Pupil Size in Insulin-dependent Diabetes

Relationship to Duration, Metabolic Control, and Long-Term Manifestations

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SUMMARY

The pupil area was measured in complete darkness by infrared TV-videopupillography in 109 insulin-dependent diabetics, aged 25–43 yr, diabetes duration 0–35 yr, and 39 control subjects, aged 26–41 yr. In darkness the pupil was 19.6% ± 4.2 (SEM) smaller in diabetics than in controls ($2P < 10^{-5}$). There was an inverse relationship between diabetes duration and pupil area (Kendall's coefficient of correlation, $\tau = -0.33$, $2P < 10^{-4}$). There was also an inverse correlation between pupil size and vibratory perception threshold ($\tau = -0.32$, $2P < 10^{-3}$). Long-term diabetics (duration ≥ 15 yr) with proliferative retinopathy had a 28.4% ± 8.1 (SEM) smaller pupil than those without ($2P = <10^{-3}$). Likewise, long-term diabetics with nephropathy had a 19.8% ± 9.1 smaller pupil than those without nephropathy ($2P = 0.035$). In the long-term diabetics there was an inverse relationship between the level of blood glucose throughout the years and pupil area ($\tau = -0.49$, $2P < 10^{-3}$). Also, high blood glucose levels throughout the years were correlated to severity of retinopathy ($\tau = 0.43$, $2P < 10^{-3}$) and nephropathy ($\tau = 0.30$, $2P = 0.024$). There was no correlation between biomicroscopic changes in the iris and the diminished pupil area. Pupil area in light was measured in 85 patients and 31 controls. In continuous light only the long-term diabetics had a smaller pupil size than the controls. Both the absolute and relative change in pupil size from darkness to light was less in the diabetic group. Measuring the pupil size in darkness is a simple, noninvasive and reproducible method that may yield information about autonomic nervous involvement in diabetes. **DIABETES *31*:442–448, May 1982.**

Abnormalities of the pupil of the eye are well known in long-term diabetes. Excessive miosis has been sporadically mentioned as one of these abnormalities.[1–3] Anyone who has been engaged in fundoscopic examinations of diabetics is familiar with the occasional difficulty caused by insufficient dilation of the pupil in these patients with parasympathicolytic agents.[4–7] Studies of the resting pupil size, uninfluenced by mydriatics have, however, yielded somewhat conflicting results in diabetics. Ohrt measured the pupil diameter in "basic" illumination and found that diabetics tended to have smaller pupils than normals, but the difference was not clear-cut.[5] Blatz, on the other hand, found that 35% of diabetics had larger than normal pupils in diffuse illumination.[7] Gliem reported a smaller pupil size in patients with long-standing diabetes with rather severe retinopathy.[8] Employing the technique of infrared TV-videopupillography, which allows direct and continuous measurement of the pupil size in complete darkness, it was demonstrated in a preliminary report that long-term diabetics have a diminished pupil size and that this abnormality correlates with the duration of the disease.[9] With the same technique Smith et al. found a diminished pupil size in diabetic patients with autonomic neuropathy, but were unable to show any correlation with the duration of diabetes or with the degree of metabolic control.[10]

In the present study, the area of the pupil in complete darkness and in continuous light is measured in a large group of juvenile, insulin-dependent diabetics to further investigating the occurrence of diminished pupil size in diabetes and to define the relationship of this abnormality to the duration and degree of metabolic aberration and to other long-term diabetic manifestations.

MATERIALS AND METHODS

SUBJECTS

One hundred and nine insulin-dependent diabetics, 43 females and 66 males, with an average age of 34.2 yr (range 25–43 yr) and a duration of diabetes ranging from 0 to 35 yr (average 16.2 yr) were studied. Most of these patients were regularly attending the outpatient clinic, and they were un-

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selected with regard to complications of diabetes including autonomic neuropathy. Also participating in the study were 39 healthy control subjects, mean age 33.2 yr (range 26–41 yr). Mean nonfasting blood glucose level at the time of the study was 202 mg/dl ± 87 (SD) in the diabetics and mean insulin requirement was 45.8 IU ± 15.4. Patients with a history of iridocyclitis and diseases unrelated to diabetes were excluded from the study. None of the patients received any drug known to influence the pupil. In order to further minimize the possible influence of age variation on the results, the selection procedure was such that the distribution of both age and duration of diabetes was almost uniform within the ranges considered (Figure 1). Informed consent was obtained from all participants.

