Abnormal serum lipoprotein levels as a risk factor for the development of human lenticular opacities

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Summary

Aim: To determine whether an association exists between the different plasma lipoprotein constituents and the prevalence of lenticular opacities in dyslipidaemic subjects.

Methods: Adult patients (n = 115) of both genders were included if their fasting total serum cholesterol concentrations exceeded the 95th percentile of normal or their serum low-density lipoprotein (LDL) : high-density lipoprotein (HDL) ratios exceeded 5. Patients were excluded if they suffered from any condition known to cause, or predispose them to, elevated lipoprotein levels or lenticular opacification. Lenticular changes were assessed by means of a slit-lamp through the fully dilated pupil.

Results: An extremely strong association (p < 0.0001) was found to exist between HDL cholesterol levels and the development of lens opacities. Below an HDL-C level of 1.5 mmol/l subjects had a seven-fold higher calculated probability of falling in the lens opacity subgroup than those with HDL-C levels above 1.5 mmol/l [odds ratio = 7.33 (95% CI = 2.06–26.10; p = 0.001)]. An equally strong association was found between high (>5) LDL:HDL ratios and the development of lens opacities (p < 0.0003). The risk of falling into the cataract subgroup if the individual’s LDL:HDL ratio exceeded 5 was 2.35 (95% CI = 1.09–5.04; p = 0.014).

Conclusions: This study strongly suggests that an association exists between low levels of HDL cholesterol and high LDL:HDL ratios on one hand and the development of adult lens opacification on the other.


Lens opacification and cardiovascular disease are two of the main causes of morbidity in humans worldwide. Lens opacity, leading eventually to cataract is responsible for an estimated 40% of the 42 million cases of blindness in the world. Heart disease on the other hand is the single greatest cause of death in developed countries. The relationship...
between cholesterol and cardiovascular heart disease is well documented. The relationship between cholesterol and lens opacity is, however, far less well appreciated. Dyslipidaemia can be defined as abnormal serum lipid levels containing one or more of the following elements: raised total serum cholesterol, raised serum triglycerides, reduced serum high-density lipoprotein cholesterol (HDL-C) levels or a low-density lipoprotein (LDL) : high-density lipoprotein (HDL) ratio greater than 5.

It has recently been shown that dyslipidaemic patients develop cortical lens opacities more frequently and at an earlier age than the normal population, and that cortical lens opacities should be regarded as one of the most common, and hence reliable, clinical signs of dyslipidaemia. The next logical question is whether total serum cholesterol or any of the different fractions that make up the lipogram (i.e. LDL-cholesterol, HDL-cholesterol, triglycerides, LDL:HDL ratio) can be associated with the high prevalence of lens opacification in the dyslipidaemic patient population. This study was designed to examine that question.

Methods

One hundred and fifteen individuals with proven dyslipidaemia were subjected to both a general physical examination by a specialist physician and a slit-lamp ophthalmic examination of the fully dilated eye by an ophthalmologist. In order to obtain a study group with maximum homogeneity and minimum risk of other cataractogenic factors, only patients meeting the following criteria were enrolled:

**Inclusion criteria:** Adults of both genders, 18 to 60 years of age with a serum total cholesterol level > 5.2 mmol/l (exceeding the 95th percentile of normal) and an LDL:HDL ratio > 5 were included in the study.

**Exclusion criteria:** Pregnant or lactating females, subjects with severe hypertension (diastolic blood pressure > 115 mm Hg), history of cardiovascular disease, 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, gasto-intestinal disease or patients who were known to be HIV antibody positive were excluded.

Fasting blood samples were obtained from each individ-ual on three occasions over a period of four weeks. Patients were only included in the study if their lipoprotein variables adhered to the inclusion criteria on each of the three visits.

Lenticular opacities were classified as cortical (water clefs, vacuoles, flakes, wedges and spokes), nuclear (normal colour, pale yellow, yellow, dark yellow or brown) or sub-capsular (anterior or posterior). Both a specialist physician and an ophthalmologist examined all the patients.

