Decreased formation of aqueous humour in insulin-dependent diabetic patients

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SUMMARY The rate of aqueous humour formation was measured by fluorophotometry in 34 insulin-dependent diabetic patients and 12 non-diabetic controls to determine whether or not aqueous flow in diabetics differed from that of normal controls, and whether or not aqueous flow among diabetics was correlated with the stage of retinopathy. Diabetic patients were divided into three groups based on the degree of retinopathy; group I without retinopathy, group II with minimal to moderate non-proliferative retinopathy, and group III with proliferative retinopathy. Aqueous flow (mean, SD) in diabetic patients was: 1.55 (0.32) $\mu\text{l}/\text{min}$ in group I, 1.51 (0.47) $\mu\text{l}/\text{min}$ in group II, and 1.26 (0.39) $\mu\text{l}/\text{min}$ in group III. No statistically significant difference was found among these three diabetic groups. Aqueous flow in the non-diabetic controls was 2.18 (0.40) $\mu\text{l}/\text{min}$, and this was statistically significantly greater than in each of the diabetic groups. Intraocular pressure, age, duration of diabetes, haemoglobin A_{1C}, and blood glucose levels had no significant effect on aqueous flow in diabetic patients.

Several studies have found that diabetic patients without retinopathy have higher intraocular pressure (IOP) than those with retinopathy, in particular, proliferative retinopathy.¹⁻⁴ We believe there has been no report on the rate of aqueous formation in diabetic patients. The purpose of this study was to investigate whether or not the degree of diabetic retinopathy is associated with an altered rate of aqueous humour formation. We also looked at possible effects of other variables on aqueous flow in diabetic patients such as IOP, age, duration of diabetes, haemoglobin A_{1C}, and blood glucose levels.

Material and methods

Thirty-four insulin-dependent diabetic patients without rubeosis iridis were included in this study. Their mean age (SD) was 36.6 (11.3) years. The duration of diabetes ranged from eight to 33 years, mean 17.3 (6.3) years. Twelve normal controls with mean age 33.1 (5.5) years were also studied.

On the morning of the fluorophotometric study to determine aqueous flow one drop of fluorescein

solution (Fluress) was applied to each eye every five minutes for a total of 10 applications. Four and a half hours after the last drop of fluorescein was applied, fluorophotometric measurements with a Fluorotron Master (Coherent; Palo Alto, CA) of the fluorescein concentrations in the cornea and anterior chamber were begun and were repeated at 30-minute intervals over two and a half hours. After the last fluorophotometric measurement the IOP was measured with a pneumatonometer (Alcon; Fort Worth, TX). Aqueous flow was calculated by the Jones and Maurice method modified by Yablonski and associates.⁵

In diabetic patients venous blood was drawn for the determination of haemoglobin A_{1c} (n=31). Blood glucose levels were determined by averaging values of the venous blood obtained at the completion of the fluorescein eye drops and at each fluorophotometric measurement (n=26).

The pupils of the diabetic patients were dilated after fluorophotometry and the fundi were examined by ophthalmoscope by one of the authors (MEY). Multiple field retinal photographs were also obtained in 20 of the diabetic patients and classified in a masked fashion by MEY. Patients were classified according to the degree of retinopathy: group I with no retinopathy, group II with non-proliferative

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Table 1 Aqueous flow and variables in diabetic patients

	No. of patients				Aqueous flow* ($\mu\text{l}/\text{min}$)
	Total	Group			
		I	II	III	

IOP (mm Hg)					
<15	20	6	10	4	1.44 (0.43)
≥ 15	14	3	8	3	1.50 (0.50)
Age (years)					
19-30	11	3	4	4	1.30 (0.40)
31-45	16	4	10	2	1.60 (0.47)
46-65	7	2	4	1	1.44 (0.24)
Duration of diabetes (years)					
1-15	17	4	12	1	1.50 (0.45)
16-33	17	5	6	6	1.40 (0.39)
HbA _{1c} (%)					
<7.5	16	4	9	3	1.47 (0.49)
≥ 7.5	15	3	8	4	1.39 (0.36)
Average blood glucose (mg/dl)					
<160	10	1	7	2	1.63 (0.35)
≥ 160	16	6	7	3	1.52 (0.38)

*Values are means (SD).

retinopathy, and group III with proliferative retinopathy.

