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Relation of Corneal Arcus to Cardiovascular Disease (From the Framingham Heart Study Data Set)

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Abstract

Corneal arcus is a lipid-rich deposit at the corneoscleral limbus that shares some similarities with the lipid deposition of atherosclerosis. Epidemiologic studies examining the association between corneal arcus and coronary heart disease (CHD) have yielded mixed results. This study was conducted to determine if corneal arcus is an independent risk factor for cardiovascular disease (CVD) and coronary heart disease (CHD). We performed a prospective analysis using Cox-proportional hazards regression models in the Framingham Heart Study Original Cohort and Offspring database. This cohort included 23,376 person-exams, 3,890 (17%) of whom were identified as having corneal arcus during their physical exam. Corneal arcus was a predictor of both CVD and CHD at 4 years [hazard ratio (HR) = 2.28 and 1.99, respectively] and 8 years of follow-up (HR = 2.52 and 2.35, $p < 0.0001$ for all). Corneal arcus was no longer predictive of either CVD or CHD, however, after adjustment for age and sex at 4 years [hazard ratio (HR) = 1.07 and 1.01, respectively] and 8 years of follow-up (HR = 1.18 and 1.17, $p > 0.05$ for all). In conclusion, corneal arcus predicts CVD and CHD in the community-based Framingham Heart Study cohort due to the strong association of corneal arcus with increasing age. To date, this is the largest and lengthiest population-based cohort study examining the direct association between corneal arcus and CVD and CHD.

Keywords

Corneal arcus; atherosclerosis; coronary heart disease; hypercholesterolemia

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From the Framingham Heart Study of the National Heart Lung and Blood Institute of the National Institutes of Health and Boston University School of Medicine.

Introduction

Corneal arcus is a recognized sign of hyperlipidemia when observed in individuals younger than 50 years old.^{1–4} It consists of lipid deposition near the corneoscleral limbus but separated from the limbus by a lipid-free zone called the lucid interval of Vogt. Arcus formation usually begins on the superior and inferior poles of the cornea and often progresses to form a complete ring without visual impairment.⁵ Its formation, although not fully understood, shares some similarities with the atherosclerotic process.⁶ Corneal arcus was first suggested as a cardiac risk factor by Virchow in 1852,⁷ and has been supported by several,^{8–15} but not all^{3, 16, 17} subsequent studies. Most of these investigations have been limited in sample size and length of follow-up. The availability of corneal arcus determinations during serial examinations and prospective follow-up for cardiovascular disease (CVD) events afforded the opportunity in the current study to examine the relationship between corneal arcus and cardiac events in the Framingham Heart Study population.

Methods

The Framingham study was initiated in 1948 as a prospective study of the incidence of clinical coronary heart disease (CHD) in men aged 30 to 60. An initial cohort of 5,209 participants (Original Cohort) was examined in an initial visit and reexamined every two years by the Framingham Heart Study staff. The offspring of the Original Cohort (Offspring Cohort), consisting of 5,124 participants, were examined every 4 years (except for an 8 year gap between the 1st and 2nd examination). Initial data included clinical, biochemical and behavioral variables whose methodology has been reported.^{18–21} Corneal arcus was determined by visual inspection of the cornea during exam cycles 11, 13, 15, 17, 19 of the original Cohort and exam cycles 2, 3, 4, 5 and 6 of the Offspring cohort. In the first 8 examinations of the Original Cohort, only the presence or absence of arcus was recorded. Starting with exam 9 for the Cohort and for all Offspring exams, arcus was graded as none, slight, moderate or marked based on its circumferential extension.

For these analyses, the primary outcomes of interest were CHD and CVD events. CHD included recognized myocardial infarction, stable and unstable angina pectoris, and CHD death. CVD events included any CHD event, stroke, transient ischemic attack, intermittent claudication, congestive heart failure, or CVD death. A panel of 3 physicians reviewed each CHD and CVD event and adjudicated the end point according to pre-established criteria.²² Surveillance for CVD consisted of regular examinations at the Framingham Heart Study clinic and review of medical records from physician office visits and hospitalizations for heart and cerebrovascular disease.