**Statistical analysis**

Subjects were identified as belonging to one of two groups, those with clear lenses and those with opacities. The significance of the difference in mean HDL-cholesterol level between the groups was tested by the Student’s t-test. A similar analysis was performed for the mean LDL:HDL-C ratio. Subjects were also classified as having LDL-cholesterol levels lower than or higher than 1.5 mmol/l, thus producing a 2 × 2 contingency table for which an odds ratio calculation was performed. For the LDL:HDL-C ratio, an odds ratio was obtained for a partition at LDL:HDL-C ratio = 5. All statistics were generated using the Statistica™ 1984–2000 (Release 5.5) by StatSoft, Inc, USA.

**Results**

The study group consisted of 115 predominantly Caucasian [94/115 (82%)] subjects. The rest of the group (21/115 or 18%) was of mixed decent. Gender distribution was 74 (64%) male and 41 (36%) female. The group was also relatively young with the mean age 49.1 years (SD = 10.2).

Table I and Fig. 1 depict the mean values of the different lipogram components in the study group (n = 115). The mean total serum cholesterol, triglyceride and LDL cholesterol levels exceeded the 95th percentile of normal, whereas the mean serum HDL cholesterol was lower than the 95th percentile of normal. The study group was divided into two cohorts, i.e. a subgroup with opacities 47 (41%) and a subgroup with clear lenses 68 (59%). Analysis of the two subgroups (Table I) suggested no difference in the mean age of the two subgroups (p = 0.07) and no differences in the following lipid parameters of the two subgroups: total serum cholesterol (p = 0.71); serum LDL cholesterol (p = 0.55); serum triglycerides (p = 0.81).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Clear lens subgroup Mean (± SD) (mmol/l)</th>
<th>Lens opacity subgroup Mean (± SD) (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>47.3 ± 9.8</td>
<td>50.9 ± 10.6</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>7.33 ± 1.90</td>
<td>7.46 ± 1.82</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>5.65 ± 1.89</td>
<td>5.84 ± 1.75</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>1.35 ± 0.35</td>
<td>1.02 ± 0.27</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>2.27 ± 1.75</td>
<td>2.34 ± 1.05</td>
</tr>
</tbody>
</table>

Fig. 1. Serum lipid parameters of the study group (n = 115) compared to the upper limit of normal i.e. 95th percentile (mmol/l).
In the lens opacity group the majority [36 (77%)] presented with cortical opacities. The subgroup with opacities included all opacities [nuclear 9 (19%), cortical 36 (77%), and posterior subcapsular 2 (4%)] (Fig. 2).

The HDL cholesterol levels of the two subgroups differed (Fig. 3). The mean HDL cholesterol level of the subgroup with clear lenses was 1.35 mmol/l (SD = 0.35 mmol/l) whereas the mean HDL cholesterol level of the subgroup with lens opacities was 1.02 mmol/l (SD = 0.27 mmol/l). This difference of 0.33 mmol/l was highly significant (p < 0.0001). In stratifying the subjects according to HDL-C levels, it was clear that above an HDL-C level of 1.5 mmol/l, the number of subjects with clear lenses increased. This was reversed with levels below 1.5 mmol/l (Fig. 3). The odds ratio (OR) for this shift to happen was 7.33 (95% CI = 2.06–26.10; p = 0.001 for the trend), which predicted that below an HDL-C level of 1.5 mmol/l, subjects had a seven-fold higher risk of falling in the lens opacity subgroup than those with HDL-C levels above 1.5 mmol/l.

Mean LDL:HDL-C ratios were also different between the two subgroups. The mean LDL:HDL-C ratio in the subgroup with clear lenses was 4.67 and in the subgroup with lens opacities, 6.24. This difference of 1.57 was highly significant (p = 0.0003). The OR was 2.35 (95% CI = 1.09–5.04; p = 0.014 for the trend) which implies that subjects with a LDL:HDL-C ratio above 5 possessed a 2.35 times greater risk of having lenticular opacities than the group with an LDL:HDL-C ratio less than 5.

