The Association of Corneal Arcus with Coronary Heart Disease and Cardiovascular Disease Mortality in the Lipid Research Clinics Mortality Follow-up Study

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Abstract: The relationship between corneal arcus (arcus senilis) and mortality from coronary heart disease (CHD) and cardiovascular disease (CVD) is examined in a prospective study of White men (n = 3,930) and women non-hormone users (n = 2,139), ages 30–69, followed for an average of 8.4 years as part of the Lipid Research Clinics Mortality Follow-up Study. After excluding those with clinically manifest CHD at baseline, corneal arcus was strongly associated with CHD and CVD mortality only in hyperlipidemic men ages 30–49 years, for whom the relative risk for CHD and CVD death was 3.7 and 4.0, respectively, after adjusting for age, total cholesterol, HDL cholesterol, and smoking status using a Cox proportional hazards model. Among 30–49 year old males, corneal arcus appears to be a prognostic factor for CHD, independent of its association with hyperlipidemia in this age-group, of about the same magnitude as other common risk factors, underscoring the usefulness of corneal arcus as a prognostic factor to the practicing clinician. (*Am J Public Health* 1990; 80:1200–1204.)

Introduction

Corneal arcus is an extracellular lipid infiltration of the peripheral cornea. It appears as a yellowish-white ring around the cornea, and is separated from the limbus by a 0.3 to 1 mm lucid zone.[1–4] These deposits consist mainly of cholesterol, cholesterol esters, phospholipids, and triglycerides.[1,5] Corneal arcus has been described in children,[3,6] but it is more prevalent among older people and therefore has been often called arcus senilis.[1–6] It occurs more often among Blacks than Whites[4,6,7] and tends to appear earlier in life in Blacks than in Whites.[1–4,6,7]

Rifkind and Dickerson[8] found an association of corneal arcus with coronary heart disease (CHD), and pointed out that its characteristics are similar to those of atherosclerotic lesions: both accumulate in relatively avascular tissues, both increase with age, and are more frequent among males. Data from the Western Collaborative Group Study indicated an association of corneal arcus with the incidence of coronary heart disease in men below age 50.[9] Moreover, it has been found to be related to risk factors of CHD such as hyperlipidemia and to occur more often among patients with familial dyslipoproteinemias.[1–5,6–18] However, data from several studies showed no independent relationship between corneal arcus and CHD and suggested that both were related to elevated serum cholesterol levels.[7,8,12,15,17]

Segal, *et al*,[18] examined the data from the Lipid Research Clinics (LRC) Prevalence Study, which is a major source of information on the occurrence of hyperlipidemia in North America, and found an independent relationship between corneal arcus and the prevalence of CHD. We here report on the relation between corneal arcus diagnosed in White participants of the LRC Prevalence Study based on the mortality from CHD and CVD during a mean follow-up of 8.4 years.

Methods

The methods of the Lipid Research Clinics Prevalence Study and of the Lipid Research Clinics Mortality Follow-up Study have been described in detail elsewhere.[19,20] In summary, the following points are relevant for the present analysis.

Prevalence Study

The Prevalence Study was conducted in the period 1972–76 in 10 Lipid Research Clinics in the United States and Canada. In the first survey (Visit 1), 60,502 individuals (out of 81,926 eligibles) representing a wide ethnic, geographic, socioeconomic, and age variation had their plasma levels of cholesterol and triglycerides determined. A 15 percent random sample of all Visit 1 participants, plus all those with high plasma cholesterol or triglyceride levels or who were taking lipid-lowering medications, plus varying (by clinic) proportions of those with borderline elevation in cholesterol or triglyceride, were invited for a more extensive examination (Visit 2). See Appendix for the definition of "high" and "borderline elevated." Overall, 85 percent of the 12,595 persons eligible for Visit 2 were actually examined. The data used in this analysis, except for a Visit 1 hyperlipidemia variable, were obtained at Visit 2.

Follow-up Mortality Study

All men and women who were at least 30 years old at Visit 2 had their vital status determined annually from 1977 through 1983. Mean follow-up was 8.4 years, with a range of 5.7 to 9.9 years. In case of death, cause was classified as coronary heart disease (CHD), cardiovascular disease (CVD), or due to other causes, using standard criteria.[20] For deaths suspected of being caused by CVD, the cases were reviewed by a panel of cardiologists. They analyzed the death certificate and information obtained from the next-of-kin and from hospitalization records if the person was hospitalized within 30 days prior to death, or from the personal physician if there had been no hospitalization within 30 days prior to

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death. Vital status is known for over 99.6 percent of the participants.

