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A. Verrotti • L. Lobefalo • E. Altobelli • G. Morgese • F. Chiarelli • P.E. Gallenga

Static perimetry and diabetic retinopathy: a long-term follow-up

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Abstract In order to evaluate if central static perimetry is useful to identify patients at risk of developing diabetic retinopathy, 60 (27 male, 33 female) adolescents and young adults (mean age, 15.9 years) with insulin-dependent diabetes mellitus were studied prospectively. No patient showed fluorescein angiographic signs of retinopathy initially. The patients were evaluated at the beginning of the study and after 8 years. At the beginning of the study, mean defect in the population was -2.34 dB as determined by perimetry; no patient showed significant impairment of foveal threshold (mean, 33.17 dB). After 8 years of follow-up, 7 patients had developed fluorangiographic signs of retinopathy. Life-table analysis showed that the overall probability of retinopathy development was significantly higher in subgroups of patients with mean sensitivity in areas 2 and 3 below the cut-off. These results suggest that central static perimetry is a useful tool in predicting the development of retinopathy in children with insulin-dependent diabetes mellitus who do not have fluorescein angiographic signs of retinopathy. This tool can help the physician to identify those patients at risk of developing fluorangiographic signs of retinopathy.

Key words Diabetes mellitus • Retinopathy • Central static perimetry • Fluorescein angiography

A. Verrotti (✉) • F. Chiarelli
Department of Pediatrics
University of Chieti
Via Vestini 5, I-66013 Chieti, Italy

L. Lobefalo • P.E. Gallenga
Department of Ophthalmology
University of Chieti, Chieti, Italy

E. Altobelli
Department of Internal Medicine and Public Health
University of L'Aquila, L'Aquila, Italy

G. Morgese
Department of Pediatrics
University of Siena, Siena, Italy

Introduction

Retinopathy is one of the most frequent long-term complications of insulin-dependent diabetes mellitus. Factors specifically related to insulin-dependent diabetes mellitus, such as its duration and control (i. e. plasma glucose) or glycated hemoglobin (HbA1c) levels, have been reported to be risk factors of retinopathy.

Several attempts have been made to develop a test predictive of the development of retinopathy [2–4]. Patients with insulin-dependent diabetes mellitus frequently exhibit abnormal central vision before the development of either overt retinopathy or a reduction in visual acuity [5–9]. In previous studies, we found that central static perimetry is able to identify patients at risk of developing retinopathy; poorly controlled patients had lower retinal sensitivity than well-controlled ones [10–13]. An understanding of the changes of central static perimetry during the initial stages of retinopathy may provide information about the real usefulness of this diagnostic tool in these patients.

The aim of this 8-year prospective study of children and adolescents with insulin-dependent diabetes mellitus was to evaluate if central static perimetry helps identify patients at risk of developing clinically detectable diabetic retinopathy.

Materials and methods

Patients

A total of 60 adolescents and young adults were enrolled in the study. At the beginning of the study all the patients met the following inclusion criteria:

1. 14–18 years of age;
2. Pubertal stage 5 according to Tanner classification [14];
3. Duration of disease ranging from 5 to 10 years;

4. Absence of microalbuminuria (albumin excretion rate <20 μg/min for an average surface area of 1.73 m^2);
5. No systemic hypertension;
6. Refractive errors less than ±1 spherical and ±1 cylindrical diopters;
7. Corrected visual acuity equal to or greater than 1.0;
8. Intraocular pressure <20 mmHg;
9. Clear optic media;
10. No fluorescein angiographic signs of retinopathy;
11. Absence of other ocular pathologies.

All patients attended the regional Pediatric Diabetes Centre and the Department of Ophthalmology of the University of Chieti and had been visiting the hospital since their diabetes was diagnosed.

