Importance of Vitreous Liquefaction in Age-Related Cataract

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Purpose. Vitrectomy is associated with the rapid progression of nuclear cataracts. This study was conducted to test the hypothesis that age-related liquefaction of the vitreous gel may also be associated with lens opacification.

Methods. Lenses from eye bank eyes were graded for nuclear, cortical, and posterior subcapsular opacities, and the amount of liquid vitreous was measured.

Results. Nuclear sclerosis (NS) grade, percent liquefaction, and age all correlated highly (P < 0.0001). After adjustment was made for age, the correlation between NS and percent liquefaction was 0.37 (P < 0.0001), and the correlation between age and NS after adjustment for liquefaction was 0.57 (P < 0.0001). After the eyes were stratified into age groups, the correlation between NS and percent liquefaction was found to be highest in eyes from donors aged 51 to 70. Cortical and posterior subcapsular opacities increased with age, but scores for these cataract types did not significantly correlate with vitreous liquefaction.

Conclusions. Loss of vitreous gel during aging increases the risk of nuclear cataracts. Preservation or replacement of the vitreous gel may protect patients from nuclear cataract. (Invest Ophthalmol Vis Sci. 2004;45:77–85) DOI:10.1167/iovs.03-0820

The mechanisms responsible for the formation of age-related cataracts in humans are poorly understood. Epidemiologic studies have identified cigarette smoking and high myopia as risk factors for nuclear cataracts;1–3 high levels of sunlight exposure, female sex, and dark iris color, for cortical cataracts;3,4–6 and steroid use or radiation exposure for posterior subcapsular cataracts.7,8 The mechanisms that link these risk factors to cataract have not been identified.

Numerous studies have shown that nuclear cataracts are associated with increased oxidative damage to the proteins and lipids of the oldest cells in the lens.9–13 Recent studies have shown that diffusion decreases within the lens with age, perhaps making the lens nucleus more susceptible to oxidative damage.14–16 However, these studies have not identified a mechanism that would explain why nuclear cataracts develop in some individuals, but not in others, or why nuclear cataracts develop in some persons at age 50 and in others after age 90.

The possibility of a relationship between the state of the vitreous body and nuclear cataract formation is suggested by several observations. Vitrectomy replaces the gel vitreous with liquid. Most patients who have undergone vitrectomy exhibit changes in the lens that cause a myopic shift and nuclear cataracts within 2 years.17–25 In contrast, when retinal surgery is performed in a manner that preserves the structure of the vitreous body, the formation of cataract and the accompanying changes in the refractive power of the lens are not accelerated.26,27 High myopia is associated with increased liquefaction of the vitreous body,28–30 and preexisting high myopia has been identified as a risk factor for nuclear cataract.31 Finally, Stickler syndrome, a hereditary disorder in which the vitreous body liquefies prematurely, is associated with the premature onset of cataract, including nuclear cataract.32–35 These studies suggest a correlation between loss of gel vitreous and the occurrence of nuclear cataract.

Because surgical or hereditary loss of vitreous structure increases the risk of nuclear cataract, it is reasonable to hypothesize that age-related vitreous liquefaction would also be associated with cataract. In humans, the vitreous body gradually liquefies with age.34 The collagen fibrils of the vitreous core aggregate into thick cables, instead of the random orientation of fine fibrils found in the gel network earlier in life.35–37 This age-related redistribution of the fibrillar components of the vitreous body leaves the spaces between the collagen cables filled with liquid, a process that has been termed vitreous syneresis, synchysis senilis, or vitreous liquefaction. The process of liquefaction begins as early as age 4, and by age 90 the vitreous may be more than 50% liquefied.38–39 During the later stages of vitreous liquefaction, the vitreous cortex may separate from the inner limiting membrane of the retina, causing posterior vitreous detachment (PVD). The factors responsible for age-related vitreous liquefaction and PVD have not been established, although light exposure, oxidation, and increased proteolytic activity have been postulated to be causes.39–45

The present study was designed to determine whether an association exists between vitreous liquefaction and the occurrence of age-related cataracts. We graded the degree of nuclear, cortical, and posterior subcapsular opacities and measured the extent of vitreous liquefaction in donor eyes. The possible relationship between lens opacification and liquefaction of the vitreous body was then assessed.

