

# Ocular Signs of Hyperlipidemia

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**H**yperlipidemia is a health problem of enormous magnitude that affects many patients. The recently updated guidelines by the National Cholesterol Education Program (NCEP III) emphasize this and address related issues, such as primary prevention of coronary artery disease (CAD) by lowering low-density lipoprotein (LDL) levels and correcting modifiable risk factors of patients with elevated lipid levels.<sup>1</sup> The diagnosis of hyperlipidemia is primarily made by using laboratory methods to analyze blood samples for their levels of various lipids. However, the presence of hyperlipidemia may also be inferred by observing lipid deposition, which can occur in various organ systems, such as the vascular system, musculoskeletal system, and eyes. This article describes arcus senilis and xanthelasma palpebrarum and discusses their significance as ocular signs of hyperlipidemia.

## ARCUS SENILIS

### General Characteristics

Arcus senilis, or corneal arcus, is described as a yellowish-white ring around the cornea that is separated from the limbus by a clear zone 0.3 to 1 mm in width (Figure 1).<sup>2</sup> It is caused by extracellular lipid deposition in the peripheral cornea, with the deposits consisting of cholesterol, cholesterol esters, phospholipids, and triglycerides. The fatty acids that make up many of the deposited lipid molecules include palmitic, stearic, oleic, and linoleic acids. Lipids are normally deposited in the cornea, but it is believed that with aging, the amount of lipids deposited increases, possibly resulting in arcus senilis.<sup>3</sup> This supports the assumption that arcus senilis may represent an extension or exaggeration of the natural process of lipid deposition in the cornea.

### Prevalence

Arcus senilis is more prevalent among the elderly, but it has been observed in younger adults and even children.<sup>2</sup> The estimated prevalence in one study was measured at 8% for those 40 to 49 years of age, 45% for those 50 to 59 years of age, and 75% for those 70 to

## OCULAR SIGNS OF HYPERLIPIDEMIA

**Arcus senilis:** A yellowish-white ring around the cornea that is caused by lipid deposition in the peripheral cornea.

**Xanthelasma palpebrarum:** Plaque-like yellow lesions near the inner canthus of the eyelids that are caused by lipid deposition in the dermis of the eyelids.

79 years of age.<sup>4</sup> In another study, the prevalence was measured at 6% to 12% in a cohort of insulin-dependent patients with diabetes who were less than 30 years of age and was measured at 49% to 54% for patients with diabetes who were more than 30 years of age.<sup>5</sup> The tendency toward increasing prevalence with age explains the usage of the popular nomenclature *arcus "senilis,"* instead of the more technically correct term *corneal arcus*.

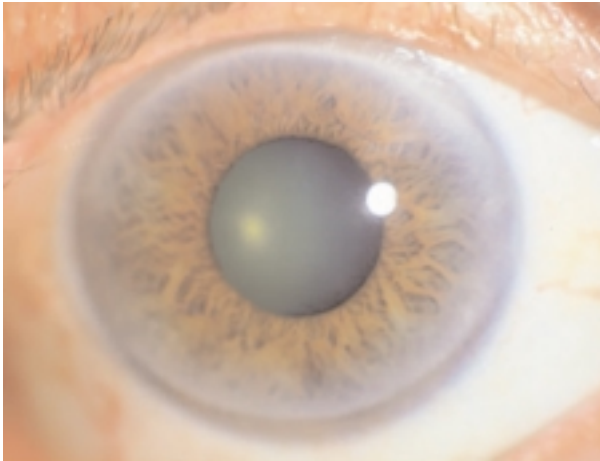
In general, arcus senilis is more common in men than it is in women.<sup>6</sup> It is also more common among patients of African descent, and when it occurs in these patients, it tends to occur earlier in life.<sup>2</sup> Arcus senilis may also be more common in patients who regularly consume alcoholic beverages, with the prevalence in one study increasing as the amount of alcohol consumption increased.<sup>7</sup> In the same study, there was a negative association between arcus senilis and obesity. Also, there was no apparent relationship between arcus senilis and cigarette smoking, diastolic blood pressure, or abnormal glucose tolerance in this study.