None of the patients or controls had been on beta blockers or carbonic anhydrase inhibitors either systemically or topically for at least four weeks before the study. None took any eye medications on the day of the study, and their insulin doses were given as usual.

Results

In no instance did the classification of photographs differ from that of the funduscopic examination. In 24 diabetic patients both eyes were classified as belonging to the same group. Eight patients had one eye in group I and the other eye in group II, and two patients had one eye in group II and the other in group III. Since no statistically significant difference was found in IOP and aqueous flow between the two eyes of these 10 patients whose classification fell into two groups, they were classified according to the worse eye. The numbers of patients in each group were, 9 in group I; 18 in group II; and 7 in group III. In all subjects the values of the IOP and aqueous flow of both eyes were averaged and treated as one eye.

The mean (SD) aqueous flow in normal controls was 2.18 (0.40) $\mu\text{l}/\text{min}$. In groups I, II, and III of the diabetic patients aqueous flow was 1.55 (0.32) $\mu\text{l}/\text{min}$, 1.51 (0.47) $\mu\text{l}/\text{min}$, and 1.26 (0.39) $\mu\text{l}/\text{min}$, respectively. All the three diabetic groups showed aqueous flow values statistically less than that in the control group ($p < 0.05$, Student's *t* test). Aqueous flow in each diabetic group, though having a trend of

decreasing rate with increasing severity of retinopathy, showed no statistically significant difference among groups ($p > 0.05$, analysis of variance).

IOP, age, duration of diabetes, haemoglobin A_{1c}, and blood glucose levels had no significant effect on aqueous flow ($p > 0.05$, Student's *t* test, Table 1). The IOP was found not to be related to the degree of retinopathy ($p > 0.05$, Fisher's exact test, Table 1).

Five patients in group III had previous panretinal photocoagulation (PRP) for proliferative retinopathy. Three patients received PRP in one eye and two in both eyes. Aqueous flow in eyes with PRP was 1.30 (0.49) $\mu\text{l}/\text{min}$ compared with 1.21 (0.36) $\mu\text{l}/\text{min}$ in eyes without PRP in group III. This difference was not statistically significant ($p > 0.05$, Student's *t* test).

Discussion

A statistically significant decrease in aqueous humour formation was found in diabetics, and this decrease was not significantly affected by the degree of retinopathy. Aqueous flow was also unrelated to the duration of diabetes, age of patients, haemoglobin A_{1c}, average blood glucose levels, and IOP. There was no significant difference in IOP between the diabetic groups with and without proliferative retinopathy. It has been suggested¹⁴ that a raised IOP may tend to protect against the onset and progression of retinopathy. However, Valone *et al.*,⁶ studying eyes with initially non-proliferative retinopathy, found that eyes with a raised IOP progressed to proliferative retinopathy as frequently as eyes with a normal IOP.

Although the number of subjects in this study may not have been large enough to detect small differences, these findings suggest that the decrease in aqueous flow may be secondary to a fundamental alteration in the physiology of the diabetic eyes. Many possible explanations exist.

The formation of aqueous humour by the ciliary body is largely an active process, requiring energy. Therefore, ischaemia of the ciliary body might be expected to decrease aqueous flow. It seems likely that the diabetic eye suffers from ischaemia because of a variety of circulatory abnormalities in diabetics, including a generalised angiopathy,⁷ an increased blood viscosity,^{8,11} and impaired oxygen release by the red blood cells due to decreased 2,3-diphosphoglycerate (2,3-DPG) and increased glycosylated haemoglobin.¹² A generalised abnormality of transport processes¹³ in diabetes may affect the ciliary body as well. Na⁺-K⁺ ATPase is related to active secretion of aqueous humour in the ciliary body, and insulin has been shown to affect the activity of this enzyme.¹³ Generalised neuropathy is common in diabetics¹⁴ and it may also affect the

ciliary body, which is innervated by the sympathetic nervous system.¹⁵

A reduced rate of aqueous flow leads to decreased delivery of nutrients to and decreased removal of metabolic wastes from avascular tissues such as the lens and trabecular meshwork. Therefore the decreased flow of aqueous humour in the insulin-dependent diabetic eye may possibly be related in part to some common diabetic ocular sequelae such as the greater incidence of cataract¹⁶ and primary open-angle glaucoma.³ Furthermore, it might predispose to the development of rubeosis iridis by impeding the washout of vasoproliferative factors released by the retina.¹⁷

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