Methods

Acquisition and Dissection of Donor Eyes

All procedures conformed to the provisions of the Declaration of Helsinki for the use of human tissue in research and were approved by the Washington University Humans Subjects Institutional Review Board.

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Board. Donor eyes, including whole globes and posterior poles provided after removal of the cornea, were obtained from Mid-America Transplant Services (St. Louis, MO), the Lions Eye Bank (Portland, OR), and the National Disease Research Interchange (Philadelphia, PA). Preliminary experiments showed that eyes obtained more than 72 hours after death were sometimes dehydrated. To provide at least a 12-hour cushion against possible dehydration, we restricted the globes used in the present study to eyes received 60 hours or less after death.

In a few cases, eyes that were initially received and dissected were later excluded from statistical analysis when it was realized that more than 60 hours had elapsed since death. The prior medical and ocular histories of most donors were not available.

Two hundred ten eyes were dissected. Of these, 16 were excluded on account of pseudophakia; 16 because of greater than 60 hours' time elapsed since death; 5 because of poor condition noted during dissection, including damage to the lens; and 2 because the age of the donor was unknown. The remaining 171 eyes were included in the statistical analysis. These eyes represented 95 donors, with 76 donors contributing two eyes, and 19 donors contributing one. Of the 19 donors who contributed one eye, in 9 cases the fellow eyes were not received, and in 4 cases the eyes are excluded because of obvious damage that occurred before shipping, in 2 cases because of poor condition noted during dissection, and in 4 cases because of pseudophakia.

Before dissection, the circumference of each eye was measured so that the amount of liquid vitreous could be corrected for globe size. A string was used to encircle the globe at its largest circumference perpendicular to the optic axis, and the length of the string was measured. From whole globes, the cornea was removed, with a scalpel used to make the initial incision at the limbus and iris scissors used to extend the incision to 360°. The iris was removed by grasping it with forceps and gently tearing it away from its insertion. A spatula was used for blunt dissection of the lens from the zonules and anterior vitreous face, being careful not to disturb the anterior face of the vitreous body excessively. The lens was lifted out of the eye and placed in a cuvette filled with Leibowitz L-15 medium (Life Technologies, Rockville, MD). The lens rested on a diagonally oriented piece of coverslip inside the cuvette (Fig. 1) and was viewed by placing the cuvette on a specially designed housing mounted on a slit lamp (model SL-7; Kowa, Tokyo, Japan). With the anterior face of the lens facing the observer, the examination of the donor lens simulated that of a live patient.

Cataracts were graded using the reference photographs and seven-decade scale originally designed for the Lens Opacification Classification System (LOCS) III for in vivo grading.28 The lenses in our sample had similar degrees of nuclear opalescence and brunescence. Therefore, the scores were combined, and a single number from 0.1 to 6.9 was assigned to quantify both opalescence and brunescence. For cortical and posterior subcapsular cataracts, instead of grading from a range of 0.1 to 1.0 for the first reference interval, we classified lenses that had grades of less than 1.0 as “0,” because minor postmortem changes could not be differentiated from trace cortical or subcapsular opacities. Grading of the lens was always performed before assessing the extent of vitreous liquefaction to ensure masking of subjective lens opacification grading.

After lens extraction, the eye was placed in a Petri dish and weighed. The eye was then oriented superior-side up in a second, preweighed Petri dish, using the posterior long ciliary arteries and extraocular muscles to establish orientation. A method similar to that of O’Malley29 and Roth and Foos,35 was used to slice the eye transversely approximately 1 mm superior to the optic nerve with a rectangular scalpel, with iris scissors used when necessary to complete the incision. This incision divided the eye into two calottes, and allowed the liquid vitreous to be readily expressed into the Petri dish. The calottes were transferred to the original Petri dish, and both dishes were reweighed to determine the amount of liquid vitreous. The weight lost from the first dish and the weight gained by the second dish (generally within 0.1 g of each other) were averaged to yield the weight of liquid vitreous.