Discussion

In many epidemiological studies, low levels of high-density (α-) lipoproteins (HDL) have been associated with increased risk for coronary artery disease (CAD), whereas a high HDL level (> 1.5 mmol/l) is widely considered to be a negative risk factor for the development of CAD. The observations in this study also suggest a clear relationship between low levels (< 1.5 mmol/l) of HDL cholesterol and the presence of lenticular opacities [OR 7.33 (95% CI = 2.06–26.10; p = 0.001)].

An LDL:HDL cholesterol ratio > 5 constitutes another widely excepted risk factor for the development of CAD. Furthermore, the observations in this study group support the relationship between high serum LDL:HDL cholesterol ratios (> 5) and lens opacities [OR 2.35 (95% CI = 1.09–5.04; p = 0.014)]. Therefore, the very same serum lipid component [low HDL (< 1.5 mmol/l) levels and high LDL:HDL cholesterol ratios (> 5)] that have been identified as risk factors for CAD are also being implicated as risk factors for lenticular opacification (mainly of the cortical variety).

The protective effect of HDL-C against CAD partly lies in the ability of HDL to act as an antioxidant in inhibiting the formation of oxidised LDL. This in turn inhibits the process of atherosclerosis. The question arises whether the same mechanism could be involved in the lens.

Oxidative damage has been considered a major factor involved in cataract formation. The lens is chronically exposed to radiation and upon ageing absorbs increasing amounts of ultraviolet light. Increased production of reactive oxygen species is a feature of most, if not all, human disease, including cardiovascular disease, cancer and cataract. Dietary antioxidants may be especially important in protecting against human diseases associated with free radical damage to cellular DNA, lipids and proteins.

Experimental work demonstrating the cataractogenic effect of oxygen and solar radiation, has led to the notion that intra-ocular generation of certain active species of oxygen under both photochemical and ambient conditions may initiate a cascade of toxic biochemical reactions, leading ultimately to cataracts and other age-related eye diseases. Therefore, according to this theory, the ambient oxygen itself serves as a pathogen after its derivatisation to its more reactive species, commonly referred to as oxygen radicals.

Furthermore, most ocular tissues including the lens, vitreous and aqueous humour contain detectable amounts of photosensitisers such as riboflavin and kynurenine. These photosensitisers can constantly generate superoxide as long as an appropriate activator (electron donor) is available and the reaction solution is exposed to light covering the wavelengths appropriate for photo-activation. These sensitisers can damage and crosslink lens proteins. The concentration of
hydrogen peroxide in the aqueous humour is also remarkably high and further increases in cases with cataract, as do the levels of $\text{H}_2\text{O}_2$ in the lens itself.\textsuperscript{19,22} The ability of the eye to deal with these oxygen radicals decreases with age. This is demonstrated by a measured decrease in the activity of antioxidant enzymes, particularly superoxide dismutase, as well as a decrease in glutathione levels in aged cataractous lenses, accounting for the loss of antioxidant protection.\textsuperscript{21,22}

The impact of free radical toxicity appears far more real in the eye and specifically the lens than anywhere else in the body. The transparency of the cornea, aqueous humour, lens and vitreous humour allows a unique situation for an incessant photochemical generation of oxygen radicals in all the ocular tissues and the bathing fluids, at least during periods of photopic vision.

Cholesterol can be oxidised readily by a variety of reactive oxygen species, yielding several products, some of which possess adverse biological effects.\textsuperscript{23} The absolute amount of cholesterol in the lens is not remarkably high, but is concentrated in lens cell membranes. These membranes are known to have the highest cholesterol content of any biological membrane. Cholesterol distribution in the lens appears to follow an unusual pattern, concentrating in the pericortical region.\textsuperscript{24} As an unsaturated lipoprotein, cholesterol is able to autoxidise. This autoxidation can be initiated by most of the reactive oxygen species. The high concentration of cholesterol in lens membranes may provide the membrane with a role in the lens as a bad (oxidant) and a good molecule (antioxidant) in cellular damage to cholesterol.\textsuperscript{25} Significant oxidation of cellular cholesterol may well result in cell injury, at least partially compatible with the damage associated with cataract formation.