Within an interval of 4 yr, 24 patients were examined on two occasions with identical measuring procedures.

METHODS

Pupillography. The area of the left pupil was measured with an infrared sensitive TV-camera (Iriscorder, Hamamatsu TV Corp., Hamamatsu, Japan), and after analogue-to-digital conversion (Schlumberger, Solarthron, A 210, Federal Republic of Germany) the measurements were handled off-line on a central computing facility (CDC Cyber 173 at the Regional EDP-Center, Aarhus University, Aarhus, Denmark). The pupillographic investigation took place in a completely dark room. A red fixation light placed at an optically infinite distance was used to prevent accomodation.

After adaptation to complete darkness for 15 min the resting pupil area was measured at a 10-Hz sampling rate for several 15-s periods and averaged. The pupil area in light was measured in the same manner, but this time during continuous illumination to the right eye with a convergent beam of light of an intensity of 512 μLumens emitted by a photostimulator in an "open-loop" fashion, thus ensuring the equality of the light stimulus to the retina irrespective of pupil size.[11] The light beam reaches the retina one pupillary diameter above the optic disc and covers an area that is about the size of the optic disc. The recordings were started 90 s after initiation of the continuous illumination. The pupil size in darkness was measured in all patients and controls, and the pupil size in light was measured in 85 patients and 31 controls. Pupil size in light was not measured in patients who had a visual acuity of less than 6/9 or in those patients who (at the ophthalmoscopic examination) had signs of retinopathy (except for a few red dots) in the area stimulated by the light. Subjects with frequent eye blinks during the recording periods and patients with cataracts were also excluded from this part of the study.

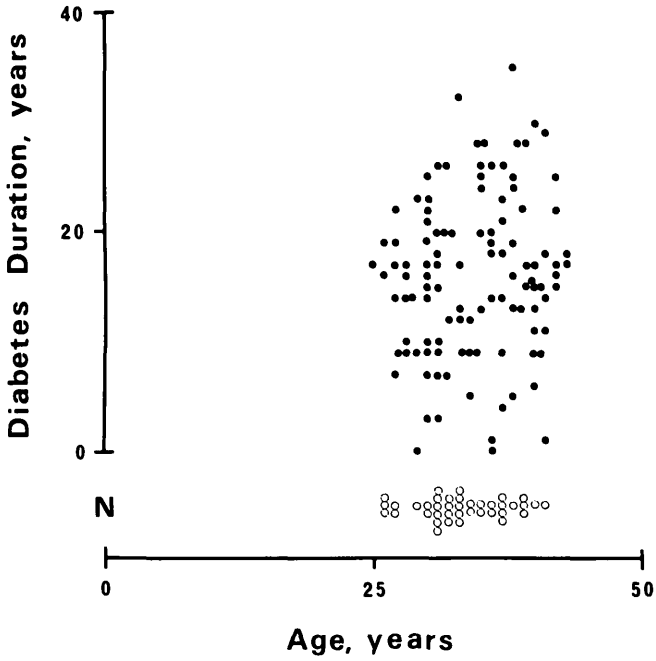


FIGURE 1. Duration of diabetes plotted against age of the diabetic subjects (●). The age distribution of the control subjects (○) is also shown.

The reproducibility of the measurements of pupil area was calculated at three levels (see Table 1). (1) Intrameasurement: coefficient of variation between the 150 measurements within each 15-s period; roughly 200,000 measurements were considered in all. (2) Intra-examination: The coefficient of variation between the mean pupil areas in each 15-s period; roughly 1000 periods were considered in all. Finally, (3) the day-to-day intra-individual coefficient of variation between the mean pupil areas of series of 15-s periods on different days was estimated.

As shown in Table 1, intrameasurement and intra-examination variation of pupil area in darkness is rather small (less than 3%). The variation of pupil area in light is in all cases larger and corresponds to the well-known physiologic phenomenon of increasing pupillary unrest or hippus with increasing illumination.[12] Also, pupillary unrest in light is less in diabetics than in normals.[9,10,13]

All measurements of the pupil were made in the daytime in order to avoid the effect of diurnal variation on pupil size.[14] Subjects were examined only when they did not feel tired or sleepy.