This research was conducted under a standing Institutional Review Board approval for the Framingham Heart Study by Boston University School of Medicine. Participants had previously provided written informed consent for the use of their collected data in scientific studies.

All measurements from the exams mentioned above were incorporated into the analysis by the method of pooling of repeated observations.²³ The pooled sample was employed to assess short-term prediction of CHD and CVD events at 4 and 8 years. A total of 31,526 Cohort and Offspring person-exams were seen at these 10 examinations. We excluded 4,425 person-exams for prevalent CVD, 250 person-exams with no follow-up, 1,134 person-exams with missing arcus data, and 2,341 person-exams with missing covariate data, leaving a total of 23,376 eligible for the analysis of 4 year prediction. For the analysis of 8 year prediction, we included exams 11, 15, and 19 for the original Cohort and exams 2, 4, and 6 for the Offspring cohort. Therefore, there were 13,469 person-exams eligible for the 8 year prediction analysis.

We performed a prospective analysis with Cox-proportional hazards regression models to assess the relationship of arcus with CVD and CHD. We initially evaluated the relationship of corneal arcus with CVD and CHD in unadjusted models. After this initial assessment, we also considered age- and sex- and multivariable-adjusted Cox-proportional hazard models. The multivariable models included the following covariates: age, sex, total cholesterol, high-density lipoprotein cholesterol (HDL-C), systolic blood pressure, hypertension treatment, diabetes, smoking and body mass index. All analyses were performed using SAS version 9.1.²⁴ A 2-sided p-value <0.05 was considered statistically significant.

Results

Characteristics of the baseline exam for each cohort are shown in Table 1. In the Cohort group, baseline mean values for age (64 years), systolic blood pressure (138 mm Hg), total cholesterol (232 mg/dL) and corneal arcus prevalence (28%) were higher than in the Offspring group. The Offspring cohort had a larger percentage of males (47%) and current smokers (35%).

Corneal arcus at both 4 and 8 years was significantly related to CVD (Table 2) and CHD events (Table 3). The hazard ratio [HR] for CVD was 2.28 and for CHD 1.99 at year 4, respectively, and 2.52 and 2.35 at year 8, respectively, $p < 0.0001$ for all. These relationships of corneal arcus to CVD and CHD events were no longer statistically significant and the HRs were substantially attenuated after adjusting for age and sex (HR = 1.07 and 1.01 at 4 years, respectively, and 1.18 and 1.17 at 8 years, respectively, $p > 0.05$ for all). After further multivariable-adjustment, the HRs were not significantly different for CVD or CHD, and the associations remained non-significant. (Results shown in Tables 2 and 3)

Discussion

The results of the present study do not demonstrate that corneal arcus is an independent risk predictor for CVD and CHD. When analyzed by crude hazard ratios, corneal arcus does predict CVD and CHD risk, but this value depends on the association of arcus with age.

The borderline p-value and confidence intervals on the adjusted model of CVD risk prediction at 8 years might represent a trend towards statistical significance. Although a larger sample population might have impacted this number towards a positive result, the hazard ratio point estimate is small and clearly not significant.

This result is consistent with results from Klein et al in the Evans County Cardiovascular Study. These investigators used data from 2,530 Caucasian patients of both genders and observed a higher 7-year incidence of CHD in white men with corneal arcus than in men without arcus. However, after adjusting the incidence rate for age, corneal arcus was no longer predictive of CHD events in any ethnic group or gender.²⁵

