

DIETARY RISK FACTORS FOR FIBRILLAR AND NON-FIBRILLAR VITREOUS DEGENERATION IN MYOPIA

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[INTRODUCTION]

[Vitreous degeneration--especially in myopes--is an important public-health problem. Nearly one of every two autopsied eyes show Grade 3 synchysis [50% liquefaction]; one in four will have suffered posterior vitreous detachment (PVD).¹ Synchysis associated with vitreous syneresis [shrinkage of the gel with exudation of the liquid component] and ophthalmoscopically detectable vitreous floaters are found in almost twice as many women as men.^{2]}

[Earliest detected in this process leading to PVD is the stage in which beginning liquefaction of the hyaluronic-acid matrix results in collapse of the interfused network of ophthalmoscopically **invisible** collagenous fibrils such that the fibrils coalesce and form ophthalmoscopically **visible** aggregates of collagenous **fibrils**.^{3,4} In the presence of PVD and in the other vitreous degenerations in which liquified-vitreous lacunae are contiguous with the internal limiting membrane of the retina, the likelihood increases for vitreoretinal traction, rhegmatogenous retinal detachment, and exogenous **cellular** debris (cellular floaters) in the vitreous compartment--complications usually seen prior to any surgical intervention.]

[Relatively rarely encountered is a full-blown proliferative retinopathy (PVR) with newly synthesized Type-I ["wound-healing"] collagenous-fibril membranes as an occasional complication of surgery and of processes that result in the migration of retinal pigment epithelium cells into the vitreus.⁵⁻¹¹ ["Vitreus" is noun-form spelling proposed by Balazs & Armand in RS Varma: Glycosaminoglycans and Proteoglycans. . . , Basel: Karger, 1982: 480-99].]

[Sixty-four percent of eyes of patients with floaters are myopic,^{12,13} whereas 93% of eyes of patients with asteroid bodies are hyperopic,¹⁴ suggesting the possibility of opposing metabolic, tissue-nutriture, environmental, or genetic processes to account for the refractive differences and disease entities. For example, depressed serum calcium-to-phosphorus (Ca/P) ratio is associated with progressive myopia, and reduction of calcium complexing with the sodium hyaluronate of the vitreous results in decreased viscosity in *in vitro* studies, while elevated serum calcium and dietary calcium appear to be associated with calcium-soap formation known as vitreous asteroid bodies and also with increasing hyperopia or decreasing myopia (Table 1).]

[We shall now review the new findings in the nutritional and ophthalmological epidemiology of both fibrillar and non-fibrillar floaters.]

[In 1984, when I last spoke in Moscow on myopia at the Sixth Symposium of the International Society on Metabolic Eye Disease, I reported that my epidemiological findings supported some important work by Avetísov, Kolosov, Kashíntseva, and others. For example, my findings as to the progression of myopia revealed the following as strongly associated risk factors:

- a) long-sustained, daily repeated closework ***stimulus to accommodation***--as measured in diopter-hours-- and ***accommodative-fatigue syndrome*** [Avetísov,¹⁵ Young,¹⁶ Lane¹⁷];

Accommodative stimulus and elevated intraocular pressure (IOP). One aspect of the effect of long-sustained, daily repeated closework stimulus to accommodation is portrayed in Figures 1, 2, and 3, as resulting in elevation of the baseline of IOP. In Figure 1 we see that, after excluding persons with dietary extremes, persons dioptrically deficient in Age-Adjusted Habitual Relative Add (AAHRA) are more likely to have elevated IOP. (A person using an habitual dioptric addition for sustained closework equivalent to the calculated "ideal" add for a statistical person of the same age is said to have AAHRA = zero diopter. A person habitually undercorrected for closework by one diopter has AAHRA = -1.00 diopter.) In Figure 2 we see the distribution of IOPs in accordance with accommodative-stimulus stress categories. Low accommodative stimulus for persons with average dietary adequacy results in a

Gaussian distribution curve with low IOPs. For persons with elevated accommodative stimulus, we find a bimodal distribution, with a significant proportion of persons developing elevated IOPs. At the bottom we see a curve representing the lower IOPs experienced by persons with enhanced nutrition as well as low accommodative stimulus, and we see another curve representing the higher IOPs experienced by persons with defective nutrition or ambulation despite low accommodative stimulus.

