Cardiovascular Topics

Serum lipid parameters and the prevalence of corneal arcus in a dyslipidaemic patient population

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Summary

Aim: **To determine whether an association exists between plasma lipoprotein constituents and the prevalence of corneal arcus in dyslipidaemic patients.**

Methods: **Adult patients (n = 115) were included if their fasting total serum cholesterol concentrations exceeded the 95th percentile or their serum low-density lipoprotein (LDL) : high density lipoprotein (HDL) ratios exceeded 5. Slit-lamp assessment of the corneas was performed.**

Results: **The study group divided into a subgroup with arcus 37% (43) and a subgroup without arcus 63% (72). Total serum cholesterol and triglyceride levels were not associated with corneal arcus. A significant difference was found ($p < 0.05$) between the mean levels of LDL cholesterol (LDL-C) in the group without arcus (5.61 ± 1.74 mmol/l) and the group with arcus (5.96 ±1.71 mmol/l). The mean serum HDL-cholesterol (HDL-C) in the group with corneal arcus was 1.04 ± 0.30 mmol/l as opposed to 1.31 ± 0.38 mmol/l in the group without arcus ($p < 0.005$ for difference). The mean LDL-C : HDL-C ratio in the group without arcus was 4.28 (SD: 1.99), and 5.73 (SD: 2.09) in the group with a corneal arcus ($p < 0.05$).**

Conclusions: **Low HDL-C levels, high LDL-C levels and LDL-C : HDL-C ratios > 5 have been implicated as risk factors of numerous circulatory diseases. The observations in this study suggest that the presence of corneal arcus in the dyslipidaemic patient correlates strongly with these same risk indicators.**

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A corneal arcus is a harmless, gray-white circular deposition of cholesterol, triglycerides, phospholipids and a small amount of apolipoprotein B at the periphery of the cornea.[1,2] Although harmless with regard to vision, the appearance of an arcus at a young age may indicate dyslipidaemia.[3,4] The composition of a corneal arcus shows a strong resemblance to the composition of an arterial atherosclerotic lesion. Therefore, it has been suggested that the occurrence of an arcus is associated with the presence of atherosclerosis,[5,6] and may be prognostic for premature coronary heart disease (CHD).[7,8] Additionally, the existence of a corneal arcus before the age of 60 is related to an enhanced thickness of the intima–media in the carotid arteries of males with hypercholesterolaemia.[9] It has been proposed that a prominent arcus should be an indication for lipid screening, and in many cases may indicate the presence of familial hypercholesterolaemia.[10-12] However, it is as yet unclear exactly which component or components of the lipogram correlate with the arcus phenomenon in dyslipidaemic patients.

The aim of this study was therefore to determine whether any associations exist between the different plasma lipoprotein constituents and the prevalence of arcus cornealis in dyslipidaemic subjects.

Methods

Patient study group

The clinical history, height, weight, blood pressure and serum lipid profile were recorded in a group of 115 patients with proven dyslipidaemia presenting to the Lipid Clinic at the Tygerberg Academic Hospital, Cape Town, South Africa. Consent was obtained from the institutional Ethics Committee before the study commenced.

A slit-lamp examination was also performed on each patient by an ophthalmologist. In order to obtain a study group with maximum homogeneity, only patients meeting

the following criteria were enrolled: adults of both genders, 18–60 years of age with a serum total cholesterol (TC) level > 5.2 mmol/l (i.e. > 95th percentile of the population) and a low-density lipoprotein cholesterol (LDL-C) : high-density lipoprotein cholesterol (HDL-C) ratio > 5. Excluded were pregnant or lactating females, or subjects with severe hypertension (diastolic blood pressure > 115 mm Hg), history of an acute coronary event within the last six months, diabetes mellitus (defined as fasting blood glucose > 7.8 mmol/l), hypothyroidism (thyroid stimulating hormone > 7.5 mU/l), any malignant tumour, significant renal impairment (serum creatinine > 170 μmol/l), history of pancreatitis, gallbladder disease including cholelithiasis, gastro-intestinal disease or patients who were known to be HIV positive.

All patients were treatment naïve and had not been on treatment with lipid-lowering medication prior to the lipograms. Fasting blood samples were obtained from each individual on three occasions over a period of four weeks. Subjects were only included in the study if their lipid parameters adhered to the inclusion criteria on each of the three visits.

Analytical methods

Triglyceride, TC and HDL-C levels were determined using a Hitachi 911 automatic analyzer (Boehringer Mannheim BV, Almere). LDL cholesterol was calculated using the Friedewald formula.

Statistical methods

Descriptive statistics including the mean, median and range were given for each independent and dependent variable. Student's *t*-test was used to assess the differences between the continuous variables; chi-square tests to asses the difference between the categorical variables in the two groups, i.e. those with corneal arcus and those without corneal arcus.