Methods

All enrolled subjects received an accurate and systematic clinical evaluation that consisted in a complete ophthalmological examination (visual acuity, slit-lamp biomicroscopy, intraocular pressure measurement, direct and indirect ophthalmoscopy, fundus retinography and fluorescein angiography). At the beginning of the stidy all the patients underwent the following visual field tests using the HFA 640 automated static threshold projection perimeter (HFA, Humphrey Instruments, San Leandro, California, USA):

- Two visual fields not evaluated in the study (threshold strategy), to reduce the learning effect [15].
- A full threshold test, program 24–2, used for study analysis.

The examination was always performed after breakfast. Before the examination, we determined the glycemia of all patients in order to rule out hypoglycemia. None of the patients had severe hyperglycemia (range, 5.7–7.6 nmol/l) or ketoacidosis at the time of the examination.

Evaluated visual field parametes were foveal threshold and mean sensitivity. In addition, the visual field was subdivided into three concentric areas as previously described [10]. The population was stratified into two subgroups for each of the following parameters (using as cut-off value the mean minus 1 standard devation):

1. Mean defect,
2. Foveal threshold,
3. Three concentric areas (up to 9°; 10°–18°; beyond 18°) [10].

Throughout an 8-year follow-up period, all patients yearly underwent a thorough ophthalmological examination (visual acuity, slit-lamp biomicroscopy, intraocular pressure measurement, direct and indirect ophthalmoscopy, fundus retinography). In all patients, the absence of diabetic retinopathy was assessed at the beginning of the study by fluorescein angiography and fundus retinopathy. The development of retinopathy was assessed during the study by fundus retinography.

Perimetry was undertaken yearly. The standard full threshold strategy and the 24–2 program were used in all tests. Fundus retinography and fluorescein angiography were performed with Kowa RC-X_F fundus camera. For fluorescein angiography, 2 ml 20% sodium fluorescein was quickly injected into the antecubital vein. Angiograms were taken with ASA 400 black-and-white film developed at ASA 1200.

The quality of metabolic control was assessed from HbA1c levels, calculated as the mean of at least six determinations in the year preceding the study. HbA1c levels were measured by high-pressure liquid chromatography (HPLC, BioRad, Laboratories, USA). All diabetics followed a conventional insulin regimen with 2–3 injections per day of human insulin. Blood pressure was measured according to the recommendations of the Second Task Force on Blood Pressure Control in Children [16].

The study was approved by the local ethics committee and was performed in accordance with the Declaration of Helsinki. Informed consent was obtained from the parents of all participants.

Statistical analysis

All data are expressed as means and SD. Only right eyes were evaluated. For statistical analysis we used the SPSS for Windows (version 7) software package (SPSS).

Only perimetric tests performed at baseline and at the end of the study were used for analysis. The basic of longitudinal analysis was a stratification of perimetric parameters (mean defect, foveal threshold and areas 1, 2 and 3).

Pearson's correlation was used to determine the relationships between: (a) year of retinopathy development and perimetric parameters; and (b) mean metabolic control at follow-up and differences of perimetric parameters between baseline and the end of the study. Multivariate analysis was used to determine the specific weight of each perimetric parameter in the retinopathy development. Unpaired *t* test was performed to evaluate differences in retinal sensitivity among the 3 perimetric areas.

Life-table analysis was performed to evaluate the incidence of retinopathy during the follow-up. Comparison between subgroups was performed using the Wilcoxon (Gehan) statistic. A p value of 0.05 was regarded as statistically significant.

Results

A total of 60 adolescent and young adults enrolled in the study (Table 1). Their average age was 15.9 years and they had been diagnosed with insulin-dependent diabetes for an average of 7.2 years.

At the beginning of the study, mean defect in the population studied was –2.34 dB (Table 2) and only 2 patients showed a mild but significant deviation from the model ($p<0.05$), when compared with normative data of the perimeter. No patient showed significant impairment of foveal thresh-

Table 1 Demographic data of the study group

	Patients (n=60)
Age, years[a]	15.9 (18)
Boys, n (%)	27 (45)
Disease duration, years[a]	7.2 (1.4)
Glycated hemoglobin (HbA1c),%	7.4 (1.5)

[a] Values are means (SD)

old and the mean value of this parameter was 33.17. As expected, the central area had mean sensitivity significantly higher than the other areas ($p<0.001$). Similarly, area 2 showed mean values significantly higher than area 3 ($p<0.001$).

