Changes in Refraction Caused by Induction of Acute Hyperglycemia in Healthy Volunteers

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Purpose: To determine whether the myopic changes and ocular hypotension after a glucose load are caused by hyperglycemia.

Methods: Oral glucose tolerance tests were conducted on seven healthy young subjects with normal vision. The changes in the hematologic parameters and the refractive system were measured periodically for 150 minutes after the glucose load.

Results: After the glucose load, there was an increase in plasma glucose level and the level of plasma osmosis, ocular hypotension, a myopic change in refractive power, shallowing of the anterior chamber, and a thickening of the lens. The degree of the myopic change exceeded the power of the residual accommodation. Normalization of the plasma glucose level led to a normalization of the intraocular pressure and a reversal of the myopic changes.

Conclusions: These findings suggest that the myopic changes that accompanied hyperglycemia were caused by a thickening of the lens resulting from a decrease in the tension of the zonule fibers of Zinn, and were secondary to ocular hypotension. Hyperopia appeared to be caused by the reversal of the myopia after normalization of plasma glucose levels. **Jpn J Ophthalmol 1999;43:398–403** © 1999 Japanese Ophthalmological Society

Key Words: Glucose load, hyperglycemia, IOP, lens, myopia.

Introduction

Diabetes mellitus causes a variety of disorders in visual function including refractive changes and accommodative disorders. In a previous study, we observed changes in the refractive accommodative system, ocular hypotension, and myopic changes after mannitol loading in healthy young people.[1] In this study, there was shallowing of the anterior chamber and thickening of the lens despite the prior administration of a cycloplegic agent. We pointed out that the molecular weights of mannitol and glucose are similar. In other studies on diabetic patients, refractive abnormalities were evaluated and a change in the crystalline lens was noted.[2] These phenomena led

us to consider that the curve of the crystalline lens may increase even though the ciliary muscle is unaffected in diabetes mellitus. We were not certain, however, whether the change in the lens in the previous experiments was related to morphologic alterations or to the ocular hypotension induced by mannitol.

To evaluate the effect of hyperglycemia on refractive changes in the present study, we first administered a cycloplegic agent to healthy volunteers followed by a glucose load with somatostatin pretreatment. Insulin secretion was partially suppressed by administering somatostatin. Changes in the refractive accommodative systems were then evaluated.

Subjects and Methods

We evaluated the refractive accommodative system in healthy Japanese volunteers, five men and two women with normal vision and normal accommoda-

tive powers. The average age was 23.2 ± 4.5 years (range 18–29), and their average weight was 62.8 ± 13.6 kg. Written informed consent was obtained from participants after we had informed them of the purpose of the study, the method of testing, side effects of drug administration (eg, the cycloplegic agent), and the countermeasures that we could take. Each subject was given an interview, physical examination, blood pressure measurement, general evaluation of hematologic and biochemical parameters, and electrocardiography.

The cycloplegic agent was 1% cyclopentolate hydrochloride. The glucose loading agent, Toleran G (Takeda, Osaka), was used at the 75 g oral glucose tolerance test level. To suppress endogenous insulin secretion during glucose loading, we administered the synthetic somatostatin, Sandostatin (Novartis, Basel, Switzerland). This agent has been shown to be nontoxic and safe in previous clinical studies,[3] and it was approved for use in this study by the Ethics Committee of Oita Medical University.

Each subject received 4 drops of 1% cyclopentolate hydrochloride in each eye, with 3 drops given at 5-minute intervals and the fourth drop administered 30 minutes later. Somatostatin (100 μg) was injected subcutaneously 30 minutes before the glucose load. After the oral glucose load was administered, the blood was sampled periodically for 150 minutes.

