Peer reviewed article

Transient hyperopic refractive changes in newly diagnosed juvenile diabetes

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Summary

Purpose: To investigate transient hyperopic refractive changes in newly diagnosed juvenile diabetics and to evaluate their clinical course after starting intensive glycemic control of severe hyperglycemia.

Methods: 20 hyperopic adolescents with newly diagnosed and uncomplicated type 1 diabetes, selected for this prospective study, were enrolled for a baseline examination and, after starting intensive insulin treatment, followed every two weeks during a four-month follow up. Standardised automated refraction and A-mode ultrasonography were performed. Poor metabolic control was an inclusion criteria.

Results: Refractive changes and hyperopic peaks preceded the start of the intensive insulin therapy in all diabetics and, therafter, refraction decreased gradually with a maximum recovery time of 94 days. A statistically significant positive correlation between refractive changes and magnitude of plasma glucose concentrations as well as HbA_{1c} percentages was observed (P <0.001). No significant modifications in the explored refractive components were recorded.

Conclusions: Transient hyperopic changes are highly dependent on the magnitude of plasma glucose concentrations and rapid correction of hyperglycemia is strictly correlated with complete recovery of refraction. To account for this phenomenon, the sorbitol production via the polyol pathway with overhydration of the lens remains the best pathophysiological hypothesis at this time.

Key words: adolescence; diabetic retinopathy; hyperopia; juvenile diabetes; refraction

Introduction

Transient refractive changes are well recognised features of diabetes [1–11] and ophthalmologists should always check for diabetes mellitus in any case of a rapidly changing refraction.

According to Duke-Elder, myopia is more often associated with hyperglycemia and hyperopia with hypoglycemia [1]. However, while Gwinup et al. confirmed this theory 50 years later [2], most other investigators suggested that elevations of blood glucose will cause hyperopia, not myopia [3–8, 10, 11]. In particular, hyperopia was reported to develop a mean of 3.4 ± 2.0 days after starting intensive insulin treatment, to progress to maximum at 10.3 ± 6.1 days and to return gradually to the baseline value between 14 and 84 days after the initial assessment [11]. However, in a first trial conducted some years ago, we found diverging results, not confirming this hyperopic increase shortly after starting intensive glycemic control [8].

Moreover, the biological basis of refractive changes in diabetic eyes has not yet been established, and the underlying mechanism is still unkown.

In the light of all these findings, the aim of the present study was to investigate transient refractive changes in a well characterized group of newly diagnosed and uncomplicated juvenile diabetic patients, and to evaluate their clinical course after starting intensive insulin treatment.

Materials and methods

Twenty highly selected postpubertal diabetic adolescents (40 eyes; 11 male and 9 female; mean age = 16.80 ± 1.3 years; range = 15–19 years), attending the Center for the Study of Diabetes (Institute of Internal Medicine II, University of Rome "La Sapienza") and classified according to the National Diabetes Data Group criteria [12], were enrolled. Selection was made by the same diabetologist and ophthalmologist on the basis of the following in-

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clusion criteria: newly diagnosed and still untreated type 1 insulin-dependent diabetes mellitus (IDDM) as evidenced by deficient C-peptide secretion; duration of the disease shorter than 1 day; poor metabolic control (HbA_{1c} >9%). In order to test a homogenous group, thus avoiding any interference by selection bias, only patients complaining of sudden blurred vision with their own glasses and showing, on admission (T0), a current prescription >+0.50 D were included in this study. Onset time of a refractive change was defined as the day on which there was a change of +0.50 D or more compared with the patient's current prescription at T0, while peak time and recovery time indicated the days on which the maximum hyperopic change and the recovery of the previous refraction were recorded respectively. According to a recent report, onset of diabetes was defined as the day on which diabetes was first recorded on the patient's chart or hospital record by a physician [13]. Following this definition, diagnosis of diabetes, baseline ophthalmologic examination (T0) and first insulin injection were done in this exact order and at the same day.