### Clinical Significance

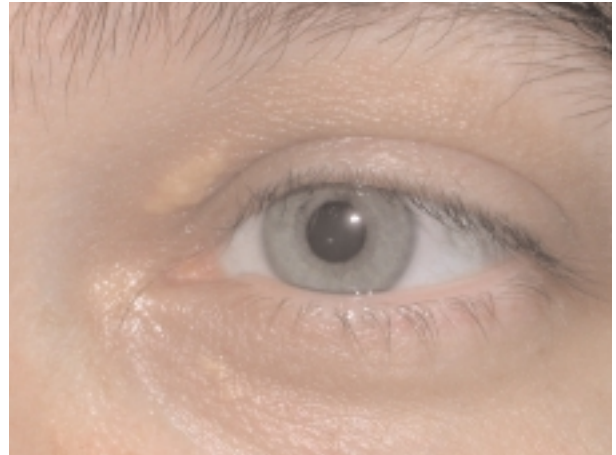
Numerous studies have been performed in efforts to find potential associations between arcus senilis and

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**Figure 1.** Arcus senilis. (Reproduced with permission from Marcia BK. Constitutional classifications of the iris. Canada: Canadian Neuro-Optic Research Institute; 1998.)



**Figure 2.** Xanthelasma palpebrarum. (Reproduced with permission from EyePlastics.com.)

hyperlipidemia and subsequent CAD. One study by a Scottish researcher showed that male patients under 40 years of age who had arcus senilis had an increased risk of CAD, but men older than 40 years and women of all ages who had arcus senilis did not have an increased risk of CAD.<sup>4</sup> Although serum lipid levels were not measured in this study, the author did comment on prior studies investigating a possible relationship between serum lipid levels and arcus senilis. He noted, however, that “the relationship . . . [is] confusing” and that “it is difficult to prove an association.”

A more extensive study of nearly 9000 patients examined the prevalence of arcus senilis in patients with both normal and elevated lipid levels.<sup>8</sup> In this study, total and LDL cholesterol levels were noted to be slightly higher in patients with arcus senilis than they were in those without arcus senilis, although the differences were not statistically significant in all age groups. This led the authors to conclude that the presence of arcus senilis may be associated with “marked aberrations of lipid metabolism,” particularly in young men, in which the differences in the levels of total cholesterol and LDL cholesterol were statistically significant.

A related study of over 3000 patients investigated the possibility of there being a relationship between arcus senilis and mortality from coronary heart disease (CHD) in patients who were hyperlipidemic and normolipidemic.<sup>2</sup> In this study, arcus senilis was shown to be a positive predictor of CHD-related mortality in males younger than 50 years of age who had normal lipid levels, and an even stronger predictor in males younger than 50 years of age who had elevated lipid lev-

els. This association was not present in men older than 50 years or in women of any age, which led the authors to conclude that arcus senilis and coronary atherosclerosis might be caused by similar factors in young men, but not in other groups of individuals. They also concluded that in older patients, arcus senilis might be caused by local factors governing lipid deposition and may have little, if any, relationship to hyperlipidemia and CAD.

A recent study of 2366 patients was performed to determine any relationship between arcus senilis and mortality in 2 groups of patients with diabetes, by studying death certificates. One group involved patients younger than 30 years of age; the other group involved patients older than 30 years of age.<sup>5</sup> The results of the study revealed no association between arcus senilis and ischemic heart disease-related mortality, stroke-related mortality, or, indeed, mortality from any cause, leading the authors to conclude that arcus senilis provides no more information about mortality risk than age does.