Data and Statistical Analysis

To control for globe size as a possible confounding factor in measurements of liquid vitreous weight, percent liquefaction instead of absolute liquid weight was used for data analyses. Percent liquefaction was calculated as follows: The volume of the eye was calculated from the measured circumference, assuming that the eye is a sphere. Vitreous volume was estimated by multiplying the eye volume by 0.8, because the vitreous occupies approximately 80% of the eye volume.46 The measured liquid weight was then divided by the vitreous volume to obtain percent liquid vitreous. We could not use methods for estimating vitreous volume that account for variations in axial length because the corneas had been removed from many of the eyes.

The Spearman rank correlation coefficient was used to analyze the relationship between lens opacity grade, percent liquefaction, and weight of liquid vitreous. Because the values of these variables were highly correlated in right and left eyes (all correlations greater than 0.90), one eye was selected at random from each of the 76 donors who had contributed two eyes. Randomization was performed as follows: (1) A list of random numbers was generated from a uniform distribution. (2) Half of the numbers were assigned to the right eyes and half to left eyes to ensure an equal probability of selection. (3) This list was sorted in ascending order to produce an ordered list. (4) The list of donors with two eyes in the sample was sorted in ascending order by identification number. (5) The ordered lists of eyes and donors were merged. Therefore, the 95 eyes that were analyzed included 76 eyes randomized as described, plus 19 eyes of donors who contributed only one eye.

NS grade and percent liquefaction correlated highly with age, possibly obscuring any potential relationship between NS grade and percent liquefaction. The partial Spearman coefficient was used to analyze the relationship between NS grade and percent liquefaction after adjusting for age and between age and NS grade after adjusting for liquefaction. Because of the large number of 0 grades for cortical or posterior subcapsular opacities, Kendall’s correlation was used to evaluate the relationships between vitreous liquefaction and grade in these cataracts.

The susceptibility of the lens to nuclear cataract is known to be low before age 50.34–36 Examination of our data showed that NS grade

FIGURE 1. (A) A pair of human lenses mounted in cuvettes in the orientation in which they were viewed by slit lamp. (B) One lens observed from the side showing the glass coverslip bracing the lens in the anterior forward position.
was high in most eyes older than 70. The relationship between NS and percent liquefaction was therefore reanalyzed after the eyes were stratified into age groups: 1 to 50, 51 to 70, and 71 to 90. Spearman coefficients were calculated for NS opacity grade versus percent liquefaction, opacity grade versus age, and percent liquefaction versus age for each age group. The relationships between time from donor death to dissection and percent liquefactions, nuclear opacity and donor age were also evaluated to determine whether time since death affects the cataract grade or extent of vitreous liquefaction.

RESULTS

One hundred seventy-one eyes of 95 donors were included in the study. Mean age was 60 ± 15 years and mean percent liquefaction of the vitreous body was 19% ± 13%.

Because the extent of vitreous body liquefaction and lens opacification grades correlated highly in fellow eyes (r = 0.90; P < 0.0001), data from one eye of each pair were selected at random for statistical analysis. For the total data set, 52% were left and 48% right eyes (n = 95). Plots of cataract severity, donor age, or percent liquefaction versus time from donor death to dissection did not demonstrate significant correlations (data not shown).

Although percent liquefaction was used in preference to absolute liquid vitreous weight in our analyses, to avoid possible confounding introduced by globe size, plots were also made of absolute liquid vitreous weight. These were essentially indistinguishable from those made of percent liquefaction (data not shown).

Because nuclear sclerotic cataracts are the most common type of cataract to occur after vitrectomy, we first analyzed the relationship between age, NS grade, and vitreous body liquefaction. The data presented in Figure 2 show that higher NS grade and greater liquefaction were associated with increased age and that higher NS grade was associated with increased liquefaction. Spearman rank correlation coefficients showed that all three relationships were highly significant (P < 0.0001). The partial Spearman correlation between NS grade

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Figure 2. Scatterplots showing the relationship between (A) NS grade (opacification) and percent liquefaction, (B) NS grade and age, and (C) percent liquefaction and age. The lines show the best linear fit to the data. The table shows the correlations between age, NS grade, and percent liquefaction.
and percent liquefaction after adjusting for age was 0.37 ($P < 0.0001$), indicating that liquefaction of the vitreous body was significantly associated with nuclear opacification, independent of age. Similarly, the partial Spearman correlation coefficient for nuclear sclerosis grade and age was 0.57 ($P < 0.0001$), showing that age was significantly associated with opacification of the lens nucleus, independent of liquefaction of the vitreous body.