Exclusion criteria were good metabolic control (HbA_{1c} <7%), "borderline" hypertension (>140/90 mm Hg), diabetic microangiopathy (retinopathy and/or nephropathy), smoking habit, pregnancy, cataract, aphakia or pseudophakia, emmetropia, astigmatism >+0.75 D, intraocular pressure >21 mm Hg, or other systemic diseases. Insulin therapy, if already started at the time of the baseline examination, and HbA_{1c} between 7–9% were also exclusion criteria.

For all patients we recorded: sex, age at diagnosis of diabetes, duration of diabetes, metabolic control, therapy, blood pressure. None of our patients was taking medication other than subcutaneous human insulin (regular and long-acting), started immediately after performing the baseline ophthalmological examination (T0).

The actual level of metabolic control was evaluated from measurements of glycosylated haemoglobin (HbA_{1c}) and blood glucose performed approximately 45 minutes before the ophthalmic examination. HbA_{1c} was determined spectrophotometrically using reagents from Bio-Rad (Richmond, CA, USA) on 3 mL of blood drawn into evacuated siliconized tubes containing EDTA. The non-diabetic range used was 4.0–6.0%. In order to determine serum glucose and other metabolic parameters, blood was drawn into evacuated siliconized tubes and measurements were made by an autoanalyzer (Boehringer Mannheim, Germany) using enzymatic methods.

The absence of microalbuminuria (30–300 mg day^{-1}: Albustix-Ames, Miles, Elkhart, IN, USA) was confirmed in a sample of early morning urine collected in the absence of infections or other renal diseases.[14] Blood pressure and serum creatinine concentrations were determined in order to evaluate renal function.

Tenets of the Declaration of Helsinki were followed. Informed consent was obtained from each subject, and Institutional Human Experimentation Committee approval was granted.

Similar procedures were used at baseline and follow-up examinations, performed by the same examiner every two weeks, after starting rapid correction of hyperglycemia, during a four-month period of close observation. Assessment of the patient's current prescription (if available) was followed by a standardised refraction, before and after cycloplegia, using an automated refractor. Cycloplegia was obtained by instillation of one drop of cyclopentolate hydrochloride 1% and one drop of tropicamide 0.5% + phenylephrine hydrochloride 0.5% in each eye, twice, at an interval of 10 minutes. Refraction was carried out on a Nidek AR-1000 autorefractometer (Nidek Co. Ltd, Gamagori, Japan) at least 20 minutes after the last cycloplegic drop, and the mean of five measurements was taken. In addition, refraction and radius of the anterior corneal curvature were measured in all subjects. In the eyes with astigmatism, the sherical equivalent was used as the refractive value, calculated using the following formula: spherical power (in diopters) + one half negative cylinder power (in diopters). A-mode ultrasonography was performed monthly on a Zeiss-Humphrey scanner (San Leandro, CA, USA), five times in each eye, in order to measure the axial length, the anterior chamber depth and the lens thickness, and the mean value was taken. The contact technique with the applanation method was used throughout the follow-up period while the immersion technique, probably more accurate but much more time-consuming, was performed only on admission (T0) and at the end of the study (T4). However, no statistically significant differences in measurements were found between both type of techniques. Sound velocity was set to 1532 m/s for acqueous and vitreous, and 1641 m/s for the lens. Correct calibration and alignment of the ultrasound device were always checked during the investigation, and only measurements with well defined echoes were accepted. Threrafter, all patients completed their ophthalmological examination with applanation tonometry and retinal biomicroscopy using high positive power precorneal lenses (Super Field and +78D Volk Lenses). Retinography and fluorescein angiography (Heidelberg Retina Angiograph, Germany) were performed on admission in order to ensure that only subjects with angiographically normal retinas were included in this study.

Data are expressed as means ± standard deviation (SD), unless otherwise indicated. Statistical analyses of data were performed using the two-tailed paired and unpaired Student *t*-test; Mann-Whitney *U*-test was applied in the case of variables with a nonparametric distribution, such as circulating HbA_{1c}. Spearman correlation coefficients (*r*) were calculated whenever appropriate. A *P* value of less than 0.05 was considered significant.