Accommodative fatigue and IOP elevation. The frequency distribution curves in Figure 3 depict the elevation of IOP associated with an index of accommodative fatigue, as measured on a BCL scale of binocular convergence variance or "looseness."^{18,19}

IOP, scleral distensibility, and myopia. A subtle, chronic elevation in IOP does *not* appear to create an increase in myopia *unless* the sclera is relatively distensible. Thomas Stuart-Black Kelly²⁰ suggested we think of conventional glaucomas as "scleral non-expansion glaucomas" as compared to the conventional high myopia which he has called "scleral-expansion glaucoma"--perhaps to gain increased concern and notoriety and hence increased interest in myopia investigations and for research funding. The scleral distensibility appears too plastic to be fully attributed to the degree of collagen crosslinking. Epidemiological data suggests that scleral distensibility is strongly influenced by calcium nutriture--apparently by calcium complexing with scleral glycosaminoglycans on collagen matrices.

- b) depression of ***calcium*** and of ***calcium in ratio to phosphorus***, not only in blood serum, but also in dietary intake, and evidence of excessive export of calcium from storage tissues [Gardiner's²¹ data, Kolosov,²² Lane^{17,23,24}];

Calcium and scleral distensibility. The evidence points to depression of calcium intake and tissue concentrations as a major factor in the development of scleral distension. Figure 4 is redrawn after Peter Gardiner.²¹ It depicts the widely misinterpreted 1958 Gardiner graph--a graph

which actually showed the prophylactic effect of supplementation with a calcium-fortified, calcium-protein complex [Casilan], but which was unfortunately attributed to an effect of "high-quality protein." High-quality protein conjures the image of muscle proteins--proteins which are high in phosphorus concentration, low in calcium, whereas casilan and milk-product proteins have elevated calcium/phosphorus concentration ratios. The high-quality protein denotation was correct, the conjured connotation misled decades of researchers! In Table 2 we see Lane's early (1978) data documenting calcium and chromium concentrations as risk factors in myopia development.

- c) likely ***export of calcium from complexing with scleral and vitreous glycosaminoglycans*** [Avetísov,15,25-28 Lane24];

- d) disturbance to ***insulin metabolism*** [Kashíntseva, Saiduzaffar, Lane] associated with elevation of intraocular pressure and depression in tissue concentrations of ***glucose-tolerance-factor chromium*** and of tissue concentrations of ***chromium in ratio to vanadium*** [Lane24];
Glucose tolerance-factor chromium (GTF Cr), accommodation, IOP, and myopia development. The effect of GTF Cr putatively is attributed to its role in potentiating insulin receptors and as a catalyst for the conversion of glucose-6-phosphate to glucose-1-phosphate and back again in storing and reaccessing glycogen reserves. Ascorbic acid also contributes to glucose tolerance. Kashíntseva²⁹ and Saiduzaffar³⁰ have independently reported the elevation of IOP as a consequence of disturbance to insulin mechanisms. In 1980 Lane³¹ reported the elevation of IOP associated with depressed tissue concentrations of chromium (Figures 5 and 6).

- e) excessive intake of ***ascorbic acid***, despite its collaboration with chromium in glucose tolerance and despite its contribution to lowering intraocular pressure [Linnér,32 Lane31].

Increased tissue concentrations of chromium [as indexed both in hair (1980)31 and in red blood cells (1988)33] collaborate with ascorbic-acid intake in lowering IOP. Figures 5 and 6 depict the interaction on IOP of accommodative stimulus stress (as represented by the Age-Adjusted Habitual Relative Add) according to parameters of enhanced nutriture as in Figure 5 and enhanced versus deficient nutriture as in Figure 6. Table 5 depicts the effect of depressed chromium concentrations on accommodation as indexed by the Positive Relative Accommodation test of binocular accommodative reserve.]17,19,24,34

It is well known that vitreous liquefaction and the appreciation of vitreous floaters are profoundly more prevalent in high myopes and become incident earlier the higher the myopia[.2,35]{(1,3).} Consequently, it is not remarkable that these very same risk factors associated with myopia progression are indeed statistically associated with vitreous liquefaction and the visibility of vitreous floaters. At issue is whether or not these factors are causative and whether other factors are so strongly related both to fibrillar and non-fibrillar degeneration of the vitreus[.13,36-39] {(2,4-7).}