Results

The study group consisted of 115 subjects, 82% Caucasian (94/115) and 18% (21/115) of mixed-race descent. The mean age was 49.1 years (SD = 10.2) with 64% (74) male and 36% (41) female. The mean values of five components of the serum lipogram, for the group as a whole, are depicted in Fig. 1. The mean TC, triglyceride and LDL-C levels exceeded the 95th percentile, whereas the mean serum HDL-C was lower than the 95th percentile of the population, confirming the dyslipidaemic profile of the group.

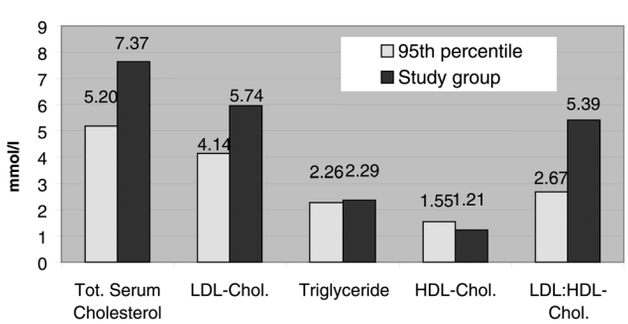

Fig. 1. Serum lipid parameters of the study group (*n* = 115) compared to the upper 95th percentile (mmol/l) demonstrating the dyslipidaemic nature of the group as a whole.

The study group was divided into two cohorts, i.e. a subgroup with corneal arcus 37% (43) and a subgroup without arcus 63% (72) (Fig. 2). Comparison of the two subgroups (Table I) showed no differences in the mean age, gender distribution, body mass index (BMI), and systolic and diastolic blood pressures between the two subgroups. A positive family history of hypercholesterolaemia and cardiovascular disease was significantly more prevalent in the subgroup with arcus.

Analysis of the serum lipograms of the two groups revealed no differences in the serum TC or serum triglyceride levels. The LDL-C and HDL-C levels of the two subgroups differed however. The mean HDL-C level of the

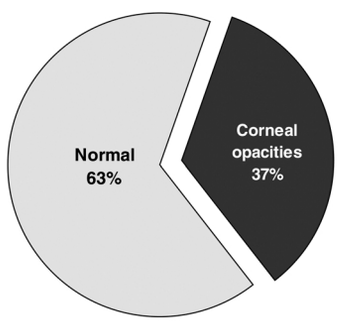

Fig. 2. The prevalence of corneal opacities divided the study group into two cohorts, i.e. those with no arcus (63%) and those with corneal arcus (37%).

TABLE I. COMPARISON OF DEMOGRAPHICS, CARDIOVASCULAR RISK FACTORS AND SERUM LIPID PARAMETERS BETWEEN THE SUBGROUP WITH NORMAL CORNEAS (63%) AND THE SUBGROUP WITH ARCUS (37%)

Variable	*No Arcus (*n = *72)*	*Arcus (*n = *43)*	*Significance*
Demographics			
Age (years)	48.5 ± 10.9	50.1 ± 14.8	
Gender (% females)	22	24	
Clinical parameters			
BMI (kg/m^2)	26.39	26.14	
Diastolic BP (mm Hg)	85 ± 13	83 ± 11	
Systolic BP (mm Hg)	124 ± 22	121 ± 17	
Family history			
Hypercholesterolaemia (%)	51	64	$p < 0.05$
Cardiovascular disease (%)	48	56	$p < 0.05$
Clinical history			
Never smoked (%)	10	9	
Myocardial infarction (%)	18	22	
Angina pectoris (%)	23	26	
Serum lipid levels			
Total cholesterol (mmol/l)	7.36 ± 1.72	7.39 ± 2.10	$p < 0.05$
LDL cholesterol (mmol/l)	5.61 ± 1.74	5.96 ± 1.71	$p < 0.005$
HDL cholesterol (mmol/l)	1.31 ± 0.38	1.04 ± 0.30	
Triglycerides (mmol/l)	2.24 ± 1.53	2.37 ± 1.28	$p < 0.05$
LDL-C:HDL-C ratio	4.28 (SD: 1.99)	5.73 (SD: 2.09)	

subgroup without arcus was 1.31 ± 0.38 mmol/l, whereas the mean HDL-C level of the subgroup with corneal arcus was 1.04 ± 0.30 mmol/l. This difference of 0.27 mmol/l was highly significant ($p < 0.005$). The mean LDL-C level in the subgroup without arcus was 5.61 ± 1.74 mmol/l, and in the subgroup with arcus 5.96 ± 1.71 mmol/l. This difference of 0.35 mmol/l was significant ($p < 0.05$). Furthermore, the mean LDL-C : HDL-C ratio in the subgroup without arcus was 4.28 (SD: 1.99) and in the subgroup with arcus, it was 5.73 (SD: 2.09). This difference of 1.45 was also significant ($p < 0.05$).