Results

Table 1 summarizes both the clinical features and the laboratory findings of the enrolled diabetics. No statistically significant differences in blood pressure, renal function and ETDRS visual acuity were found between the baseline (T0) and the last (T4) examinations. All subjects had transparent dioptric media and angiographically normal retinas at T0, and no onset of cataract or retinopathy was observed during the study. Microalbuminuria was never detected and no other systemic diseases were present. By means of the intensive insulin treatment, a significant improvement of glycemic control was achieved in all subjects at the end of the study period (tables 1, 2).

Refraction and glycemic control

The clinical course of refractive changes and metabolic control is shown in tables 2 and 3. In

order to avoid interference by accommodation in our adolescent diabetics, only standardized refraction, obtained after cycloplegia, was considered and indicated in these tables. The onset times of both refractive changes and hyperopic peaks preceded the start of the intensive insulin therapy in all the enrolled diabetics and, therafter, refraction decreased gradually with a maximum recovery time of 94 days (table 3). With very few exceptions, patients characterized by higher plasma glucose concentrations and higher HbA_{1c} on admission, had a larger maximum hyperopic change (table 2); a statistically significant positive correlation between refractive changes and magnitude of plasma glucose concentrations as well as HbA_{1c} percentages was observed (tables 2 and 4).

No significant changes in axial length, anterior corneal curvature, lens thickness or anterior chamber depth were recorded (table 5). No statistical differences in change of astigmatism were found during the study.

Table 1

Clinical and biochemical findings of the enrolled type 1 diabetics (n: mean ± SD; ND: newly diagnosed diabetes; NS: *P* value not significant; R: right eye; L: left eye).

Patients (N = 20)	on admission (T0)	after 4 months (T4)	P Value
Age (years)	16.80 ± 1.3	–	–
Sex (M, F)	11/ 9	–	–
Age at diagnosis of diabetes (years)	16.80 ± 1.3	–	–
Duration of diabetes (years)	ND	–	–
Systolic blood pressure (mm Hg)	122.7 ± 9.4	121.1 ± 5.7	NS
Diastolic blood pressure (mm Hg)	74.1 ± 9.1	72.2 ± 7.2	NS
Fasting glycemia (mg/dl)	423.3 ± 31.4	170.2 ± 11.1	<.001
Glycosylated haemoglobin (%)	10.5 ± 1.0	7.3 ± 0.5	<.001
Insulin therapy	no	yes	–
Microalbuminuria	absent	absent	–
Creatinine (mmol/L)	74.48 ± 11.26	72.81 ± 13.30	NS
Diabetic retinopathy	absent	absent	–
Other systemic diseases	none	none	–
ETDRS visual acuity [LogMAR]	1.08 ± 0.15 [0.03]	1.07 ± 0.24 [0.03]	NS
Refractive error (D)	R + 3.51 ± 0.46	R + 1.75 ± 0.39	<.001
	L + 3.56 ± 0.51	L + 1.86 ± 0.48	<.001

Table 2

Metabolic control achieved in the juvenile diabetic patients and clinical course of transient refractive changes after cycloplegia (n: mean ± SD; T0: on admission; T4: after 4 months; R: right eye; L: left eye).