DESIGN OF THE STUDY

This case-control study included 59 optometric patients, ages 29 through 80, for whom nutrition histories and biomedical tests had been completed. It is the first phase of an ongoing study now tabulating data from more than 200 patients[.36-39] {(4-7).}

For this retrospective study we drew the first 33 patients with vitreous floaters from a chronologically accumulated file of patients. Thirty-one of these patients were judged to have recently incident floaters or recently worsening floaters, and became the cases. All had vitreous floaters visible with direct ophthalmoscopy during the ascension test. The controls were all the remaining patients from the same patient population and time period with the same testing--some 26 patients for whom we could say with some confidence that no floaters were visible on the ascension test[.36-39] {(4-7).}

RESULTS and DISCUSSION

Decreasing myopia or increasing hyperopia.

In this study, eyes decreasing in myopia or increasing in hyperopia were **11** times less likely to present with fibrillar degeneration of the vitreus than all other patients > 40 years old (odds ratio [{}][OR] = 11.1, $p = 0.012$ (by Fisher "Exact Test), with OR 95% confidence interval (CI) = 1.25 to 98.58 for the OR[{}].

Several explanations for the association with myopic change have been proposed in the literature. This new study enlarges the list of possible explanations.

ESOD.

Quite new is our finding{s} that patients with diet-responsive [copper-zinc intracellular] erythrocyte superoxide dismutase (ESOD) < (8.75 units / mg Hemoglobin {Hb}) have OR = **30**--30 times the probability that they will develop ophthalmoscopically-visible aggregates of collagenous, **fibrillar** vitreous floaters than patients with higher ESOD levels., $p = 0.00057$, with 95% confidence interval (CI) = 3.0 to 296.6 [(Table 4)].

Patients (ages 37-80) with emmetropia or myopia and depressed ESOD < 8.75 units/mg Hb appear **55.0X** more vulnerable than all others to fibrillar degeneration of the vitreus [(Table 5)], while emmetropia and myopia alone only convey OR = **4.28** for these same patients.

ESOD and focussed-light energy locus.

Professor Kubêna[,40] in his presentation at the Moscow International Symposium on Myopia, reported on his group's experiments which suggested that light energy focusing in front of the retina within the vitreus, as in [undercorrected] myopia, contributes to thermal effects in the premacular vitreus and the scleral conus region, producing local vitreous liquefaction.

Our preliminary evidence suggests that:

- a) patients whose myopia is habitually "undercorrected" [undercompensated] or whose hyperopia is habitually "overcorrected" when outdoors appear especially vulnerable to fibrillar degeneration, and
- b) the effect likely is light triggered with probable thermal consequences, but especially with chemical consequences resulting in generation of inadequately countered superoxide radicals when superoxide dismutase activity is inadequate.

We have defined the quantity, "**Habitual Relative Daylight Distance Addition (HRDDA)**," as the average excess of positive focal power in diopters for each eye individually, as customarily used outdoors for distance vision in daylight hours or under other high-energy lighting arrangements. An "uncorrected" one-diopter myope, not using compensating lenses outdoors, is defined as having *HRDDA* = +1.00 diopter.

For ages 37-80, for *ESOD* < 5.0 in eyes with *HRDDA* > 0.00 diopter, we find *OR* = 29.57, *p* = 0.0114, *OR* 95% *CI* = 1.26--695.10 for odds favoring fibrillar degeneration, as compared with all other eyes. For *ESOD* < 3.1, estimated *OR* = 105.0, *p* = 0.008, with estimated 95% *CI* = 1.7 to 6465.1, for increased risk of fibrillar degeneration in eyes with positive *HRDDA* [(Table 6)] {(Table 1). }

One explanation suggests that high-energy environmental light focused within the vitreous compartment in the presence of oxygen may be a major risk factor for vitreous syneresis and vitreous floaters when associated with depression of *ESOD*. Unbound oxygen is not normally abundant in the vitreous, and *SOD* is normally abundant in the tissues surrounding much of the vitreous, especially in the cellular retinal interface and the ciliary epithelium, and putatively to some degree within the cellular cortical tissue layer of the vitreous, a 100 to 200 micrometer (μm) thick layer adjoining the retina and ciliary body, but is not believed to be present in the normally acellular remainder of the vitreous[.41] {(8).}

The new relationships highlighted in these tables are, as we have seen, highly significant. They were determined by what we believe to be methods free of investigator bias, but there are several ways in which the data can be improved. For example, we can employ more adequate strategies for estimating focussed solar radiation exposure of the vitreous. However, we shall be more comfortable when the results are replicated. We do have refractive, fibrillar-floater, and *ESOD* data now collected on more than 200 patients, and we shall soon be able to report these additional results. While the data is compatible with an hypothesis that the effect may be partly attributable to *SOD*'s role as a first line of defence in the eye against photo-oxidative insult as to the light-induced generation of superoxide radicals, we need more data points before we can rule out other possible sources of statistical error.