Mean duration of disease and mean HbA1c values were similar in patients above and below the cut-off for all perimetric measurements (data not shown).

Out of 60 patients, 7 developed retinopathy during the study as determined by retinography (Table 3). No patient at the end of the study had more than background retinopathy at fluorescein angiography (data not shown).

Life-table analysis (Fig. 1) showed that the cumulative proportion of patients resisting retinopathy ("survivors") at the end of follow-up was lower in all groups below the cut-off. The lowest proportions of survivors was found in patients below the cut-off for perimetric area 3 (Table 4). Wilcoxon statistics revealed no significant difference between patients above and below the cut-off for perimetric area 1 ($p=0.2135$). The overall probability of retinopathy development was significantly higher in patients below the cut-off for areas 2 and 3 ($p=0.230$ and $p=0.0007$, respectively).

Further evidence for the relationship between retinal sensitivity in areas 2 (9°–18°) and 3 (above 18°) and development of retinopathy was shown by Pearson's correlation (r=0.273, $p=0.017$ and r=0.415, $p<0.001$, respectively) (Fig. 2). Multivariate analysis confirmed relationship between perimetry impairment and development of retinopathy ($p<0.001$). Particularly, the between-subjects effects for areas 2 and 3 were strictly related to the development of retinopathy ($p=0.16$ and 0.041, respectively).

Table 2 Perimetric parameters at study entry, cut-off values and stratification of patients into groups based on position with respect to cut-off values, for 60 patients

	Mean value (SD), dB	Cut-off, dB	Patient Stratification, n	
			Above cut-off	Below cut-off
Mean defect	-2.34 (1.18)	-3.52	45	15
Foveal threshold	33.17 (1.71)	31.46	56	4
Area 1 (up to 9°)	32.22 (1.58)	30.64	51	9
Area 2 (10°–18°)	30.85 (2.12)	28.73	46	14
Area 3 (beyond 18°)	29.71 (2.59)	27.12	41	19

Table 3 Year of diagnosis of retinopathy, and perimetric parameters and HbA1c levels at the 8-year follow-up, for the 7 patients who developed retinopathy.

Patient	Retinopathy diagnosis, study year[a]	Mean defect, dB	Foveal threshold, dB	Area 1, dB	Area 2, dB	Area 3, dB	HbA1c, %[b]
1	2	-1.02	32.00	33.20	27.90	25.60	7.3 (1.4)
2	4	-4.12	33.00	30.30	28.20	25.80	7.5 (1.3)
3	5	-3.84	34.00	34.60	28.60	26.80	7.7 (1.3)
4	3	-4.57	35.00	33.00	28.50	25.60	7.7 (1.4)
5	7	-4.12	34.00	33.20	35.00	26.40	7.9 (1.2)
6	6	-1.84	33.00	31.80	34.80	30.80	7.6 (1.3)
7	5	-2.74	33.00	34.10	28.40	27.00	7.2 (1.4)

[a] Time during the 8-year study when retinopathy was diagnosed

[b] Values are mean (SD)