For evaluating the effects of the glucose load, we measured the levels of blood sugar and the endocrine insulin. We then evaluated seven ocular functions considered to relate to the refractive accommodative system: (1) the intraocular pressure determined with a Goldmann applanation tonometer; (2) the visual acuity determined by the Landolt chart; (3) the refraction determined by an objective method using an autorefractometer (ARK-2000; Nidek, Tokyo), and the subjective visual acuity was corrected according to the objective data; (4) the accommodative power determined by an accommodative polyrecorder (NS-9E; Kowa, Tokyo); (5) the curvature of the cornea determined with a keratometer (ARK-2000; Nidek, Tokyo); (6) the depth of the anterior chamber measured with a Haag-Streit pachometer; and (7) the axial length, anterior chamber depth, lens thickness, and vitreous cavity length determined by ultrasonic biometry (Alpha 20/20; Storz, Claremont, CA, USA). The first four factors assessed the functional characteristics, and the last three factors evaluated the morphological characteristics of the eye. We measured these parameters before and at 30-minute intervals for 150 minutes after glucose administration, the instillation of cyclopentolate hydrochloride, and the subcutaneous injection of synthetic somatostatin.

Data are reported as mean ± standard deviation. The significance of the differences in the pre- and post-glucose loading for each variable was tested by the paired t-test. The biochemical data recorded before and after glucose loading were compared using an unpaired t-test. A level of $P < .01$ was considered statistically significant.

Results

Blood Sugar and Insulin Levels After Glucose Administration

Changes in blood sugar and insulin levels after glucose administration are shown in Figure 1. The subcutaneous injection of Somatostatin reduced the insulin level for 180 minutes to below the normal basal level of secretion of 12 μU/mL. Somatostatin did not cause significant adverse systemic symptoms in any of the seven participants, as shown in the evaluations made 180 minutes after subcutaneous injection.

After the glucose load, the mean blood sugar level rose significantly from 70.0 to 279.3 mg/dL ($P < .01$; Table 1). Although the insulin level also showed an increase, it was still within the range of basal secretion. No significant changes occurred in the total protein, blood urea nitrogen, and sodium levels, but the typical marked rise in the plasma osmotic pressure was observed (Figure 2).

Ocular Changes After Glucose Administration

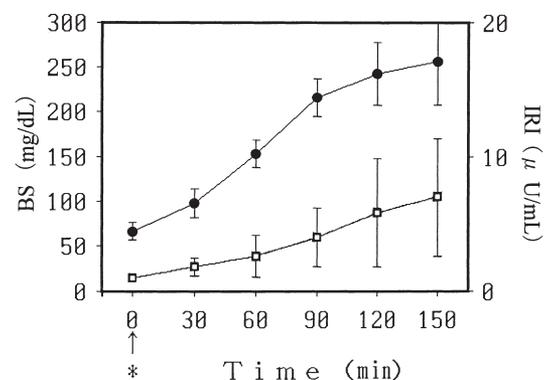**Functional parameters.** Changes in intraocular pressure, plasma osmotic pressure, and refraction

Figure 1. Changes in blood sugar (BS) and levels of endocrine insulin (IRI). Closed circles: BS levels (n = 7); open squares: IRI levels (n = 7). IRI was suppressed below level of basal secretion. BS increased after glucose administration. Error bars are ±SD. *Start of administration of oral glucose load (75 g).
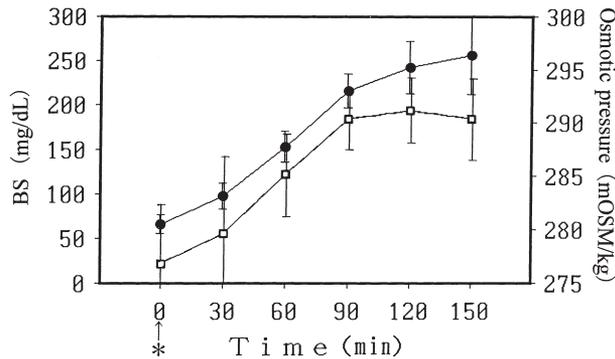
Figure 2. Changes in blood sugar (BS) and plasma osmotic pressure. Closed circles: BS levels (n = 7); open square: osmotic pressure (n = 7). BS levels and osmotic pressure rose almost simultaneously. Error bars are ±SD. *Start of administration of oral glucose load (75 g).
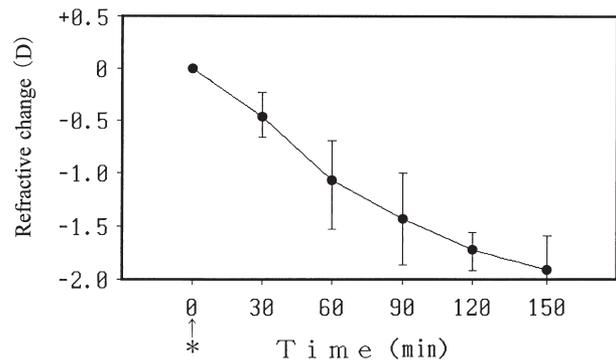