Patient No	sex (M/F)	age (years)	glycemia T0 (mg/dl)	glycemia T4 (mg/dl)	HbA_{1c} T0 (%)	HbA_{1c} T4 (%)	refractive error T0 (R/L; D)	refractive error T4 (R/L; D)
1	M	18	440	165	10.6	7.1	+3.50 / +2.75	+1.75 / +1.50
2	M	17	419	157	10.1	7.0	+3.50 / +3.00	+1.50 / +1.00
3	M	18	470	187	12.9	8.5	+4.25 / +3.75	+2.00 / +2.25
4	F	19	465	179	12.4	8.3	+4.00 / +4.00	+2.25 / +2.00
5	M	16	409	182	10.6	7.4	+3.00 / +3.50	+1.50 / +2.00
6	F	16	471	195	11.9	7.7	+3.75 / +4.00	+1.75 / +2.25
7	F	17	455	184	12.0	7.7	+3.75 / +3.75	+1.50 / +1.25
8	M	19	388	162	10.0	7.1	+3.50 / +3.50	+1.50 / +1.50
9	M	18	375	163	9.8	6.8	+3.00 / +3.00	+1.25 / +1.00
10	M	15	425	177	11.2	7.0	+3.25 / +3.50	+1.25 / +2.00
11	F	16	402	165	10.4	6.9	+3.50 / +3.75	+1.75 / +2.50
12	F	16	431	168	10.1	6.9	+3.50 / +4.00	+1.50 / +1.75
13	F	17	389	158	9.6	7.1	+3.25 / +3.00	+1.50 / +1.50
14	M	15	368	152	9.1	6.6	+2.75 / +2.75	+1.25 / +1.25
15	F	18	412	170	10.5	7.5	+4.25 / +4.50	+2.50 / +2.50
16	F	18	423	174	10.2	7.3	+4.50 / +4.50	+2.50 / +2.50
17	M	16	401	168	9.3	7.0	+3.50 / +4.00	+2.00 / +2.00
18	M	17	456	172	10.8	7.5	+3.25 / +3.25	+1.50 / +2.00
19	F	15	454	168	10.0	6.9	+3.00 / +3.50	+2.00 / +2.25
20	M	15	412	159	9.5	6.8	+3.25 / +3.25	+2.25 / +2.25

Table 3

Clinical course of hyperopic changes after cycloplegia (T0: on admission; T4: after 4 months; R: right eye; L: left eye).

Patient No	sex (M/F)	age (years)	difference in refractive error T0–T4 (R/L; D)	onset time of hyperopic change	peak time of hyperopic change	recovery time of hyperopic change (days after T0)
1	M	18	+1.75 / +1.25	T0	T0	78
2	M	17	+2.00 / +2.00	T0	T0	86
3	M	18	+2.25 / +1.50	T0	T0	94
4	F	19	+1.75 / +2.00	T0	T0	81
5	M	16	+1.50 / +1.50	T0	T0	58
6	F	16	+2.00 / +1.75	T0	T0	77
7	F	17	+2.25 / +2.50	T0	T0	88
8	M	19	+2.00 / +2.00	T0	T0	78
9	M	18	+1.75 / +2.00	T0	T0	72
10	M	15	+2.00 / +1.50	T0	T0	75
11	F	16	+1.75 / +1.25	T0	T0	70
12	F	16	+2.00 / +2.25	T0	T0	90
13	F	17	+1.75 / +1.50	T0	T0	68
14	M	15	+1.50 / +1.50	T0	T0	71
15	F	18	+1.75 / +2.00	T0	T0	72
16	F	18	+2.00 / +2.00	T0	T0	70
17	M	16	+1.50 / +2.00	T0	T0	60
18	M	17	+1.75 / +1.25	T0	T0	71
19	F	15	+1.00 / +1.25	T0	T0	66
20	M	15	+1.00 / +1.00	T0	T0	52

Discussion

Diabetics complaining of disturbed visual acuity, such as difficulty in reading or driving and blurred vision with their own glasses, are not uncommon in daily clinical practice [15, 16]. Moreover, it is also a frequent observation that glasses prepared during this time usually do not fit after a few months. It is therefore recommended that the prescription of spectacles be delayed as much as possible until the refractive state has stabilised [11, 16].