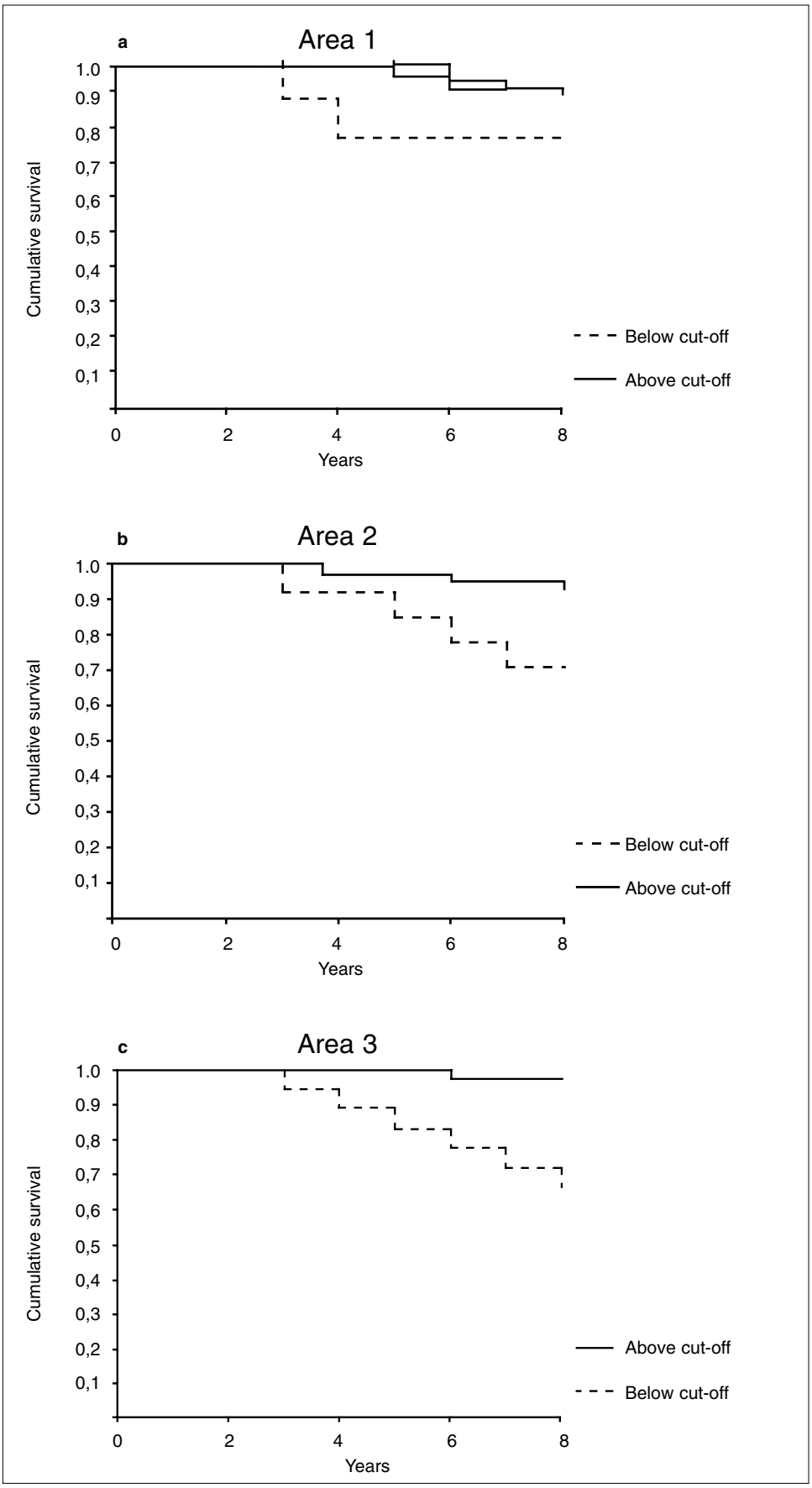

Fig. 1a-c *Life-tables analyses for the development of retinopathy.* **a** Perimetric area 1. Comparison of survival experience using Wilcoxon (Gehan) statistics, p=0.2135. **b** Perimetric area 2, p=0.0230. **c** Perimetric area 3, p=0.0007

Table 4 Cumulative proportion of survival at the end of follow-up for each evaluated subgroup