Figure 4. Changes in refractive error (n = 14). Average change of −1.93 D in refractive disorder was observed 150 minutes after glucose load despite instillation of cyclopentolate. Error bars are ±SD. *Start of administration of oral glucose load (75 g).

from the period just before to 150 minutes after the glucose load are shown in Figures 3 and 4. Changes in intraocular pressure and refraction are expressed in terms of the change from the baseline levels. Whereas the plasma osmotic pressure rose from a mean of 277.9 to 294.9 mOsm/kg, the mean intraocular pressure fell by 6.9 mm Hg. In all subjects, the corrected visual acuity and corneal curvature were unchanged after the glucose load. Despite the instillation of cyclopentolate hydrochloride, we observed a mean change in refraction of −1.93 diopters (D).

Morphologic Changes. The values for the depth of the anterior chamber determined by pachometry and ultrasonic biometry are shown in Table 1. No significant differences were noted in the values obtained by the two methods before and after the glu-

cose load. Because the results of ultrasonic biometry closely matched those observed with pachometry, only the values obtained by ultrasonography were used in our analysis of the morphological changes of the eye.

Ultrasonic biometry showed that the depth of the anterior chamber decreased and the thickness of the lens increased significantly 150 minutes after the glucose load. There were no significant changes in the vitreous cavity or axial length (Figure 5). The overall findings are summarized in Table 2.

We conclude that the −1.93 D myopic change was probably not caused by ciliary muscle contraction because the mean residual accommodation averaged only 0.65 D after the instillation of cyclopentolate hydrochloride. We further conclude that the myopic changes resulted from a thickening of the lens, based on the observed decrease in the depth of the anterior chamber and the thickening of the lens.

The changes over time are shown in Table 3. Six hours after the glucose load, the blood glucose level, refractive changes, plasma osmosis, and the intraocular pressure all returned to normal.
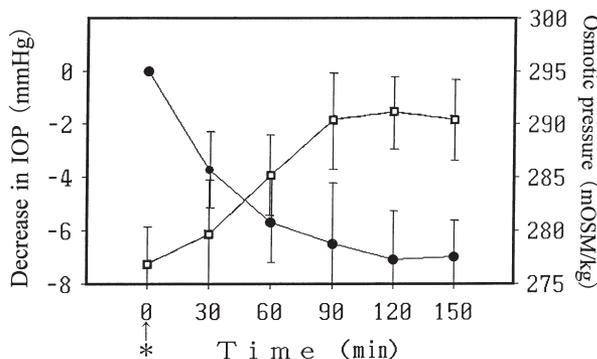
Discussion

Several reports have described the refractive changes associated with elevated or depressed blood glucose levels. Myopic changes resulting from a rise in the blood glucose level and hyperopic changes resulting from a fall in the blood glucose level have been reported previously.[4] However, these reports did not identify the mechanisms involved. Refractive disorders have been reported to vary according to the type of disease, degree of glucose tolerance, and

Figure 3. Changes in plasma osmotic pressure and intraocular pressure (IOP). Closed circles: IOP (n = 14); open square: osmotic pressure (n = 7). Whereas plasma osmotic pressure rose, IOP fell by −6.9 mm Hg. Error bars are ±SD. *Start of administration of oral glucose load (75 g).