## **XANTHELASMA PALPEBRARUM**

### **General Characteristics**

Xanthelasma palpebrarum, or simply xanthelasma, is described as plaque-like yellow lesions near the inner canthus of the eyelids that may emanate from the medial portions of the upper and lower eyelids (**Figure 2**).<sup>9,10</sup> They can be soft, semisolid, or firm.<sup>11</sup> They may occur multiply and symmetrically, and adjacent lesions may coalesce.

Xanthelasma is caused by infiltration of the dermis of the eyelids by xanthoma cells, which are histiocytes

that store lipids in cytoplasmic vacuoles. The main lipid associated with xanthelasma is cholesterol, and it is usually esterified to unsaturated fatty acids.<sup>12</sup>

The etiology of xanthelasma is unknown. A plausible hypothesis that has been proposed is that lipids from the plasma leak out of the vascular system (and into the dermis) owing to some form of vascular trauma. It is thought that the process of blinking may be sufficient to cause increased vascular leakiness and therefore xanthelasma.<sup>10</sup>

There are at least 2 conditions that may mimic xanthelasma<sup>10</sup>: lipoid proteinosis and lichen sclerosus et atrophicus. In both of these conditions, however, the eyelids are firmer and have pearly elevations at their margins. The differences in the characteristics of these conditions, as compared with the characteristics of xanthelasma, are attributable to the fact that the substance that is deposited in relation to each condition is not lipids but rather is an amorphous substance (in lipoid proteinosis) and collagen (in lichen sclerosus et atrophicus).

#### Prevalence

Xanthelasma is more common in women than it is in men (prevalence, 1.1% vs 0.3%, respectively). Like arcus senilis, its prevalence tends to increase with age.<sup>8,9,11</sup>

#### Clinical Significance

Numerous studies have been performed to find any associations between xanthelasma and hyperlipidemia and subsequent CAD. An early British study determined the prevalence of hyperlipidemia in 98 female and 15 male patients with xanthelasma.<sup>13</sup> In this study, 55% of the patients had hyperlipidemia, compared with approximately 16% of randomly selected patients without xanthelasma. The effect of consuming a low-cholesterol diet was also studied, and although the diet lowered serum cholesterol levels (as expected), there was no regression of the xanthelasma. Interestingly, in 2 patients who had xanthelasma surgically excised, the lesions did not recur.

Another study compared lipid levels in 53 patients with xanthelasma and 40 age-matched patients without xanthelasma.<sup>14</sup> In this study, the patients with xanthelasma were divided into normolipidemic and hyperlipidemic subsets, and then these groups were compared with normal control subjects. The authors found that the subset of patients with xanthelasma and normolipidemia had elevated levels of LDL and very low-density lipoprotein (VLDL) cholesterol, as well as decreased levels of high-density lipoprotein (HDL)

cholesterol when compared with normal control patients. This observation suggested that patients with normolipidemia and xanthelasma have an abnormal lipid pattern that may accelerate the development of atherosclerosis and CAD. Likewise, patients with hyperlipidemia and xanthelasma had elevated LDL and VLDL cholesterol levels and decreased HDL cholesterol levels. The authors' final conclusion was that regardless of lipid levels, patients with xanthelasma should be screened for premature CAD.

Several other studies<sup>8,9,11,15</sup> have corroborated the aforementioned findings. Since these studies were performed, more detailed information regarding the association between xanthelasma and hyperlipidemia and CAD has become available. Some studies have shown that serum apolipoprotein B levels are elevated in patients with xanthelasma, a finding that correlates with elevated risk of CAD.<sup>16</sup> Likewise, plasma lipid peroxidation has been shown to be increased in patients with xanthelasma and normal lipid levels, which may further explain the increased risk of atherosclerosis in these patients, considering that lipid peroxidation promotes atherosclerosis.<sup>16</sup>

An interesting corollary to understanding the significance of xanthelasma is the likelihood of its regression with treatment of hyperlipidemia. One study that examined this possibility investigated the effect of both probucol and pravastatin on regression of xanthelasma.<sup>17</sup> In this study, 36% of the patients given probucol demonstrated regression of xanthelasma, whereas only 6% of patients given pravastatin demonstrated regression. The postulated reason for the ability of probucol to cause regression was its activation of the reverse cholesterol transfer mechanism—in effect, it has the ability to remove lipids from the xanthelasma. In contrast, pravastatin's only effect is to lower serum lipid levels, which may explain its ineffectiveness in causing regression of xanthelasma. One property of pravastatin that probucol does not have, however, is its ability to prevent xanthelasma and other forms of lipid deposition.