Previous studies suggested that younger eyes are less susceptible to nuclear cataract, even after vitrectomy. Data in Figure 2 suggest that the oldest eyes have the highest NS grades, even when vitreous liquefaction was in the lower range for this age group. Therefore, the relationship between vitreous liquefaction, lens opacification grade, and age was analyzed by age groups ($\leq 50$, 51–70, and $>70$ years). The distribution of the sample by age group was: $\leq 50$, 22%; 51 to 70, 51%; and older than 70, 27%. The correlation between NS grade and percent liquefaction was highest in the 51 to 70 age group (Fig. 3). In this group, the association between NS grade and percent liquefaction was greater than between age and NS grade and between age and percent liquefaction (Fig. 4). In the 51 to 70 age group, the partial Spearman correlation between

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<th>Spearman Coefficient</th>
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Figure 3. Scatterplots showing the relationship between NS grade (opacification) and percent liquefaction in different age groups. (A) All subjects, (B) $\leq 50$, (C) 51 to 70, (D) and more than 70 years. The table shows the correlations between percent liquefaction and NS grade for eyes in the different age groups.
DISCUSSION

To date, the vitreous body has been most often studied with regard to its involvement in retinal disease, especially proliferative diabetic retinopathy and macular hole.\textsuperscript{26,47} The possible role of vitreous body degeneration in the etiology of age-related lens opacification has received little attention, even though nuclear cataracts are a frequent consequence of vitrectomy.\textsuperscript{18–25}

It is unlikely that the cause of postvitrectomy cataracts is the underlying retinal disease that was the impetus for vitrectomy. Patients who undergo vitrectomy during the removal of preretinal membranes often experience development of nuclear cataracts, as do patients who have a vitrectomy during other types of retinal surgery. However, individuals who undergo surgery for preretinal membranes who do not undergo vitrectomy do not have nuclear cataracts or the myopic shift that typically precedes nuclear cataracts.\textsuperscript{26,27} Furthermore, retinal diseases that often require vitrectomy, like macular hole, retinal detachment, and diabetic retinopathy, are not themselves associated with rapid-onset nuclear cataracts. It is only when treatment of these conditions involves vitrectomy that rapidly developing nuclear cataracts occur. One cannot rule out the possibility that the infusion fluids or drugs used during vitrectomy contribute to postvitrectomy cataracts. However, we believe it significant that the attribute shared by both postvitrectomy and age-related nuclear cataracts is the destruction of the vitreous gel.

Previous studies suggested a link between degeneration of the vitreous body and nuclear sclerotic cataract. In a study of patterns of vitreous liquefaction in donor eyes, O’Malley observed a larger than expected extent of vitreous body liquefaction in both eyes of seven donors in which one eye was aphakic (presumably as a result of cataract surgery) and the other phakic.\textsuperscript{39} Because the amount of liquefaction was similar in the phakic and aphakic eyes, the cataract surgery was not the cause of the increased loss of gel vitreous. Rosen\textsuperscript{50} observed that 94 of 100 patients with nuclear sclerosis also had posterior vitreous detachment, a higher rate than would be expected for the age of the patients in his series.\textsuperscript{39} He also commented that the degree of nuclear sclerosis appeared to be proportional to the extent of vitreous detachment. Given that vitreous detachment is highly correlated with, and likely the result of, vitreous liquefaction,\textsuperscript{28,51} an association might be inferred between vitreous liquefaction and the formation of nuclear sclerotic cataract.