Table 1. Major Changes in Clinical Parameters of 14 Eyes of 7 Subjects

Parameter	Before Glucose Load	150 Minutes Later
BS (mg/dL)*	70.0 ± 9.87	279.3 ± 40.9
IRI (μU/mL)*	2.0 ± 1.15	9.33 ± 4.35
Plasma osmosis (mOsm/kg)*	277.9 ± 6.8	294.9 ± 3.4
Total protein (g/dL)	7.06 ± 0.35	6.93 ± 0.33
BUN (mg/dL)	12.8 ± 1.4	12.5 ± 1.7
Na (mEq/L)	137.1 ± 1.4	135.9 ± 1.7
	Data above: (n = 7 persons)	
	Data below: (n = 14 eyes)	
Depth of anterior chamber* (Pachomatry) (mm)	3.78 ± 0.11	2.61 ± 0.45
Depth of anterior chamber* (Ultrasonic biometry) (mm)	3.97 ± 0.42	2.75 ± 0.56

BS: blood sugar (glucose); IRI: endocrine insulin; BUN: blood urea nitrogen; Na: blood sodium.
*$P < .01$

methods of treatment.[2,5–8] For these reasons, we studied the effects of reproducible hyperglycemia in healthy men and women while minimizing the systemic effects. For instance, the administration of a glucose load leads to hyperglycemia in a patient with glucose intolerance, but this does not occur in a healthy person. In the latter, the insulin level is increased by the glucose load and hyperglycemia is not induced. Therefore, in the present study of healthy subjects, we used somatostatin in conjunction with the glucose load to induce hyperglycemia. Somatostatin inhibits insulin secretion and can be administered safely to healthy people.[3] There are no reports of refractive disorders as a side effect of this agent.

Under these conditions, the glucose load produced an adequate degree of hyperglycemia in healthy sub-

jects. Although the plasma osmotic pressure rose at the same time, other biochemical parameters showed no significant changes. Therefore, the elevation of plasma osmotic pressure was considered to be related to the rise in blood glucose concentration. The molecular weight of glucose is 180, which is similar to that of the osmotic diuretic mannitol, 182. The rise in osmotic pressure (28–42 mOsm/kg) induced by the intravenous infusion of mannitol is equivalent to a rise in blood glucose level of 300–600 mg/dL.[9] The increase in the blood glucose over time was paralleled by the rise in the osmotic pressure. Therefore, the rise in osmotic pressure resulted from an increase in the concentration of plasma glucose, which was not affected by insulin levels because of the prior somatostatin administration.

A nearly saturated plasma glucose concentration was attained under these conditions. Glucose remains in the extracellular fluid and essentially does not move into the intracellular fluid. Havener described a similar phenomenon.[10] Thus, the induction of transient hyperglycemia induced an increase of osmotic pressure in our healthy subjects.
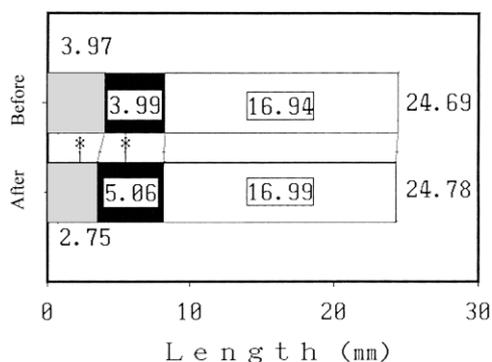

Figure 5. Echographic changes observed before and after glucose loading (n = 14). Mean depth of anterior chamber was significantly decreased from 3.97 ± 0.45 to 2.75 ± 0.56 mm. Mean lens thickness was significantly increased from 3.99 ± 0.46 to 5.06 ± 0.51 mm. There was no significant difference in vitreous cavity or axial length. Error bars are ±SD. White: vitreous cavity length; gray: depth of anterior chamber; black: lens thickness.