#### CONCLUSION

The association between either arcus senilis or xanthelasma and hyperlipidemia and CAD is not entirely clear. Arcus senilis may be associated with hyperlipidemia and an elevated risk of CAD primarily in young men and may be a normal part of aging in some individuals. Patients with xanthelasma seem to have an elevated risk of CAD irrespective of their lipid levels. Perhaps the most clinically relevant conclusion that can be drawn from the above discussion is that any patient with either sign should be screened for hyperlipidemia

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and CAD, given the possibility that an increased risk does exist.

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#### REFERENCES

1. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001;285:2486–97.
2. Chambless LE, Fuchs FD, Linn S, et al. The association of corneal arcus with coronary heart disease and cardiovascular disease mortality in the Lipid Research Clinics Mortality Follow-up Study. *Am J Public Health* 1990; 80:1200–4.
3. Tschetter RT. Lipid analysis of the human cornea with and without arcus senilis. *Arch Ophthalmol* 1966;76: 403–5.
4. Cooke NT. Significance of arcus senilis in Caucasians. *J R Soc Med* 1981;74:201–4.
5. Moss SE, Klein R, Klein BE. Arcus senilis and mortality in a population with diabetes. *Am J Ophthalmol* 2000; 129:676–8.
6. McAndrew GM, Ogston D. Arcus senilis and coronary artery disease. *Am Heart J* 1965;70:838–40.
7. Hickey J, Maurer B, Mulcahy R. Arcus senilis: its relation to certain attributes and risk factors in patients with coronary heart disease. *Br Heart J* 1970;32:449–52.
8. Segal P, Insull W, Chambless LE, et al. The association of dyslipoproteinemia with corneal arcus and xanthelasma. The Lipid Research Clinics Program Prevalence Study. *Circulation* 1986;73(1 Pt 2):1108–18.
9. Bates MC, Warren SG. Xanthelasma: clinical indicator of decreased levels of high-density lipoprotein cholesterol. *South Med J* 1989;82:570–4.
10. Depot MJ, Jakobiec FA, Dodick JM, Iwamoto T. Bilateral and extensive xanthelasma palpebrarum in a young man. *Ophthalmology* 1984;91:522–7.
11. Bergman R. The pathogenesis and clinical significance of xanthelasma palpebrarum. *J Am Acad Dermatol* 1994; 30(2 Pt 1):236–42.
12. Anderson DR. Ultrastructure of xanthelasma. *Arch Ophthalmol* 1969;81:692–4.
13. Dean FD. Xanthelasma and hyperlipoproteinemia. *Clin Chim Acta* 1976;66:189–93.
14. Watanabe A, Yoshimura A, Wakasugi T, et al. Serum lipids, lipoprotein lipids and coronary heart disease in patients with xanthelasma palpebrarum. *Atherosclerosis* 1981;38:283–90.
15. Ribera M, Pinto X, Argimon JM, et al. Lipid metabolism and apolipoprotein E phenotypes in patients with xanthelasma. *Am J Med* 1995;99:485–90.
16. Bergman R. Xanthelasma palpebrarum and risk of atherosclerosis. *Int J Dermatol* 1998;37:343–5.
17. Fujita M, Shirai K. A comparative study of the therapeutic effect of probucol and pravastatin on xanthelasma. *J Dermatol* 1996;23:598–602.

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