	Above cut-off	Below cut-off
Area 1	0.90	0.78
Area 2	0.94	0.71
Area 3	0.98	0.67

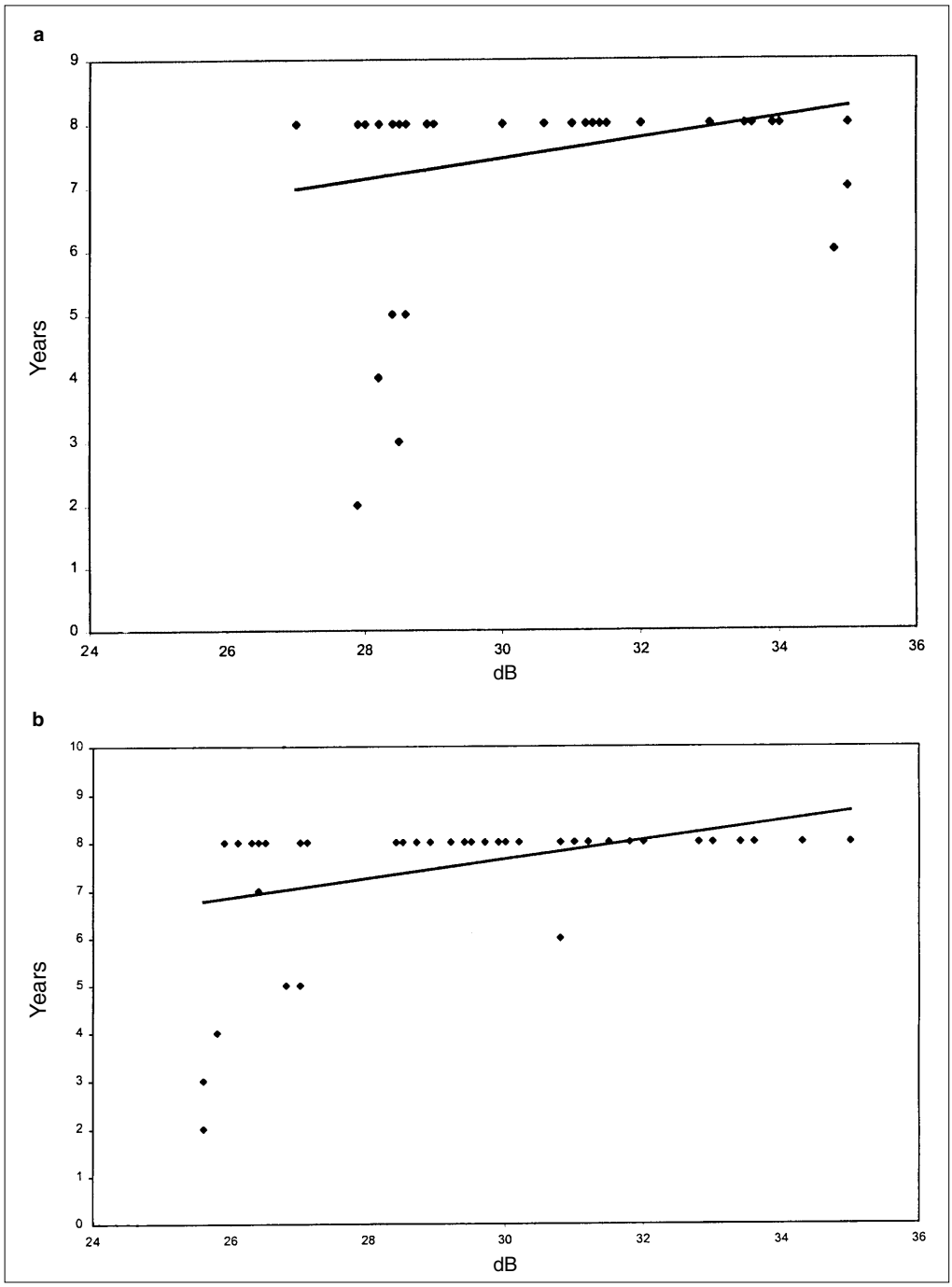

Fig. 2a, b *Relationship between retinal sensitivity and development of retinopathy.* **a** Area 2. (9°–18°). Pearson's correlation, r=0.273, p=0.017. **b** Area 3 (>18°). Pearson's correlation, r=0.415, p<0.001

Discussion

In recent years, techniques other than fluorescein angiography, such as vitreous fluorophotometry [17], electroretinographic oscillatory potentials (ERG) [18], contrast sensitivity [9, 19], nyctometry [20], retinal dark adaptation [21], and color vision test [8, 22], have been used for the early diagnosis and follow-up of diabetic retinopathy. In particular, several authors have underlined the usefulness of perimetry in detecting retinal defective areas in patients affected with diabetes without and with signs of retinopathy [10, 12, 13, 23–26].

