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Abnormalities of human vitreous structure in diabetes

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Abstract. Patients with diabetes experience vitreous degeneration, characterized by "precocious" liquefaction and posterior vitreous detachment. Biochemical studies have detected that hyperglycemia alters vitreous collagen, changes that might be responsible for the observed vitreous degeneration. This study was undertaken to identify if there are morphological changes within the vitreous of diabetic patients that are consistent with the biochemical data and to identify how these could underlie the observed clinical phenomena. Ten eyes from 5 humans (4 normals aged 6, 11, 56, 82; 1 aged 9 with type I diabetes) were obtained at autopsy. Eyes were dissected in the fresh state and studied by dark field slit microscopy without fixatives or dyes. In normals, a transition was observed from a homogeneous structure in youth to one that contained fibers in middle-age, which degenerated and were associated with significant liquefaction in old age. In the diabetic child, the vitreous structure contained prominent fibers whose appearance was similar to middle-aged normals and not the age-matched controls. This study characterizes the morphological manifestations of precocious senescence of vitreous in a patient with diabetes. The abnormal vitreous fibers are likely the result of biochemical changes in collagen that are related to hyperglycemia – a phenomenon that could be inhibited by drug therapy.

Introduction

Diabetes has profound effects on extracellular matrices and connective tissues throughout the body, primarily via non-enzymatic glycation [9] and abnormal cross-linking of collagen [2]. These biochemical changes induce so-called "precocious senescence" of various tissues and organs in the diabetic patient [1, 2, 9, 10].

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It is known that vitreous in diabetic patients undergoes precocious liquefaction and posterior vitreous detachment [5, 20]. Furthermore, abnormal collagen cross-linking and non-enzymatic glycation have been detected in vitreous of diabetic humans [18]. Such destabilization of the molecular network within vitreous contributes to the aforementioned clinical observations. Since new blood vessels arising from the retina grow into the posterior vitreous cortex [4], any structural abnormalities within vitreous could result in traction upon these new blood vessels. Subsequent vitreous hemorrhage and traction retinal detachment are the sequelae causing vision loss in advanced proliferative diabetic retinopathy.

This investigation was undertaken to determine whether structural abnormalities exist within vitreous of patients with diabetes that are consistent with the biochemical changes and the observed clinical abnormalities.

Materials and methods

Morphological analysis

Human eyes were obtained at autopsy and studied within 48 h of death. No fixative or contrast media were employed. The sclera, choroid, and retina were dissected off the corpus vitreous, which was left intact and attached to the anterior segment, as previously described [12, 14, 16]. Using sutures through the limbus, the specimen was mounted on a lucite frame and immersed in a lucite chamber containing an isotonic saline solution.

Dark-field microscopy was performed using a slit-lamp beam to illuminate a horizontal plane through the corpus vitreous. Photographs were taken from above with a 35 mm camera (Nikon F3, Nikon Inc., Japan) and Ilford XP400 film. This approach achieved an illumination-observation angle of 90°, maximizing the Tyndall effect.

Study population

Ten eyes from five subjects were studied with these techniques. Table 1 contains the clinical characteristics of this study population.