Also, we can recite a litany of other, non-dietary myopia-associated factors which may increase the risk for vitreopathies.

The important message is that depressed ESOD activity is diet responsive, after ascertaining whether the difficulty is attributable to copper or its antagonist zinc, or both--as the minerals that limit the body's ability to synthesize the enzyme.

Quite important are three other risk factors:

1. Calcium/phosphorus ratio. Not counting the intake of less-well utilized supplemental calcium, the effect of depressed intake of food calcium in ratio to food phosphorus is significantly increased risk of vitreous floaters in general, with $OR = 3.5$ [(Table 7)]. All the patients with **non-fibrillar** floaters have especially quite low food calcium-to-phosphorus intake ratios, with a mean of 0.45 [(Table 8)].

A number of studies discussed by Lane[37] {(5)} appear to explain the effect of calcium complexing on conformation and packing of hyaluronate chains and hence of increasing vitreous viscosity[.42-45] {(9-12).}

It may or may not be coincidental that post-menopausal women not only have special problems with calcium metabolism but also are at greater risk of developing vitreous floaters.

2. Ascorbic acid. The vitreus, via the ciliary muscle, is the most effective tissue in the body for concentrating ascorbic acid[.46] {(13).} Here is where too much ascorbic acid first becomes evident and critical.

In nested age-and-gender-matched pairs, $OR = 8$ for increased risk of vitreous floaters with ascorbic-acid supplementation greater than 1500 mg/day (Table 9). This becomes **22.67-fold** increased risk for aggregated collagenous **fibrillar** floaters in women over 40 years old--women taking in more than 1500 mg ascorbic acid daily [(Table 10)]. Men have increased risk of **non-fibrillar** floaters with increased ascorbic-acid intake.

In 1980, Hofmann and Schmut[47] {(14)} reported in their *in vitro* study that SOD can be effective in preventing liquefaction of the vitreous hyaluronic acid, but that it is not effective against *in vitro* ascorbate-induced liquefaction. We are testing the hypothesis that excessive ascorbate intake may

(a) directly affect the vitreus, and/or

- (b) indirectly affect liquefaction by its preventing copper uptake, thereby limiting SOD synthesis, and by its interference both with calcium and chromium uptake and transport.

3. Chromium/vanadium ratio. As noted earlier, chromium potentiates insulin receptors, thereby promoting efficient glucose uptake from the bloodstream, and governs the conversion and reconversion of glucose to glycogen and back again. Vanadium is chromium's principal antagonist.

In age-gender-race matched pairs when chromium concentration is low in ratio to vanadium, OR = 8.0 for increased risk of floaters [(Table 11). In Figure 7], we see the large difference in (red-blood-cell chromium)/(red-blood-cell vanadium) ratios between high myopes with their low chromium-to-vanadium ratios and genuine hyperopes with high ratios.

{We have} [Figure 8 supports] other evidence that chromium uptake is abetted when ascorbate supplementation is between 500 and 1300 mg per day. All the floater cases, except for one female data point, have relatively low chromium-to-vanadium ratios.

A public-health caution is appropriate to advise prudence and to avoid and/or protect against:

- (a) excessive exposure to bright sunlight, sunlamps, or similar intense, high-energy light transmission, at least when normal protective mechanisms (such as SOD concentration and activity) may be compromised;
- (b) excessive supplementation of ascorbic acid;
- (c) excessive, imbalancing supplementation of zinc or copper;
- (d) excessive intake of foods rich in phosphorus (muscle proteins as in meat, fish, poultry, and grain concentrates such as wheat bran); and
- (e) excessive intake of foods rich in vanadium (large marine fish, kelp, commercial poultry, and grain concentrates,, such as wheat bran).

In the interest of public health we need to promote the practice of eating more fresh fruits and fresh vegetable salads.

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