It has been suggested in different contexts that cholesterol may act as an antioxidant.\textsuperscript{26} The high concentrations of cholesterol in the lens would enable it to perform a role in the lens comparable to that ascribed for albumin in the plasma.\textsuperscript{27} The lens could in this regard be considered to be ‘the albumin of the eye’. Girao et al.\textsuperscript{28} (1999) were the first to propose that cholesterol may act as an antioxidant in the lens;\textsuperscript{29} in particular HDL cholesterol, because of its well-known ability to protect the body from the oxidative damage found in cardiovascular disease.\textsuperscript{24} Girao et al.’s initial study was designed to establish whether HDL cholesterol acts as an antioxidant in the bovine lens.\textsuperscript{30} They found that oxidation of bovine lens membrane resulted in the production of lipid hydroperoxides, consumption of endogenous vitamin E and formation of cholesterol oxides and concluded that HDL-C presents important characteristics generally ascribed to an antioxidant molecule.

The lens cell membrane has the highest concentration of cholesterol in the body. The cholesterol-to-phospholipid (C:P) mole ratio in the lens ranges between 1 and 4. In contrast, plasma membranes of typical eukaryotic cells have C:P mole ratios between 0.5 and 1.0. The only other known membrane with C:P mole ratios comparable to the lens are diseased, atherosclerotic, vascular smooth muscle cell membranes. Adequate vision relies on lens transparency, which in turn is severely affected by any change in the lens membrane structure or composition. Altering of the lens lipid composition or structure may cause lenticular opacities. These lens lipids are prone to oxidative damage. HDL cholesterol may indeed act as an antioxidant, protecting the lens against this oxidative onslaught. Cholesterol may therefore be regarded both as a bad (oxidant) and a good molecule (antioxidant) in the lens.

The proposed mechanism by which photopic vision, via both a photochemical and non-photochemical pathway, produces free radicals is summarised in Fig. 4. Normal mechanisms exist by which these reactive oxygen species are inactivated, but should these mechanisms fail, cytotoxicity results either directly as damage to cellular DNA, lipids and protein, or indirectly via the oxidation of cholesterol and cholesterol oxidation products. A lack of adequate anti-oxidants, including HDL-cholesterol, will result in lens damage by the reactive oxygen species produced by daily photopic vision.

**Fig. 4. Schematic summary of proposed mechanism by which photopic vision leads to the production of free radicals, cholesterol oxidation and lens opacities.**

**Conclusions**

Low HDL-C levels (< 1.5 mmol/l) and an elevated LDL:HDL ratio (> 5) present significant cataractogenic risk factors, whereas the lens is protected by high HDL-C levels (> 1.5 mmol/l) and low LDL:HDL ratios (< 5) in the dyslipidaemic patient. These are exactly the same risk factors that have often been implicated in the development of atherosclerotic circulatory disease. It is true that low HDL levels can frequently be linked to a genetic predisposition but HDL...
levels can also be reduced by other factors. These include obesity, sedentary lifestyle, cigarette use, diabetes mellitus, uraemia, nephrotic syndrome, and several drugs like thiazide diuretics, retinoids, beta-blockers, androgenic steroids and most progestational drugs.\textsuperscript{30} Could human age-related cataract therefore be regarded as a preventable condition because of this association of low HDL levels with lifestyle factors? Because these factors are potentially modifiable by lifestyle changes, these observations may prove important, as the modification of these parameters could constitute an effective mode of prevention or retardation in a subgroup of patients who develop cataracts at an early age.

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References