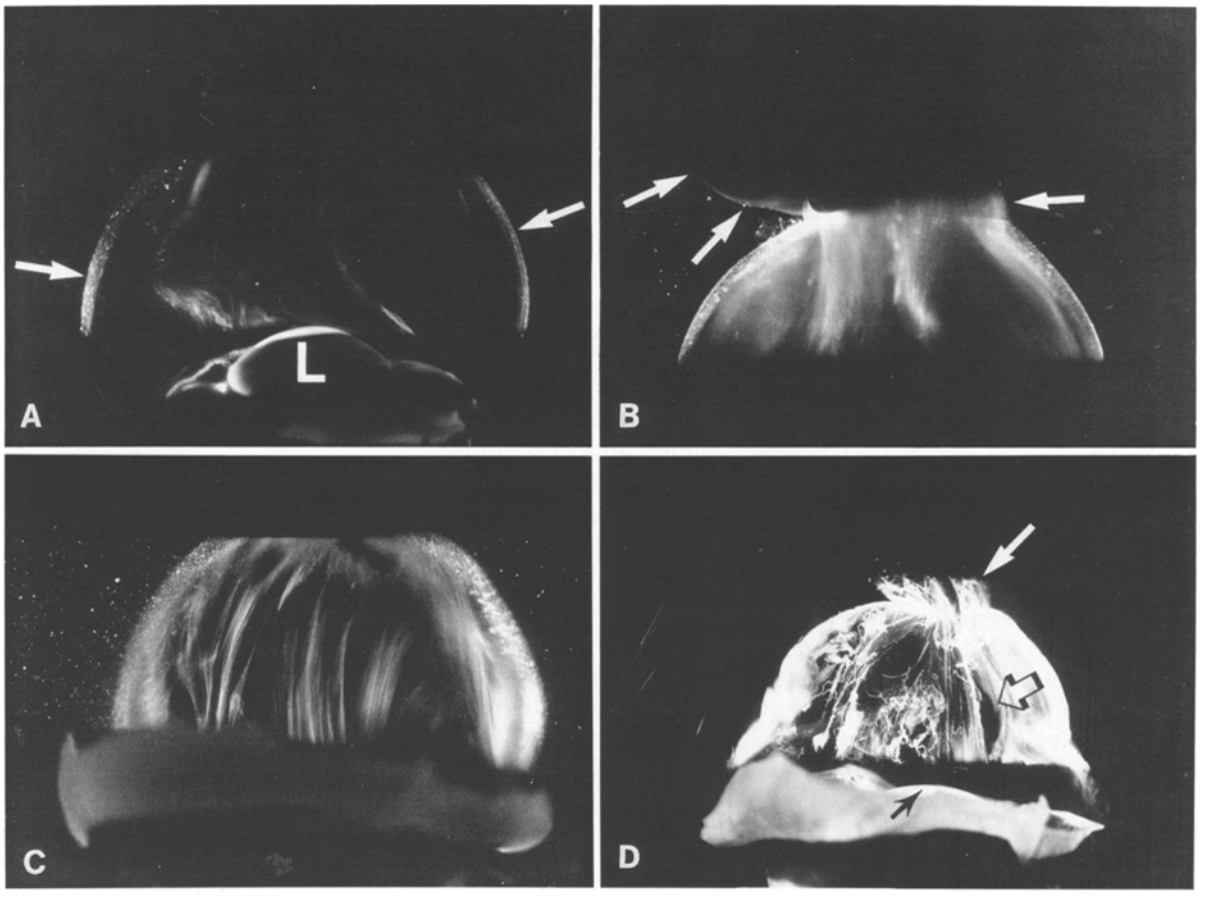

Fig. 1A–D. Dark-field slit microscopy of human vitreous morphology at different stages of life. The anterior segment is below and the posterior pole is above in these optical horizontal sections. (Specimens courtesy of the New England Eye Bank, Boston, Mass.). **A** Whole vitreous in a 6-year-old boy (cause of death: motor vehicle accident) demonstrates a dense vitreous cortex (*arrows*) and no fibers within the corpus vitreous (*L*, lens). **B** Whole vitreous in an 11-year-old boy who died as a result of a head injury. Same findings are noted in Fig. 1A, even though vitreous extrudes out of the posterior vitreous cortex (*arrows*), placing sagittal traction on the central vitreous. **C** Whole vitreous of a 56-year-old woman who died of cardiac arrest. Fibers with an anteroposterior orientation are present in the central vitreous. Adjacent to these fibers are areas devoid of structure, filled with liquid vitreous. **D** Whole vitreous of an 82-year-old white women. The corpus vitreous is collapsed (syneresis) and contains aggregated fibers extruding through the posterior vitreous cortex into the retrohyaloid space (*white arrow*). The central vitreous has lacunae (*open black arrow*) adjacent to the fibers. The *closed black arrow* indicates posterior aspect of lens

Table 1. Clinical characteristics of the study population

Subject	Age	Sex	Ophthalmological history	Medical history	Cause of death
1	6	M	None	None	Motor accident
2	11	M	None	None	Head injury
3	56	F	None	ASHD	Cardiac arrest
4	82	F	None	COPD	Respiratory arrest
5	9	F	None	Diabetes	Trauma

ASHD, Atherosclerotic heart disease; COPD, Chronic obstructive pulmonary disease

Results

Figure 1 demonstrates the appearance of vitreous structure in subjects 1 to 4. The anterior segment is below and the posterior pole is above in all photographs. In young subjects (Fig. 1A, B) the vitreous is quite clear. Only the vitreous cortex scatters incident light, giving the appearance of a dense membranelike structure surrounding the corpus vitreous. No pockets of liquid vitreous ("lacunae") are present.