At this time, there is no agreement about the diabetic influence on refraction, even though the concept that diabetes mellitus may affect refraction with both short term fluctuations and more permanent alterations is well known. The generally accepted view is that the diabetes-related short term fluctuations of visual acuity are primarily caused by accumulation of sorbitol and fructose into the lens by the sorbitol pathway with a decreased lens refractive index following water influx [2, 5–8, 11, 16]. However, while a thickened lens, a decreased anterior chamber depth and a transient cataract were previously found by Saito et al using photographic biometric methods [6], no significant changes in axial length, anterior corneal curvature, lens thickness or anterior chamber depth, on the contrary, were more recently observed during intensive glycemic control of severe hyperglycemia using A-mode measurements [11]. Moreover, with regard to the more permanent alterations in refraction, a statistically significant positive correlation between duration of juvenile diabetes and lens thickness was assessed some years ago by means of a twin control method [9], and the higher correlation observed in the monozygotic compared with the dizygotic twins suggested to the authors that also genetic factors, and not only duration of the disease, may play a role in the determination of lens thickness [9]. In a successive study, the decreasing anterior chamber depth and axial length as well as the lowering of lens power and lens refractive index were found with increasing duration of diabetes, and the authors hypothesized a diabetes-related decreased growth of the eye in the axial direction before puberty [10].

Refractive changes were also measured in healthy volunteers after induction of acute hyperglycemia and a significant ocular hypotension – causing thickening of the lens, decreased tension of the Zinn's zonule fibers and myopia – was found [17]. In this study, hyperopia appeared to be sec-

Table 4

Statistical analyses of the data (T0: on admission; T4: after 4 months; R: right eye; L: left eye).

	Spearman coefficient (r)	P value
Fasting glycemia T0 vs fasting glycemia T4	0.49	<0.001
HbA_{1c} T0 vs HbA_{1c} T4	0.57	<0.001
Refractive error T0 vs refractive error T4	R 0.62 L 0.68	<0.001 <0.001

Table 5

Refractive components (n: mean ± SD; NS: *P* value not significant; R: right eye; L: left eye).

	eye	on admission (T0)	after 4 months (T4)	P value
Axial length (mm)	R	23.78 ± 1.1	23.59 ± 1.7	NS
	L	23.64 ± 1.0	23.68 ± 0.8	NS
Corneal curvature radius (mm)	R	7.54 ± 0.2	7.51 ± 0.4	NS
	L	7.58 ± 0.3	7.56 ± 0.1	NS
Anterior chamber depth (mm)	R	3.33 ± 0.3	3.35 ± 0.1	NS
	L	3.31 ± 0.5	3.33 ± 0.4	NS
Lens thickness (mm)	R	4.10 ± 0.4	4.13 ± 0.5	NS
	L	4.12 ± 0.1	4.11 ± 0.8	NS

ondary to the reversal of myopia after glycemic normalisation.

Finally, refractive changes in diabetic patients were recently studied during intensive glycemic control and it was concluded that the degree of transient hyperopia, associated with rapid correction of hyperglycemia, is highly dependent on the daily rate of plasma glucose reduction over the first seven days of treatment [11].

In the light of all these findings, our work was designed to investigate transient refractive changes in newly diagnosed and uncomplicated juvenile diabetic patients, in order to evaluate their clinical course after starting intensive glycemic control of severe hyperglycemia. To avoid any therapeuthic interference with our data, as suggested by Okamoto et al. [11], all diabetic subjects were required to present a poor metabolic control on admission (HbA_{1c} >9%) and to have not yet started insulin therapy at the time of the baseline examination. Moreover, unlike this previously published report [11] in which type 1 and type 2 diabetics of different disease duration and clinical conditions were enrolled, retinopathy, microalbuminuria and any type of systemic diseases were all exclusion criteria (table 1).

Results from this study, conducted in a very homogenous and carefully selected group of type 1 diabetics, confirmed the known significant and positive correlation between refractive changes and magnitude of plasma glucose concentrations (tables 2 and 4) but not the previously published report of a hyperopic increase shortly after starting intensive glycemic control. On the contrary, not only the refractive changes but also the hyperopic peaks were already present prior to starting insulin therapy and, thereafter, refraction decreased gradually with a maximum recovery time of 94 days (table 3). In accordance with Okamoto et al. [11], patients characterized by higher plasma glucose concentrations and higher HbA_{1c} on admission, had a larger maximum hyperopic change (table 2).

