ± 0.40	<0.0001
≥0.9	28	5.60 ± 1.05		28	0.90 ± 0.25	
C-Peptide (nM)						
0–0.03	36	6.00 ± 1.15		36	1.45 ± 0.60	
0.04–0.29	34	5.70 ± 1.25	<0.05	34	1.20 ± 0.40	<0.0001
0.30–0.91	57	5.65 ± 1.20		57	1.10 ± 0.35	
≥0.92	57	5.40 ± 1.05		57	0.90 ± 0.20	
Glycosylated hemoglobin (%)						
≤8.4	45	5.30 ± 1.10		45	1.05 ± 0.35	
8.5–9.5	50	5.55 ± 1.00	<0.005	50	1.10 ± 0.40	0.21
9.6–10.8	44	5.85 ± 1.30		44	1.15 ± 0.50	
≥10.9	45	5.95 ± 1.20		45	1.20 ± 0.45	
Creatinine (μM)						
≤0.8	40	5.70 ± 1.30		40	1.25 ± 0.50	
0.9–1.2	101	5.55 ± 1.10	0.55	101	1.15 ± 0.40	<0.0001
≥1.3	42	5.85 ± 1.15		42	0.95 ± 0.35	
Urine protein						
Absent	134	5.65 ± 1.15	0.51	134	1.15 ± 0.45	<0.01
Present	32	5.80 ± 1.35		32	0.95 ± 0.30	
older-onset (no insulin)						
Sex						
Women	89	5.80 ± 1.30	0.17	89	1.15 ± 0.35	0.06
Men	73	5.50 ± 1.15		73	1.05 ± 0.40	
Duration (yr)						
5–9	82	5.60 ± 1.25		82	1.05 ± 0.40	
10–14	45	5.60 ± 1.35	0.80	45	1.15 ± 0.35	0.53
≥15	35	5.70 ± 1.10		35	1.15 ± 0.35	

Table 1—*Continued*

	Total cholesterol (mM)			HDL cholesterol (mM)		
	N	Mean ± SD	*P*	*N*	Mean ± SD	*P*
Diastolic blood pressure (mmHg)						
≤67	40	5.20 ± 1.35		40	1.15 ± 0.40	
68–76	40	5.60 ± 1.00	<0.005	40	1.10 ± 0.40	0.99
77–84	42	5.70 ± 1.20		42	0.95 ± 0.25	
≥85	38	6.00 ± 1.30		38	1.20 ± 0.45	
Body mass (kg/m^2)						
≤25.0	34	5.35 ± 1.25		34	1.25 ± 0.40	
25.1–28.3	34	6.05 ± 1.35	0.64	34	1.05 ± 0.30	<0.05
28.4–32.9	35	5.85 ± 1.25		35	1.05 ± 0.30	
≤33.0	35	5.60 ± 1.10		35	1.05 ± 0.45	
C-peptide (nM)						
≤0.29	4	5.80 ± 1.55		4	1.45 ± 0.40	
0.30–0.90	36	5.90 ± 1.20		36	1.25 ± 0.30	
0.91–1.29	41	5.85 ± 1.30	<0.0001	41	1.10 ± 0.30	<0.0001
1.30–1.88	40	5.70 ± 1.20		40	1.10 ± 0.50	
≥1.89	41	5.00 ± 1.10		41	0.95 ± 0.35	
Glycosylated hemoglobin (%)						
≤7.1	40	5.70 ± 1.40		40	1.30 ± 0.50	
7.2–8.0	44	5.80 ± 1.10	0.74	44	1.10 ± 0.30	<0.05
8.1–9.1	37	5.55 ± 1.20		37	1.00 ± 0.35	
≥9.2	40	5.55 ± 1.25		40	1.05 ± 0.30	
Creatinine (μM)						
≤0.8	41	5.80 ± 1.35		41	1.25 ± 0.50	
0.9–1.2	82	5.60 ± 1.30	<0.005	82	1.10 ± 0.35	<0.01
≥1.3	38	5.45 ± 1.05		38	1.00 ± 0.35	
Urine protein						
Absent	142	5.80 ± 1.25	0.25	142	1.10 ± 0.40	0.17
Present	9	5.25 ± 1.10		9	0.95 ± 0.30	

of a relationship between total cholesterol and the presence of both urinary protein and higher serum creatinine. Perhaps in this group there are independent effects. A relationship between cholesterol and antihypertensive medication cannot be evaluated because of the small number of users.

Although we found no relationship between cholesterol and body mass, the biological effects of body mass may be important in influencing the relationships of the other variables to the lipid levels (e.g., glycosylated hemoglobin and blood pressure).

Table 2 shows the distribution of subjects by the cholesterol guidelines of the National Cholesterol Education Program (18). The public health significance of the findings in our study suggests that if a positive effect of tighter glycemic control on chronic complications of diabetes is found and medical management is altered to try to achieve tighter control, then there may be added benefit in the reduction of serum cholesterol. We await the results of the Diabetes Control and Complications Trial (19) to shed light on these issues.

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Table 2—*Distribution of subjects by cholesterol levels according to National Cholesterol Education Program guidelines*

Cholesterol levels (mg/dL)	Younger-onset		Older-onset using insulin		Older-onset not using insulin	
	N	%	*N*	%	*N*	%
<5.15	162	53	64	35	60	37
5.15–6.15	89	29	65	35	50	31
6.20+	53	17	55	30	52	32

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