Ophthalmoscopic examination was made in mydriasis and was reported in terms of a 4-point scale: 0, no changes; I, only red dots (microaneurysms or punctate hemorrhages,

TABLE 1
Coefficient of variation (%)

		Intrameasurement*	Intra-examination†	Day-to-day, intra-individual‡
Pupil area in darkness	Diabetics	2.26	1.68	3.25 (8)
	Control	2.20	2.11	8.14 (7)
Pupil area in light	Diabetics	6.28	3.34	7.98 (8)
	Controls	9.08	7.13	12.68 (5)

* Variation between 150 measurements per period.
† Variation between approximately 10 periods per subject.
‡ Variation between subject mean pupil areas on different days (the number of subjects is shown in parentheses).

corresponding to the early stage of clinical retinopathy);[15] II, larger hemorrhages and/or exudates (intermediate stage); and III, proliferative changes.

Biomicroscopy of the iris was performed with a Zeiss split lamp in 76 patients. The observed abnormalities are reported as rubeosis iridis (neovascularization at the surface of iris), porosity or defects of the pigment seam at the pupillary margin, and loss of pigment from the pigment epithelium using the criteria described by Ohrt.[5,6]

As a simple measure of peripheral nervous function the vibratory perception threshold[16] was estimated on the great toe at 100 Hz by means of a biothesiometer with variable amplitude (expressed in volts, range 0–50 V) (Biomedical Instrument Corp., Chagrin Falls, Ohio).

Nephropathy was defined as persisting proteinuria (albustix and sulfosalicylic acid method) present on at least five consecutive attendences to the outpatient clinic.

As a measure of the quality or degree of metabolic control throughout the previous years, the blood glucose concentration from one attendance to the outpatient clinic each year (the attendance closest to May 15th was chosen arbitrarily) was used and the average of these annual values calculated for each long-term diabetic (duration ≥ 15 yr), excluding patients seen for less than 5 yr in our outpatient clinic. The fact that patients tend to visit the clinic more frequently in periods of metabolic derangement was taken into account in the calculations of the average by giving the individual blood glucose concentration the weight of the time interval from the previous attendance.

Statistical analysis. For comparison between groups, the Student's *t* test was carried out. Group mean values are given in terms of mean ± SD, indicating the variability of the parameter in question. Mean differences between groups are given as mean ± SEM, indicating the confidence of the difference. For testing the strength of correlations Kendall's τ[17] was calculated, except for a closer study of the relationship between pupil sizes in darkness and in light, where an analysis of the ordinary, parametric least-square regression was performed. A 5% level of significance was used throughout the study.

RESULTS

Resting pupil area in darkness was significantly diminished in diabetics as compared with controls, 27.7 mm² ± 8.3 (SD) versus 34.5 mm² ± 6.3 ($2P < 10^{-5}$). There were no differences in average pupil area between the sexes in either the diabetics or the controls, nor was there any correlation between age and pupil area in either group. There was an inverse correlation between pupil area and the duration of diabetes ($\tau = -0.33$, $2P < 10^{-4}$) (Figure 2).

As mentioned earlier, the pupil size in light was not studied in patients who had diminished vision and/or retinopathy in the area used for stimulation. This group of 24 patients had a pupil area in darkness of 24.2 ± 9.5 mm² (SD), which was less than that of the remaining 85 patients, who had a pupil area of 28.7 mm² ± 7.6. The latter group was still, however, significantly smaller than that of the controls ($2P < 10^{-4}$) and inversely correlated to the duration of diabetes ($\tau = -0.29$, $2P = 0.0011$).