Exclusions

Excluded from all CVD analysis were participants with possible or definite CHD at baseline, according to the presence of one of the following: angina pectoris diagnosed by the Rose Questionnaire[21] or during the treadmill test; use of angina medications, antiarrhythmics, digitalis or propranolol; exclusion from the treadmill test because of congestive heart failure, R-on-T type premature ventricular contraction, ventricular tachycardia, parasystolic focus, atrial flutter or atrial fibrillation; or resting ECG evidence of diagnostic or equivocal myocardial infarction.[22] Female users of estrogens or progestogens were excluded because of the small number who had corneal arcus. Black participants were excluded because of small numbers. Individuals invited to Visit 2 because of borderline hyperlipidemia were also excluded for statistical reasons, as explained below, as were individuals invited solely because of use of lipid-lowering medication. Finally, those with nonfasting (<12 hours) or missing lipid values and pregnant women were excluded from the analysis.

Corneal Arcus Diagnosis

The interviewers were trained to identify corneal arcus in the Visit 2 using a uniform protocol.[23,24] They stood in front of the participants so that their eyes were at the same level during the examination, which was usually done in natural (rather than artificial) light, the source of which was tangential to the eye. The upper and lower poles of the eyes were examined. Interviewers were directed to look for a whitish fatty material at the periphery of the cornea. The corneoscleral junction had to be observable for a diagnosis of corneal arcus to be made. For these analyses only positive answers were regarded as indicative of corneal arcus and an "uncertain" response was considered as negative.

Laboratory Methods

A detailed description of the laboratory processing procedures is provided in the LRC Program Laboratory Methods Manual[25] and reviewed elsewhere.[26]

Statistical Methods

Visit 2 sample data are analyzed to draw inferences about a population like that of Visit 1. In order to account in analysis for the sampling scheme, the data are treated as a stratified random sample, with two strata: hyperlipidemics, all of whom were invited to Visit 2, and normolipidemics (including borderline hyperlipidemics), 15 percent of whom were invited to Visit 2. For simplification, the oversampling of borderline hyperlipidemics and of users of lipid-lowering medication were excluded. It should be emphasized that borderline hyperlipidemics were not in general excluded, but only the oversampling invited to Visit 2. Because of the higher proportion of hyperlipidemics in the sample relative to the population, weighting techniques were used in the estimation of overall population parameters.

CHD and CVD mortality rates (deaths per 1,000 person-years of follow-up) were calculated for corneal arcus cases and non-cases, for each age/sex group, by lipid strata and weighted across lipid strata. Confidence intervals or tests of statistical significance are not given for these descriptive statistics, but rather are reserved for the models' fit. Age groups are 30–49 and 50–69. Similar mortality rates were also calculated with respect to other possible prognostic factors besides corneal arcus. These factors are given below, along with cutpoints which define the categories (greater than or equal to versus less than cutpoint) for which mortality rates were calculated:

- Serum cholesterol level (240 mg/dl).
- Fasting serum triglyceride level (250 mg/dl).
- Low density lipoprotein (LDL) cholesterol level (160 mg/dl).
- High density lipoprotein (HDL) cholesterol level (40 mg/dl).
- Body mass index (BMI) (30 kg/m^2).
- Smoking status (current versus ex- or nonsmoker).
- Family history of coronary heart disease (either at least one parent died of CHD or experienced angina before the age of 60 or at least one sibling died of CHD before the age of 60).
- Graded exercise test (positive ECG showed a significant ST elevation or depression or a significant change in the ST integral value—for details see Gordon, *et al*[27]).
- Ischemia on resting ECG excluding myocardial infarction (either evidence of left ventricular hypertrophy or other significant ischemia; Minnesota codes 3.1-3.3 with 4.1-4.3 or 1-3-1 through 1-3-6, or 2.1, 4.1, 4.2, 5.1, 5.2, 6.1, 8.1, or 8.2).

In considering the effects of possible confounding variables on the relation in males aged 30–49 between corneal arcus and CHD and CVD mortality, survival models were fit, by lipid sampling stratum, using Cox proportional hazards models. In addition to arcus status, survival status and baseline age, the following baseline variables were considered: continuous [total cholesterol, LDL cholesterol, HDL cholesterol, alcohol consumption (g/day), body mass index (kg/m^2), systolic blood pressure, triglyceride]; dichotomous [family history of CHD (yes = 1, no = 0), smoking (yes = 1, no = 0)]. These variables were added one at a time to the "basic" model, with survival status the dependent variable and corneal arcus and age independent variables, and discarded if the corneal arcus survival association was not changed by their inclusion.