To our knowledge, the present study is the first to examine the association between vitreous liquefaction and age-related lens opacification. In eyes of 95 donors, the correlation between the extent of nuclear opacification and percent liquefaction was highly significant after adjusting for age. Age was also significantly associated with nuclear opacification, independent of the extent of vitreous liquefaction. Liquefaction of the vitreous body was not significantly associated with the presence of cortical or posterior subcapsular cataracts. This result is consistent with other reports showing that different risk factors contribute to the etiology of the three major types of age-related cataracts.\textsuperscript{1–5}

The magnitude of the correlation between vitreous liquefaction and nuclear opacification was greatest in the 51 to 70 age group, suggesting that it is in this age group that the lens may be most susceptible to the consequences of vitreous body liquefaction. It was also within the 51 to 70 age group that we found the greatest variability in the extent of vitreous liquefaction (Fig. 2C), a result that is similar to the observations of O’Malley in his study of the extent of vitreous body degeneration in 800 donor eyes.\textsuperscript{39}

The Link between Vitreous Liquefaction and Nuclear Opacification

If liquefaction of the vitreous body is a significant risk factor for nuclear cataract, it is important to identify the changes that follow the destruction of the vitreous gel, either during aging or after vitrectomy, that contribute to the opacification of the lens nucleus. Several possibilities can be considered.
It is possible that one or more essential metabolites may be lost after vitreous degeneration and the absence of this material may contribute to the formation of nuclear cataracts. Although this possibility cannot be ruled out at this time because the composition of the vitreous body is complex, examination of gel and liquid vitreous has found that they have similar composition. It is also possible that the factors responsible for the liquefaction of the vitreous body independently cause nuclear opacification or that opacification and hardening of the lens nucleus somehow lead to degeneration of the vitreous body. The causes of age-related vitreous liquefaction are not known, although it has been suggested that light, oxidative damage, or increased proteolytic activity may be responsible. Several studies have shown that increased sunlight exposure is not associated with increased risk of nuclear cataracts. Therefore, sunlight exposure is not likely to explain the relationship between vitreous liquefaction and opacification of the lens nucleus. Oxidative damage to lens proteins and lipids is a hallmark of nuclear cataracts. Therefore, increased oxidative stress in the eye may contribute to vitreous degeneration and formation of nuclear cataract. It is not apparent how elevated levels of proteases could lead to selective damage to the lens nucleus without damaging the outer cells of the lens, or how opacification and hardening of the lens nucleus might alter the properties of the vitreous, although these possibilities cannot be ruled out.

Nuclear opacities occur frequently in the first 2 years after vitrectomy, as well as being more prevalent in eyes with liquefaction of the vitreous body. Therefore, it seems possible...
that it is the loss of the gel state of the vitreous body that increases the risk of nuclear cataract. In an eye with an intact vitreous gel, soluble substances, such as growth factors, ions, and metabolites, are redistributed by the relatively slow process of diffusion. The concentration of these molecules should be highest near the tissues that produce them or transport them out of the eye. Liquefaction or removal of the vitreous body, which permits the fluid in different regions of the eye to intermix rapidly, would prevent the formation of these gradients and rapidly distribute solutes throughout the posterior segment of the eye.

One solute that should be significantly altered in its distribution in the eye after loss of the vitreous gel is oxygen. Oxygen diffuses from the retinal arterioles into the vitreous body and the cells of the inner retina consume oxygen, removing it from the vitreous body. Most of these competing processes result in a steep, standing oxygen gradient within the narrow band of vitreous gel that is closest to the retinal arteries and arterioles (Fig. 6A). Oxygen concentration measured around the lens is remarkably low in the intact human eye. Throughout the central and anterior vitreous body, the partial pressure of oxygen is approximately 16 mm Hg (~2% O₂). Comparably low oxygen levels (~1.8%) have been measured in the anterior chamber near the surface of the lens capsule. Most tissues show signs of hypoxia when oxygen levels fall below 5%. Thus, the lens is normally exposed to especially low levels of oxygen.