Pupil area in continuous light was 20.9 mm² ± 7 (SD) in the diabetics and 22.9 mm² ± 5.9 in the controls, the difference being insignificant ($2P > 0.15$). In the group of long-term diabetics (duration ≥ 15 yr) the pupil area in light of 18.9 mm² ± 7.2 (SD) was, however, less than that of the controls ($2P = 0.012$). Both the absolute and the relative change in pupil area from darkness to light were smaller in the diabetics than in the controls: 7.8 mm² ± 0.5 (SEM) versus 11.8 mm² ± 0.7 ($2P = 10^{-5}$), and 27.6% ± 1.3 versus 34.1% ± 2.0 ($2P = 0.0088$). This means that for a given resting area, the diabetic pupil constricts less in constant light than the normal pupil. This phenomenon is clearly illustrated by the displaced regression lines in Figure 3. The figure also illustrates the strong correlation between pupil

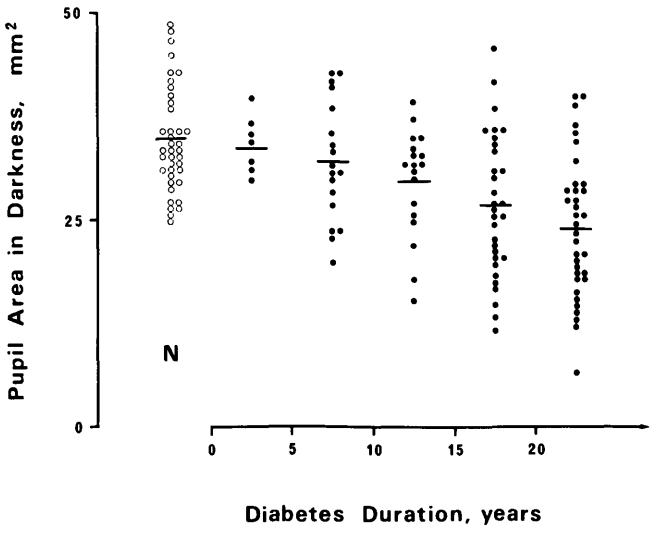
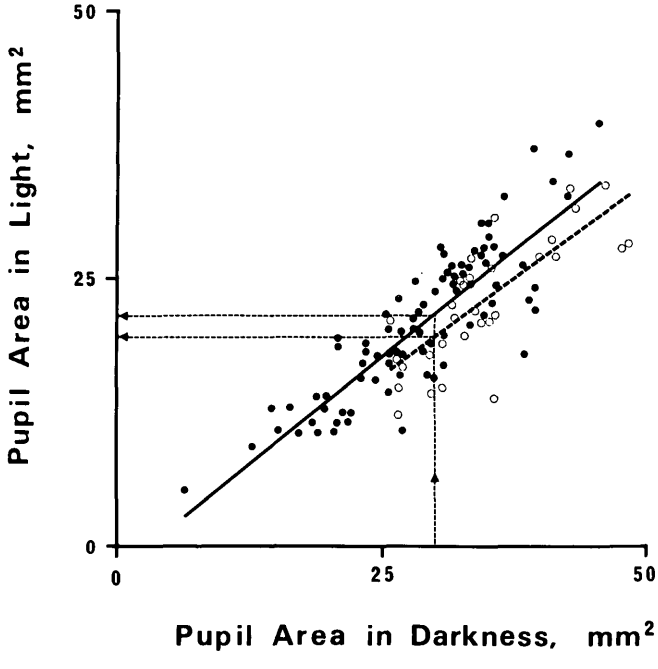


FIGURE 2. Relationship between pupil area after adaptation to darkness and the duration of diabetes in the diabetic subjects (●). The values for the control persons (○) are also shown. Bars indicate mean values in each 5-yr period of diabetes, and the last period is open-ended.

FIGURE 3. Relationship between pupil area in darkness and in light. Diabetics: ●. Controls: ○. The regression lines in the two groups (diabetics, solid line; controls, dashed) are shown. The thin dashed lines show the smaller pupil area during continuous illumination in controls than in diabetics with the same pupil area in darkness.



size in darkness and in light for both diabetics ($r = 0.87$, $2P < 10^{-6}$) and controls ($r = 0.79$, $2P < 10^{-6}$).

As expected, the diabetics had a significantly elevated vibratory perception threshold (VPT) of 18.9 V ± 10.6 (SD) as compared with the control mean of 9.9 V ± 2.9 ($2P < 10^{-6}$). There was an inverse correlation between pupil area in darkness and the VPT in the diabetic group ($\tau = -0.32$, $2P < 10^{-3}$) (Figure 4). In both the diabetic and the normal group the males tended to have a higher VPT, but in neither case was the difference statistically significant. There was a significant, but weak, positive correlation between the VPT and the duration of diabetes ($\tau = 0.18$, $2P = 0.032$) (Figure 5).