Results

For men free of coronary heart disease at baseline, stratified by two age groups and by lipid sampling strata, the prevalence of corneal arcus, the total follow-up time, the mortality rates from CHD and the relative risk are presented in Table 1. In addition, results are given for the two sampling strata combined, with the stratum-specific results weighted to yield estimates of mortality rates for the Visit 1 population. A high relative risk of CHD mortality was associated with the diagnosis of corneal arcus among hyperlipidemic men under 50 years of age but not among older men. Table 2 shows the same trend when mortality from CVD is considered instead of CHD.

In female non-hormone users, the low prevalence of corneal arcus and the small number of CHD and CVD events preclude any kind of analysis in the younger age group; in the older group, where its prevalence and the number of events increase, the same lack of predictive value for CHD and CVD mortality is observed as in the older men (data available on request to authors).

The proportional hazards models of time to CHD or CVD death (Table 3) show that corneal arcus is an independent prognostic factor for mortality from CHD or CVD in men ages 30–49 years in the hyperlipidemic sampling stratum; for normolipidemic younger men its presence does not appear

TABLE 1—Estimated CHD Mortality Rates (deaths per 1000 person-years of follow-up) by Age Group and Corneal Arcus Status, Excluding Those with Prior Manifestations of CHD: Males

Age (years)	Sampling Stratum	Corneal Arcus Status	N	Number CHD Deaths	Total Follow-up Time (person-years)	Estimated CHD Mortality Rate	Estimated Relative Risk
30–49	Hyperlipidemic	No	1315	10	11237.6	0.89	6.7
		Yes	85	4	675.1	5.93	
	Normolipidemic	No	1202	8	10339.5	0.77	3.4
		Yes	46	1	377	2.65	
	Total*	No	2517	18	21577.1	0.79	4.7
		Yes	131	5	1052.6	3.74	
50–69	Hyperlipidemic	No	311	13	2504.2	5.19	0.0
		Yes	68	0	583.1	0.00	
	Normolipidemic	No	597	18	5031.9	3.58	0.9
		Yes	115	3	947.5	3.17	
	Total*	No	908	31	7536.16	3.64	0.8
		Yes	183	3	1530.6	2.99	

*Mortality rates weighted across sampling strata.

TABLE 2—Estimated CVD Mortality Rates (deaths per 1000 person-years of follow-up) by Age Group and Corneal Arcus Status, Excluding Those with Prior Manifestations of CHD: Males

Age (years)	Sampling Stratum	Corneal Arcus Status	N	Number CHD Deaths	Total Follow-up Time (person-years)	Estimated CHD Mortality Rate	Estimated Relative Risk
30–49	Hyperlipidemic	No	1315	13	11237.6	1.16	6.4
		Yes	85	5	675.1	7.41	
	Normolipidemic	No	1202	14	10339.5	1.35	2.0
		Yes	46	1	377	2.65	
	Total*	No	2517	27	21577.1	1.32	3.2
		Yes	131	6	1052.1	4.23	
50–69	Hyperlipidemic	No	311	22	2504.2	8.79	0.0
		Yes	68	0	583.1	0.00	
	Normolipidemic	No	597	26	5031.9	5.17	1.0
		Yes	115	5	947.5	5.28	
	Total*	No	908	48	7536.2	5.31	0.9
		Yes	183	5	1530.6	4.98	

*Mortality rates weighted across sampling strata.

TABLE 3—Estimated CHD and CVD Hazard Ratio, Comparing Subjects with Corneal Arcus to Those Without; Adjusted for Age, Total Cholesterol, HDL-C, and Smoking*, Men Aged 30–49 Years

Lipid Stratum	CHD Hazard Ratio	(95 Percent Confidence Interval)	CVD Hazard Ratio	(95 Percent Confidence Interval)
Hyperlipidemic	3.7	(0.9,14.7)	4.0	(1.2,12.9)
Normolipidemic	2.2	(0.3,20.1)	1.3	(0.2,10.4)

*LDL-cholesterol, alcohol consumption, BMI, systolic blood pressure, and triglyceride were also considered, but had no effect on the C.A./survival association, so were discarded.

to be of the same importance. The covariates included are age and those whose inclusion in the model substantially modified the estimates of relative hazard of CHD or CVD mortality as related to corneal arcus. These covariates are total cholesterol, HDL-cholesterol, and smoking. With or without these additional covariates the relative hazards are similar for normolipidemics, but for hyperlipidemics the relative hazards adjusted for age alone are about 1.6 times those for models presented in Table 3.