The origin of these transient refractive changes is still not clearly understood. According to the above mentioned report [11], no significant modifications in axial length, anterior corneal curvature, lens thickness or anterior chamber depth were recorded after cycloplegia in our diabetic patients (table 5), even though some published studies have already highlighted that cycloplegia itself might determine significant changes in ocular refractive components [18, 19]. In particular, after the topical application of 2% homatropine solution [18] or 1% atropine sulphate ointment [19] and by using an ultrasound biomicroscope (UBM) or A-mode measurements respectively, it was found that the anterior chamber depth and the iris thickness increased while the lens thickness, the vitreous chamber length, the ciliary body as well as the ciliary process thickness decreased. As a result, the anterior chamber became deeper, the anterior chamber angle narrower and the iris-lens contact distance shorter with a decreased iris-zonule distance. The ciliary body became thinner and moved backward causing an increased ciliary process-lens distance; the total axial length increased in hyperopic but decreased in myopic eyes. Even the corneal topography, obtained with a computerized video-keratoscope, was found to be significantly influenced by the cycloplegic action.

Nevertheless, given the high magnitude of accommodation that characterizes hyperopic adolescents, cycloplegia is surely "a must" in these kind of patients in order to avoid any accomodative interference in the refractive changes that may be found. Moreover, in accordance with Okamoto et al. [11], by measuring refraction under the same cycloplegic conditions before and after glycemic control and by using cyclopentolate hydrochloride 1% and tropicamide 0.5% solutions instead of atropine or homatropine (thus avoiding a very deep cycloplegia), it might be possible to reduce the risk of false results.

Therefore, in agreement with other authors, we concluded that hyperopia might be caused by intraocular functional changes (e.g. decreased lens refractive index) that may occur in the absence of any morphological alteration. Regarding this matter, the sorbitol production via the polyol pathway with overhydration of the human lens remains the best hypothesis at this time [2, 5–8, 11, 16]. However, the exact mechanism of the decreased refractive index and why it takes so long to reverse completely (up to three months in some cases) remains obscure.

In conclusion, it is now clear that juvenile diabetes may influence refraction on different levels and that a rapid glycemic control in the early stages could possibly minimize the refractive changes.

However, further papers investigating the pathophysiology of transient refractive changes in poorly controlled diabetics are needed. In the meantime, it remains a correct way of acting to advise these patients that they may require frequent changes of spectacles in the presence of a persistently high hyperglycemia and, therefore, prescription of new glasses should be delayed as much as possible untill stabilisation of refraction is complete.

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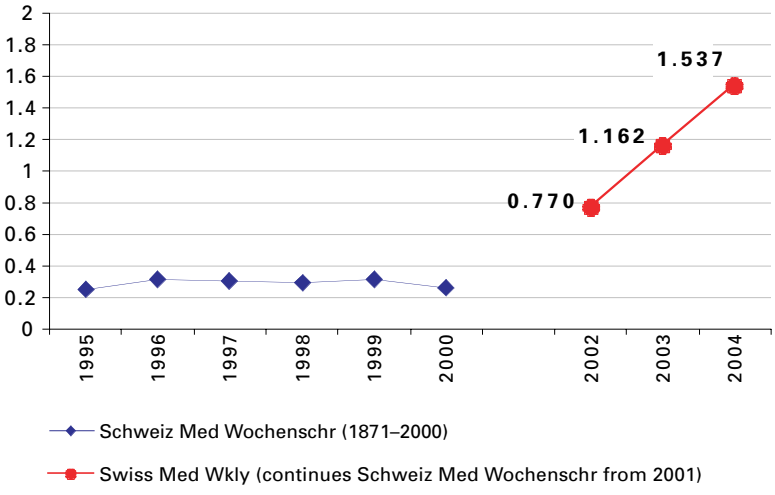

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