Table 2. Changes in Clinical Data Variables 150 Minutes After Glucose Loading

Variable	Difference From Pretreatment Level	
Decrease in intraocular pressure	−6.9 ± 1.7*	(mm Hg)
Refractive change (myopia)	−1.93 ± 0.39*	(D)
Residual accommodative power	0.65 ± 0.16	(D)
Anterior chamber shallowing	−1.21 ± 0.50*	(mm)
Lens thickening	1.14 ± 0.41*	(mm)

Note. Significant changes after glucose loading (n = 14 eyes).
*$P < .01$.

Table 3. Changes in Clinical Data Variables 300 Minutes After Glucose Loading

Variable	Before Glucose Load	300 Minutes Later
BS (mg/dL)	70.0 ± 9.87	96.0 ± 24.8
IRI (μU/mL)*	2.0 ± 1.15	2.7 ± 3.94
Plasma osmosis (mOsm/kg)	279.4 ± 5.9	279.2 ± 6.5
	Data above: (n = 7 persons)	
	Data below: (n = 14 eyes)	
Intraocular pressure (mm Hg)	14.0 ± 1.89	12.4 ± 1.40
Refractive error (D)	−0.26 ± 0.27	−0.46 ± 0.39

*P < .01.

In evaluating the ocular changes that occurred during the period of high osmotic pressure, we emphasize the following two points. First, we instilled cyclopentolate hydrochloride gradually into the eye so as to minimize its effects on the autonomic nervous system. Second, we studied young subjects to exclude the effect of aging on the accommodative function of the lens. Each subject demonstrated a low level of lens nuclear sclerosis and had normal accommodative power.

Two particularly noteworthy findings emerged: (1) the intraocular pressure fell in conjunction with the increase in the blood glucose level, and (2) myopic changes occurred in spite of the pretreatment with cyclopentolate hydrochloride. We can infer that the drop in intraocular pressure can be ascribed to the rise in plasma osmotic pressure.

The myopic changes virtually paralleled the rise in osmotic pressure and the drop in intraocular pressure. The myopic changes exceeded the reduction in accommodative power to 0.65 D, caused by the instillation of cyclopentolate hydrochloride. Thus, myopic changes occurred in the hyperopic eyes that had low accommodative power caused by the prior instillation of cyclopentolate hydrochloride, complicated by the ocular hypotension caused by hyperglycemia.

The present findings resembled the myopic changes previously reported to be induced by the administration of mannitol.[1] The morphologic data revealed no major changes in the axial length or corneal curvature after the glucose load. Therefore, the myopic changes were most likely caused by the thickening of the lens with an anterior shift of the anterior pole of the lens resulting in a shallowing of the anterior chamber. Although we observed the lens thickening and anterior chamber shallowing to a similar degree in these healthy subjects, a previous study of diabetic patients reported that hyperopia appeared while the lens thickened during their treatment.[2] These authors

suggested that the lens cortex swelled because of biochemical changes, and that the hyperopia was caused by a change in the refractive index of each cortical layer.

In the present study, the anterior pole of the lens showed an anterior shift after the increase in blood glucose level. However, myopic changes resulted. Our subjects were young, which means that there should be little change in the lens nucleus resulting from aging. Also, the glucose load was administered over a short period of time and the blood sugar returned to normal in about 6 hours. Even if the lens cortex had become swollen, the refractive index of the cortex exceeded the aqueous index, and the refractive changes were myopic and caused a shift in the lens anterior pole. Therefore, it is unlikely that the biochemical changes in each lens layer were responsible for the low refractive changes (hyperopia).[11,12] Instead, we believe that the thickening of the lens was due to the viscoelasticity that is peculiar to the juvenile lens, and the thickening led to the high refractive change (myopia).