Figure 1C demonstrates vitreous structure in middleage (subject 3). There are fibers within the central regions that have an anteroposterior orientation. Previous studies [16] have shown that these fibers consist of aggregates of collagen packed in bundles of parallel fibrils. Adjacent to these fibers are areas of liquid vitre-

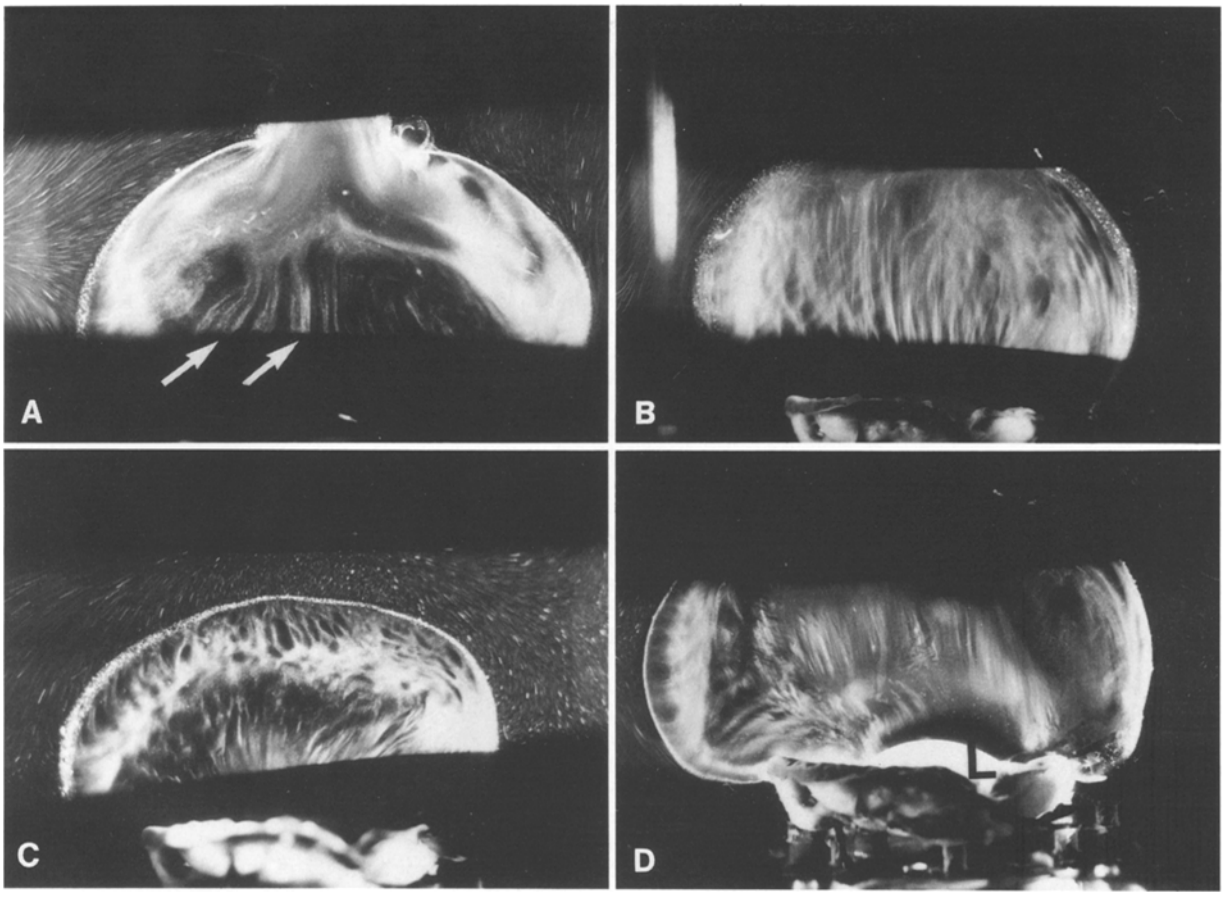

Fig. 2A–D. Whole vitreous in a 9-year-old girl with type I diabetes. (Specimens courtesy of the New England Eye Bank, Boston, Mass.). **A** Right eye shows extrusion of vitreous through the posterior vitreous cortex (at the top of the photograph). The subcortical vitreous appears very dense and scatters light intensely. Centrally, there are vitreous fibers (*arrows*) with an anteroposterior orientation and adjacent areas of liquefaction. **B** Central vitreous in the left eye of same patient shows prominent fibers that resemble those seen in non-diabetic adults (Fig. 1C). **C** Peripheral vitreous in the left eye of same patient shows fibers inserting into the vitreous cortex with adjacent pockets of liquid vitreous. **D** Anterior vitreous in the left eye of same patient shows fiber insertion into the vitreous base about the lens (*L*)