Discussion

The study group was meticulously selected in an effort to ensure a clinically homogeneous group of patients. It is important to note that patients were included only if abnormal lipid levels were their only risk factor for coronary artery disease. It is generally accepted that premature corneal arcus under the age of 50 years is an indicator of dyslipidaemia and not a risk factor for CHD. Previous studies have found correlations between arcus and age, and arcus and cholesterol levels, particularly the LDL-C concentration. Corneal arcus has not been described to be associated with diabetes, hypertension, obesity, triglycerides and HDL-C levels, but it does have a higher prevalence in males.

Low plasma levels of HCL-C are a strong independent predictor of CHD.[13,14] Evidence suggests that HDL-C has a direct beneficial effect on the arterial wall. Metabolically, HDL particles with their apoprotein A play a role in the removal of cholesterol from peripheral cells, including those in atherosclerotic plaques.[15] Apolipoprotein A-I (apoA-I), the major apoprotein in HDL, plays a role in the removal of cholesterol from macrophages, leading to the reduction of the cholesterol content of these cells in atherosclerosis. At least two specific receptors participate in mediating this protective effect. Intravenous infusion of HDL in rabbits has been shown to prevent atherosclerosis,[16] and the over-expression of the human apoA-I gene in mice stimulates the regression of pre-existing atherosclerosis.[17] HDL delivers cholesterol to the liver in a process referred to as 'reverse cholesterol transport'.[18] HDL also has other functions that may contribute to its ability to protect against CHD, including anti-inflammatory and antioxidant properties.[19] The composition of a corneal arcus shows a strong resemblance with the composition of an arterial atherosclerotic lesion. Therefore, it has been suggested that the occurrence of an arcus is associated with the presence of atherosclerosis.

Previous studies have shown that gender plays a significant role in the development of arcus. Females are less likely to develop arcus than men. This is also true for CHD and reduced HDL-C plasma levels. It has been reported that the occurrence of arcus in premenoposal women is rare.[20] The higher HDL-C levels in women are related to the endogenous oestrogen. These levels decline with age, as do HDL-C levels. Both subgroups contained comparable numbers of females and it is therefore unlikely that gender could have skewed the results.

Compared with Caucasians, blacks of both genders have been shown to have higher mean levels of HDL-C.[21] This would mean that any study that enrolls a large proportion of black patients would be skewed towards a higher mean level of HDL-C, and accordingly it would be difficult to demonstrate a relationship between HDL-C and the development of arcus in a group with a very diverse ethnic background. Our study group was predominantly of Caucasian stock with only 18% of mixed-race origin and no black persons. Hence it is unlikely that the results were skewed toward higher HDL-C levels due to race alone. Hoogerbrugge *et al*.[22] has also suggested a relationship between HDL-C and arcus in a study group made up of only 200 Caucasians, but with no other race groups included.

The incidence of arcus tends to increase with age in all race and gender groups. In fact Friedlander was of the opinion that the occurrence of corneal arcus approached 100% in people over 80 years of age.[23] Furthermore, it is accepted that mean HDL-C levels generally decline with age. The mean age of the subjects in our study group was 49 years, hence age is unlikely to be a contributory factor to the high prevalence of arcus in this study group. In addition, no age difference was demonstrated between the two subgroups in our study.

Conclusions

It is widely postulated that the corneal lesions found in corneal arcus strongly resemble the vessel wall changes found in atherosclerotic lesions. HDL-C protects the vessel wall against these changes. We suggest that the same protective effect is afforded by HDL-C in the corneal peripheral stroma in young dyslipidaemic patients. Conversely, the presence of corneal arcus in dyslipidaemic patients below 50 years of age is suggestive of low HDL cholesterol levels.

Low levels of HDL-C, high levels of LDL-C, and LDL-C : HDL-C ratios > 5 have often been implicated as risk factors in the development of numerous circulatory diseases. The observations in this study suggest that the presence of corneal arcus in the dyslipidaemic patient correlate strongly with these same risk indicators.

References

1. Sheraidah GAK, Winder AF, Fielder AR. Lipid-protein constituents of human arcus. *Atherosclerosis* 1998; **40:** 91–98.
2. Winder AF. Factors influencing the variable expression of xanthelasmata and corneal arcus in familial hypercholesterolemia. *Genet Eye Dis Birth Defects* 1982; **18:** 449–462.
3. Segal P, Insull W, Chambless LE, Stintett S, La Rosa JC, Weissfeld L. The association of dyslipoproteinemia with corneal arcus and xanthelasmata. *Circulation* 1986; **I**: 108–118.
4. Hoeg JM. Familial hypercholesterolemia. What the zebra can teach us about the horse. *J Am Med Assoc* 1994; **271:** 543–546.
5. Rifkind BM, Dickerson C. The incidence corneal arcus in ischemic heart disease, it relation to serum lipid levels. *Lancet* 1965; **I:** 312–314.
6. Rosenman RH, Brand RJ, Scholtz RI, Jenkins CD. Relation of corneal arcus to cardiovascular risk factors and the incidence of coronary disease. *N Engl J Med* 1974; **291:** 1322–1324.
7. Chambless LE, Fuchs FD, Linn S, Kritchevsky SB, Larosa JC, Segal PO. The association of corneal arcus with coronary disease and cardiovascular mortality in the lipid research clinics mortality follow-up study. *Am J Public Health* 1990; **80:** 1200–1204.