Although several studies have dealt with reliability and predictibility of techniques to evaluate the presence of initial retinopathy, it is still unclear whether the abnormalities found by these functional tests reflect functional retinal abnormalities that precede vascular lesions or whether they result from reversible metabolic abnormalities in the retina. Unfortunately, all these methods, but fluorescein angiography, provide mass answers without any information on the location of the defect, whereas visual field test allows the detection of localized functional defects, in both retinopathic and not-retinopathic subjects [12, 13, 23–27]. On the other hand, the presence of scotomata unrelated to morphologically detectable alterations has already been reported [10, 23]. This evidence encouraged us to evaluate the usefulness of visual field test in predicting the development of morphological changes secondary to diabetic retinopathy. The possible predictive value of this simple, noninvasive diagnostic tool in non-retinopathic diabetic patients with microalbuminuria was suggested in previous reports [10, 12, 13]. Our previous baseline evaluation suggested that it is possible to detect a significant retinal sensitivity impairment which can be considered an early sign of retinal damage [10], confirming that computerized perimetry may detect early changes of visual function in diabetic patients prior to the appearance of microvascular retinal damage. These data are in agreement with findings of Bek et al. [24, 25] who found, in patients with diabetic retinopathy, scotoma located at about 30° assessed by computerized perimetry; these scotoma corresponded to morphologically normal areas at fluorescein angiography.

Long-term follow-up of the patient population studied previously [10], aimed at addressing the issue of whether achromatic perimetry can identify those diabetic patients at risk to developing fluorescein angiographic signs of retinopathy, foused on selected diabetic adolescents. When we subdivided the diabetics according to perimetric values, we obtained similar HbA1c values for each subgroup, without any significant difference among the different subgroups. Our study suggests that computerized perimetry can help find patients at risk of developing retinopathy. Particularly, the presence of a reduced sensitivity in the outer sectors of the central visual field (beyond 10°) is highly related to the development of retinopathy in an 8-year follow-up. Eyes with initial impairment of visual field had a higher rate of development of retinopathy than eyes with higher retinal sensitivity beyond 9° of the visual field. Because the different subgroups of patients were similar for their quality of metabolic control, their age, duration of disease and presence of other microvascular complications, and because they followed the same regimen of insulin treatment, our longitudinal data suggest that the presence of reduced sensitivity can have an important predictive value for the development of retinopathy. Our data are in agreement with those of Gandolfo and Zingirian [28] who for the first time reported the presence of central and paracentral scotomatas in 50% of non-retinopathic diabetic patients who have shown some evidence of diabetic retinopathy within 12 months after the visual field examination. Therefore, computerized perimetry may be a useful tool for identifying those diabetic patients at risk of developing fluoroangiographic signs of retinopathy. It hould be performed regularly in all diabetic patients, in particular in those who have risk factors (e.g. long duration of disease, poor metabolic control) for retinopathy.

The practical application of our data can be seen in the detection of eyes with a high probability of progression to retinopathy that should be evaluated with fluorescein angiography. Moreover, the metabolic control of these patients must be strictly monitored and careful and frequent clinical and laboratory controls must be carried out. In conclusion, our data suggest that perimetry is useful in predicting the development of retinopathy in insulin-dependent diabetes mellitus children without fluorescein angiographic signs of retinopathy. This method can help the physician to identify those patients at risk of developing fluorangiographic signs of retinopathy.

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