What then is the mechanism for the myopic change observed in subjects with hyperglycemia? One possibility is the thickening of the lens caused by a relaxation of the zonule of Zinn induced by ocular hypotension. In a previous study on the effects of controlling the tension of the choroidal membrane of animal eyes in vitro, a rise in intraocular pressure produced choroidal tension, which led to a decrease in the refractive power of the lens.[13,14] That would suggest that a tractional force on the zonule of Zinn through the choroid was present. If the presence of zonular tension through the choroid is generated by normal intraocular pressure, this pressure would lead to ocular hypotension and zonular tension would decrease. That decrease would in turn reduce the radius of the lens curvature and increase the anterior shift of the lens anterior pole.[15,16] The above did not result in ciliary muscle contraction, but did produce relaxation of the zonule of Zinn, and subsequently caused a thickening of the lens. In light of our previous report, it appears that normal intraocular pressure is associated with the generation of tension in the zonule of Zinn via the choroid.

In the present study, the blood glucose level returned to normal after the glucose tolerance test, and the previously lowered intraocular pressure returned to normal about 6 hours later. At the same time, the changes in refraction and the myopic changes were reversed, returning to baseline, ie, a hyperopic reversal phenomenon occurred. These results suggest that the hyperopia indicated a recovery

of the myopic changes accompanying the reversal of the hyperglycemia.

In evaluating refractive disorders in patients with diabetes mellitus, one must be aware that hyperglycemia can alter intraocular pressure as well as the refractive index.

References

1. Furushima M, Imaizumi M, Nakatsuka K. Changes in refraction in cycloplegic eyes following systemic hyperosmotic mannitol. Rinsho Ganka (Jpn J Clin Ophthalmol) 1992;46:829–32.

2. Saito Y, Ohmi G, Kinoshita S. Transient hyperopia with lens swelling at initial therapy in diabetes. Br J Ophthalmol 1993;77:145–8.

3. Tanaka K, Kumagai M, Morio K, et al. Single administration of somatostatin analogue, SMS 201-995 in healthy subjects. Journal of Clinical Therapeutics and Medicines 1988;4:365–91.

4. Duke-Elder S. Changes in refraction in diabetes mellitus. Br J Ophthalmol 1925;9:167–87.

5. Dobbs RE, Smith JP, Chen T. Long-term follow up of lens changes with Scheimpflug photography in diabetes. Ophthalmology 1987;94:881–90.

6. Fledelius HC. Refractive change in diabetes mellitus around onset poorly controlled. Acta Ophthalmol 1987;65:53–7.

7. Fledelius HC, Miyamoto K. Diabetic myopia—is it lens induced? Acta Ophthalmol 1987;65:469–73.

8. Riordon EP, Pascoe PT. Refractive change in hyperglycemia: hypertropia, not myopia. Br J Ophthalmol 1982;66:500–5.

9. Barry KG, Khoury AM. Mannitol and isosorbide. Arch Ophthalmol 1969;81:695–700.

10. Havener WEH. Ocular pharmacology, 4th ed. St Louis: CV Mosby, 1978, 440.

11. Jacob TJC, Duncan G. Glucose-induced membrane permeability changes in the lens. Exp Eye Res 1982;34:445–53.

12. Plonen JTH. Changes of refraction in the adult eye due to changing refractive indices of layers of lens. Ophthalmologica 1981;183:86–90.

13. Kamikawatoko S, Tokoro K, Azuma H, Imai S, Ishida A. Mechanical characteristics of the bovine choroid. Nippon Ganka Gakkai Zasshi (J Jpn Ophthalmol Soc) 1994;98:733–7.

14. Kamikawatoko S, Tokoro K, Sogo K, Imai S, Ishida A, Azuma H. Simultaneous measurement of the tension, elongation and refractive power of the bovine lens zonule. Nippon Ganka Gakkai Zasshi (J Jpn Ophthalmol Soc) 1996;100:660–4.

15. Brown N. The change in shape and internal form of the lens of the eye on accommodation. Exp Eye Res 1973;15:441–59.

16. Obstfeld H. Crystalline lens accommodation and anterior chamber depth. Ophthalmic Physiol Opt 1989;9:36–40.