The relative risk of the diagnosis of corneal arcus in the 30–49 year old male group is compared in Table 4 to that of other possible risk factors. As can be seen there, corneal arcus appears to be at least as statistically strong a prognostic factor for CHD as obesity, hypo-HDL, ischemia on resting ECG, hypertriglyceridemia and family history of CHD, and not very different in magnitude from the relative risk from smoking habit, hypertension, hyper-LDL, and hypercholesterolemia. Details concerning this relation are given in Segal, *et al.*[18]

Discussion

In men under 50 years of age, corneal arcus has been shown in a prospective study to be a predictor of CHD

TABLE 4—Estimated Mortality Rates (per 1000 person-years) and Relative Risks of Death from CHD in Asymptomatic Men Aged 30–49 Years, by CHD Risk Factor Status

		Hyperlipidemic Stratum		Normolipidemic Stratum		Population Estimates*	
Risk Factor	Status	Death Rate	Relative Risk	Death Rate	Relative Risk	Death Rate	Relative Risk
Corneal Arcus	Yes	5.93	6.66†	2.65	3.44	3.74	4.73
	No	0.89		0.77		0.79	
Current Smoker	Yes	2.00	4.26††	1.72	5.73††	1.78	5.56††
	No	0.47		0.30		0.32	
Quetelet Index	≥30	1.27	1.55	0.96	—	1.00	3.57
	<30	0.82		—		0.28	
Hypertensive	Yes	1.96	2.33	2.68	7.66††	2.48	5.90††
	No	0.84		0.35		0.42	
LDL-C Level	≥160	1.84	3.61††	3.33	9.79††	2.39	6.83††
	<160	0.51		0.34		0.35	
HDL-C Level	<40	1.76	2.71†	1.66	3.95†	1.68	3.73††
	≥40	0.65		0.42		0.45	
Ischemia on Exercise ECG	Present	9.79	9.79	10.00	14.29	9.94	13.25
	Absent	1.00		0.70		0.75	
Ischemia on Resting ECG	Present	7.64	7.64	2.15	2.56	2.70	3.14
	Absent	1.00		0.84		0.86	
Cholesterol Level	≥240	2.19	—	5.21	12.71††	2.59	6.64
	<240	—		0.41		0.39	
Triglyceride Level	≥250	1.73	1.94	2.37	3.04	1.78	2.25
	<250	0.89		0.78		0.79	
Family History of CHD	Present	2.17	2.44	0.96	1.17	1.21	1.46
	Absent	0.89		0.82		0.83	

*Weighted across sampling strata.
†$0.05 < p < 0.10$, two-sided test.
††$0.01 < p < 0.05$, two-sided test.

mortality, independent of presence of hyperlipidemia, and a stronger predictor for hyperlipidemics. Above the age of 50 its diagnosis does not appear to be positively related to the subsequent manifestation of a fatal CHD event. These findings help to clarify previous discussion about this relation,[7,28] confirming the observations made in retrospective,[8,29] cross-sectional,[18,30] and prospective studies.[9] They are in agreement with the interpretation that corneal arcus and coronary atherosclerosis share common determinants in young men, while local factors are more important for its occurrence in older persons.[8,12]

The findings in women confirm the low prevalence of corneal arcus in the young age group,[30,31] which with the low mortality rates rules out the possibility of drawing conclusions about its relation to CHD and CVD mortality. In the older group, where the prevalence of corneal arcus and the mortality rate increase, there is the same lack of relation observed in older men.

The ability to detect patients at high risk of CHD has been of continuous concern, considering the frequent presentation of the disease as sudden death[32] and its devastating consequences, especially in the families of young men. The magnitude of the corneal arcus risk in this age group compared to other usual screening tests (Table 4) highlights the utility of this simple and inexpensive tool as a prognostic factor and reinforces the importance of its diagnosis during the physical examination. This is noteworthy, considering that it had lower prevalence in the baseline of this population-based cohort than in some studies which used hospitalized or referred patients. The fact that, in this study, corneal arcus was detected only by a single examination, without the use of slit lamp, could have resulted in some misclassification.[17] However, such misclassification would be independent of either lipid status or later CHD mortality, so would only bias our results toward the null, that is, toward finding no association between it and CHD mortality. The association between corneal arcus and hyperlipidemia *alone* would suggest evaluation of the lipid profile of young men with corneal arcus. The findings in this paper indicate that it also may be prudent to suggest that all young patients with corneal arcus should undergo a detailed evaluation of their other CVD risk factors.

APPENDIX
Age-Specific Cutpoints Used for Selecting Participants for Visit 2

	Cholesterol (mg/dl)*		Triglyceride (mg/dl)**	
Age Group	Borderline Cutpoint	Elevated Cutpoint	Borderline Cutpoint	Elevated Cutpoint
30–39	220	240	150	250
40–49	225	260	150	300
50–59	245	280	150	300
60+	245	280	150	300

*Conversion factor to SI Units (mmol/L): 0.02586
**Conversion factor to SI Units (mmol/L): 0.1129

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