8. Klein B, Klein R, Haseman J, Maready J, Hames C. Corneal arcus and cardiovascular disease in Evans County, Georgia. *Arch Intern Med* 1975; **135:** 509–511.
9. Rouhiainen P, Salonen R, Rouhiainen H, Salonen JT. Association of corneal arcus with ultrasonographically assessed arterial wall thickness and serum lipids. *Cornea* 1993; **12:** 142–145.
10. Corneal arcus [editorial]. *Lancet* 1984; **I:** 376.
11. Thompson G. Clinical identification of high risk hyperlipidemia. In: Laker M, Neil A, Wood C, eds, *Cholesterol Lowering Trials: Advice For the British Physician Royal College of Physicians*, London: Gazelle Book Services; 1993: 33–44.
12. Winder AF, Jolleys JCW, Day LB and Butowski PF. Corneal arcus: case finding and definition of individual clinical risk in heterozygous familial hypercholesterolemia. *Clin Genet* 1998; **54:** 497–502.
13. Gordon DJ, Probstfield JL, Garrison RJ, Neaton JD, Castelli WP, Knoke JD, *et al*. HDL cholesterol and cardiovascular disease: four prospective American studies. *Circulation* 1989; **79:** 8–15.
14. Assmann G, Schulte H, von Eckardstein A, Huang Y. HDL cholesterol as a predictor of coronary heart disease risk: The PROCAM experience and pathophysiological implications for reverse cholesterol transport. *Atherosclerosis* 1996; **124:** S11–S20.
15. Lacko AG, Barter P, Ehnholm C, van Tol A. International symposium on basic aspects of HDL metabolism and disease prevention. *J Lipid Res* 2000; **41:** 1695–1699.
16. Badimon JJ, Badimon L, Fuster V. Regression of atherosclerotic lesions by HDL plasma fraction in the cholesterol-fed rabbit. *J Clin Invest* 1990; **85**: 1234–1241.
17. Benoit P, Emmanuel F, Caillaud JM, Bassinet L, Castro G, Gallix P. Somatic gene transfer of human apoA-1 inhibits atherosclerosis progression in mouse models. *Circulation* 1999; **99:** 105–110.
18. Eriksson M, Carlson LA, Miettinen TA, Angelin B. Stimulation of fecal steroid excretion after infusion of recombinant proapolipoprotein A-I: Potential reverse cholesterol transport in humans. *Circulation* 1999; **100**: 594–598.
19. Navab M, Hama SY, Cooke CJ, Anantharamaiah GM, Chaddha M, Lin G. Normal HDL inhibits three steps in the formation of mildly oxidzied LDL. *J Lipid Res* 2000; **41:** 1481–1508.
20. Boas EP. Corneal arcus and atherosclerosis. *J Mt Sinai Hosp* 1945; **12:** 79–83.
21. Wilcosky TC, Kwiterovich PO Jr, Glueck CJ, Suchindran CM, Laskarzewski P, Christensen B. Dyslipoproteinemia in black participants – The Lipid Research Clinics Program Prevalence Study. *Circulation* 1986; **73:** 119–125.
22. Hoogerbrugge N, Happee C, van Domburg R, Poldermans D, van den Brand MJ. Corneal arcus: indicator for severity of coronary atherosclerosis? *Neth J Med* 1999; **55:** 184–187.
23. Friedlaender MH, Smolin G. Corneal degenerations. *Ann Ophthalmol* 1979; **11:** 1485–1495.

Comment

This clinically relevant study shows that in patients with a serum cholesterol level over 5.2 mmol, arcus cornealis associates with a more atherogenic lipid profile. The patients were predominantly white, middle-aged males, of whom 37% had arcus cornealis. An arcus was more common in patients with a family history of hypercholesterolaemia and of cardiovascular disease. An arcus was associated with a higher LDL-C, lower HDL-C and, in consequence, a higher LDL-C:HDL-C ratio. It would be of interest to know if similar relationships exist across a broader patient group (including more women, the elderly, and races other than whites), and also the relationship between arcus and a direct measurement of atherosclerosis, such as carotid intima–media thickness.

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