ous that scatter light less intensely than the fibers, due to a relatively low concentration of collagen and a high concentration of hyaluronan and water. This appearance has been associated with the phenomenon of synchisis (vitreous liquefaction) that occurs with aging [13].

Figure 1D shows the appearance of vitreous in an 82-year-old woman (subject 4). There are coarse fibers and pockets of liquid vitreous. The overall size of the corpus vitreous is reduced due to escape of liquid vitreous during collapse (syneresis) of the corpus vitreous – a phenomenon related to posterior vitreous detachment during advanced aging.

Figure 2 shows the appearance of vitreous structure in a 9-year-old girl with a 5-year history of type I diabetes and no diabetic retinopathy (subject 5). In comparison to non-diabetic children of similar ages (Fig. 1A, B), the corpus vitreous of this diabetic subject demonstrates a prominent fibrous structure with liquefaction. The fibers insert into the vitreous base surrounding the lens (Fig. 2D), a finding that has previously been described in non-diabetic humans of middleage [3]. Early lacuna formation is present in the peripheral vitreous (Fig. 2C). The structure of this vitreous is more similar to that observed in vitreous of middleaged (Fig. 1C) and older (Fig. 1D) non-diabetic humans than age-matched controls (Fig. 1A, B).

Discussion

These findings confirm previously described observations of changes in vitreous structure during aging [12]. This study has furthermore detected evidence of fiber formation and liquefaction of vitreous in a young child with diabetes. Vitreous structure in this subject (no. 5) was very different from vitreous structure in non-diabetic children of similar ages (subjects 1, 2) and was similar to vitreous structure in non-diabetic humans of middleage (subject 3).

Such morphologic abnormalities in the corpus vitreous of a child with only a 5-year history of diabetes and no diabetic retinopathy are quite striking. However, studies [6, 19] have shown that 40–52% of children with 5-year duration of diabetes have joint contractures that result in limited joint mobility. This is particularly interesting when one considers that vitreous and articular

cartilage are both composed of type II collagen. Furthermore, there is a strong positive correlation between the extent of limitation in joint mobility and the degree of diabetic retinopathy [11].

The reported morphological findings in vitreous are consistent with clinical observations of vitreous degeneration in diabetes [5, 20]. Such changes are also consistent with the phenomenon of "precocious senescence" of other tissues in diabetic patients. Studies by Hamlin et al. [7] and Monnier et al. [9] have linked the development of precocious aging changes to biochemical abnormalities of collagen related to diabetes and hyperglycemia. The findings in vitreous presented herein may also be the result of abnormal collagen cross-linking and nonenzymatic glycation of vitreous, phenomena that have been identified in diabetic patients [18] and that have been described as the cause of collagen fibril aggregation in other tissues [1].

Further elucidating the molecular events underlying this process is important in view of the role that vitreous synchisis (liquefaction) and syneresis (collapse) can play in exacerbating proliferative diabetic retinopathy. New vessels that have grown into the vitreous cortex prior to these developments will experience traction, inducing vitreous hemorrhage and/or traction retinal detachment. Therapeutic regimens designed to inhibit or limit the degree of vitreous degeneration in diabetes could thus have salubrious effects in preventing severe visual loss, since studies have shown that separation of the vitreous cortex from the internal limiting lamina of the retina is associated with these blinding sequelae [8]. Alternatively, an innocuous method to induce posterior vitreous detachment prior to the growth of new vessels into the posterior vitreous cortex could be very beneficial as preventive therapy. This concept is supported by the findings [21] that new vessels that grow in areas where vitreous is already detached have an "abortive" appearance and are not likely to be clinically significant. Indeed, part of the therapeutic effect of panretinal laser photocoauglation may be the induction of posterior vitreous detachment [17], so that any subsequent neovascularization will not be able to grow into the vitreous cortex, thus having a better prognosis.

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