When the retina is not bounded by the vitreous gel, as occurs after vitrectomy or posterior vitreous detachment, oxygen from the retinal vessels would be carried away from the surface of the retina by fluid movement and distributed throughout the liquefied portion of the vitreous (Figs. 6B, 6C). Fluid movement over the unbounded inner surface of the retina should occur frequently (for example, after most movements of the head or eyes). Redistribution of oxygen from well oxygenated (perfused) to hypoxic (nonperfused) areas of the retina has been demonstrated after vitrectomy or posterior vitreous detachment and is believed to explain the beneficial effects of these conditions in diabetic retinopathy and branch retinal vein occlusion. In a similar manner, circulation of the vitreous fluid after vitrectomy or degeneration of the vitreous gel could expose the lens to higher concentrations of oxygen than in an eye with an intact vitreous gel (Figs. 6B, 6C). In agreement with these predictions, our recent studies demonstrate that, in human eyes, vitrectomy leads to loss of the normal gradient of oxygen in the eye and increases the level of oxygen close to the lens (Shui Y-B, et al. IOVS 2003;44:ARVO E-Abstract 3022). An increase in oxygen around and within the lens is also found in rabbits after vitrectomy (Dillon J, et al. IOVS 2003;44:ARVO E-Abstract 3501).

Exposure of the lens to elevated levels of oxygen can cause cataracts. Patients treated with hyperbaric oxygen therapy for 1 hour each day for a year or more showed frank nuclear cataract or early signs of nuclear opacification, including a myopic shift. Studies of shorter duration have also shown that hyperbaric oxygen treatments cause a shift toward myopia. Pecataractous changes are also seen in the lenses of experimental animals if they are regularly exposed to hyperbaric oxygen.

Based on these observations, we suggest the intact vitreous gel normally helps to maintain the low level of oxygen around the lens by preventing bulk flow of the vitreous fluid. Degeneration or destruction of the vitreous gel would allow more oxygen to reach the lens, and increased exposure of the lens to oxygen causes nuclear cataract (Fig. 6C).

**Association between Age, Vitreous Liquefaction, and Opacification of the Lens Nucleus**

Many studies, including the present one, have shown that age is an important risk factor for lens opacification. Data from the present study also show that liquefaction of the vitreous body is a risk factor for nuclear opacification when eyes of all ages were considered together. However, when eyes were divided into age groups, the relationship between liquefaction of the vitreous body and nuclear opacification grade in subjects younger than 50 years was low and statistically not significant in this study. This suggests that, in younger individuals, the lens may be less susceptible to oxygen or other harmful consequences of vitreous body liquefaction. A similar result was found for cataract risk after vitrectomy: patients older than 50
were 10 times more likely to have nuclear cataract within 2 years after surgery than those younger than 50.18

Laboratory studies have suggested that between ages 30 and 50 a barrier to the diffusion of small molecules forms between the lens cortex and nucleus.14–16 Reduced glutathione, a metabolite that normally protects the proteins and lipids of the lens from oxidative damage,11,69 is produced in the lens cortex and reaches the lens nucleus by diffusion.14,70 The formation of a diffusion barrier in the lenses of older individuals would be expected to decrease the amount of reduced glutathione available to the lens nucleus, thereby increasing its susceptibility to oxidative damage. Consistent with this view, glutathione levels are low and an increased proportion of this glutathione is found in the oxidized state in nuclear cataract.10,11,13,14,7,12 Therefore, oxygen or other oxidants have greater potential to cause damage to the lens nucleus of older individuals. These observations provide a possible explanation for the contribution of age to the risk of nuclear cataract.

In the oldest age group studied (>70 years), opacification of the lens nucleus was high, no matter what the extent of vitreous liquefaction. This may indicate that the age-related increase in the susceptibility of the lens to oxidative injury is the most important determinant of opacification in this age group. However, cataract surgery is also more frequent in this age group. Because pseudophakic eyes were excluded from our study, it is possible that we preferentially excluded individuals with higher levels of vitreous liquefaction because these individuals had already had cataract surgery. Although we measured the extent of vitreous liquefaction in the pseudophakic eyes (data not shown), we could not relate these measurements to nuclear opacification, because we did not have information about the types of cataracts that led to lens removal. Additional studies would be needed to explore more fully the contribution of vitreous body liquefaction to nuclear cataracts in this age group.

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