Our results, however, are at variance with results from both the Western Collaborative Group Study,¹⁵ and the Lipid Research Clinic Mortality Follow-up Study⁹ where arcus predicted CHD independent of age. Rosenman et al,¹⁵ in a retrospective analysis of the Western Collaborative Group Study reported that the incidence of myocardial infarction was increased in subjects with corneal arcus, but only in young men aged 39 to 49. The average annual incidence of symptomatic myocardial infarction in this age group was 6.8 per 1000 subjects with, versus 3.2 per 1000 without, corneal arcus $p < 0.001$. The odds ratio of the association for CHD between subjects aged 39–49 years with and without corneal arcus was 1.57 after adjusting for age, serum cholesterol and smoking. Chambless et al,⁹ using The Lipid Research Clinics Mortality Follow-up Study data concluded that corneal arcus was a predictor of CHD, independent of total cholesterol, serum HDL-C and smoking, among hyperlipidemic men aged 30 to 49 years (estimated relative risk of 6.7). For normolipidemic men in the same age group,

the presence of corneal arcus did not appear to have the same strength of association (estimated relative risk 3.4). Such results suggested that arcus may be independent of lipid levels in its ability to predict CHD.

Several factors may have contributed to our inability to relate corneal arcus to CVD and CHD risk. Corneal arcus in the present study was determined by visual inspection alone, and it is not clear how often visual inspection was aided by illumination. Visual inspection without ancillary illumination may under-diagnose arcus and a slit-lamp examination yields a more precise characterization of arcus location and extension.¹¹ Also, there was not apparent attempt made during the physical examination to differentiate true arcus from other confounding corneal opacities. This is readily understandable since corneal arcus was not a major emphasis of the Framingham Study and was not even included in all examinations.

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Table 1

Baseline participant characteristics

Characteristic	Baseline Exam Cohort (n=2400)	Baseline Exam Offspring (n=4271)
Age (years)	64 (8)	45 (10)
Male	39 %	47 %
Body mass index (Kg/m ²)	26 (4)	26 (5)
Systolic Blood Pressure (mm Hg)	138 (20)	122 (17)
Total Cholesterol (mg/dL)	232 (42)	204 (40)
High-density lipoprotein-cholesterol (mg/dL)	53 (16)	49 (14)
Low-density lipoprotein cholesterol (mg/dL) [†]	154 (39)	133 (36)
Triglycerides (mg/dL) [‡]	115 (54)	109 (94)
Hypertension Therapy	22 %	10 %
Current Smoker	27 %	35 %
Diabetes	6 %	3 %
Arcus	28 %	6 %
Arcus Category		
None	72 %	94 %
Slight	17 %	4 %
Moderate	8 %	1 %
Marked	3 %	1 %

* Values are expressed as mean (standard deviation) except where noted.

[†] Baseline low-density lipoprotein cholesterol data were missing in 1552 and 56 participants of the Original Cohort and Offspring Cohort respectively.

[‡] Baseline triglycerides data were missing in 1550 and 1 participant of the Original Cohort and Offspring Cohort respectively.

Table 2

Association of corneal arcus with incidence of a first cardiovascular disease event, 4-year and 8-year prediction

	4-year prediction		8-year prediction	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Arcus, Yes vs. No				
Unadjusted	2.28 (2.02–2.57)	<0.0001	2.52 (2.15–2.95)	<0.0001
Age- and Sex-adjusted	1.07 (0.95–1.22)	0.27	1.18 (0.99–1.39)	0.06
Multivariable adjusted	1.04 (0.92–1.18)	0.54	1.14 (0.96–1.35)	0.13

Table 3

Association of corneal arcus with incidence of a first coronary heart disease event, 4-year and 8-year prediction

	4-year prediction		8-year prediction	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Arcus, Yes vs. No				
Unadjusted	1.99 (1.70–2.33)	<0.0001	2.35 (1.91–2.89)	<0.0001
Age- and Sex-adjusted	1.01 (0.85–1.20)	0.88	1.17 (0.94–1.47)	0.16
Multivariable adjusted	0.99 (0.83–1.17)	0.89	1.14 (0.92–1.43)	0.24