Ophthalmoscopy. Fifty-nine diabetics (54%) had no ophthalmoscopic evidence of retinopathy, 19 (17%) had red dots only, 14 (13%) had larger hemorrhages and/or exudates, and 17 (16%) had proliferative changes. As expected, the degree of retinopathy was correlated to the duration of diabetes ($\tau = 0.52$, $2P < 10^{-6}$). In long-term diabetics (duration ≤ 15 yr) the degree of retinopathy was positively correlated to VPT ($\tau = 0.40$, $2P < 10^{-4}$). Figure 6 shows the relationship between the pupil area in darkness and retinopathy in long-term diabetics. There was no difference in pupil size between stage 0, I, and II of retinal changes. However, patients with proliferative retinopathy had a significantly smaller pupil than those without: 19.7 mm² ± 7.4 (SD) versus 27.4 mm² ± 8.0 ($2P < 10^{-3}$), which again was smaller than that of the controls ($2P < 10^{-4}$). Only 5 of the 43 patients with less than a 15-yr duration of diabetes had retinopathy (stages I and II).

Iridoscopy. Of the 76 patients who underwent slit lamp examination, 7 had porosity of the pigment seam (in three of these cases the changes were bilateral), 2 had loss of pigment (bilateral), and 2 had a minor degree of rubeosis iridis (a few small capillaries on the anterior surface of the iris, unilaterally). These 11 patients all had a duration of diabetes that was 15 yr or more. This group of patients with biomicroscopic changes had a mean pupil area in darkness of 26.6 mm² ± 6.3 (SD), which was not significantly different from the value of 23.7 mm² ± 8.0 in the remaining long-term diabetics ($2P = 0.37$).

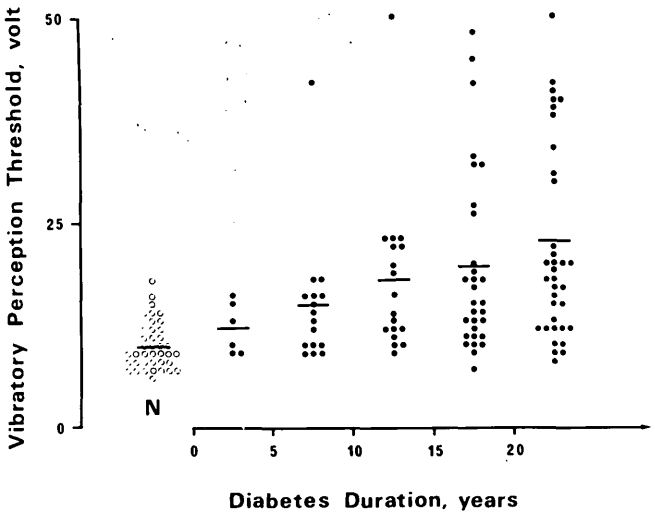


FIGURE 5. Vibratory perception threshold and duration of diabetes (●). The values for controls (○) are also shown. Bars indicate mean values.

Proteinuria. This was present in 15 patients (14%), who all had a diabetes duration of ≥ 15 yr. Their mean pupil size was significantly smaller than that of the remaining long-term diabetics, 21.4 mm² ± 8.3 (SD) versus 26.7 mm² ± 8.3, $2P = 0.035$, and their VPT was significantly higher, 26.3 V ± 13.5 (SD) versus 19.0 V ± 10.3, $2P = 0.028$. There was a positive correlation between nephropathy (i.e., the presence of proteinuria) and the degree of retinopathy ($\tau = 0.44$, $2P < 10^{-3}$).

Diabetes control. Fifty-four diabetics fulfilled the criteria for

FIGURE 4. Relationship between pupil size in darkness and vibratory perception threshold in diabetics. Diabetes duration < 15 yr, ●; ≥ 15 yr, *. The horizontal line indicates the lowest value for the pupil size in the controls and the vertical line the highest value for VPT in the controls.

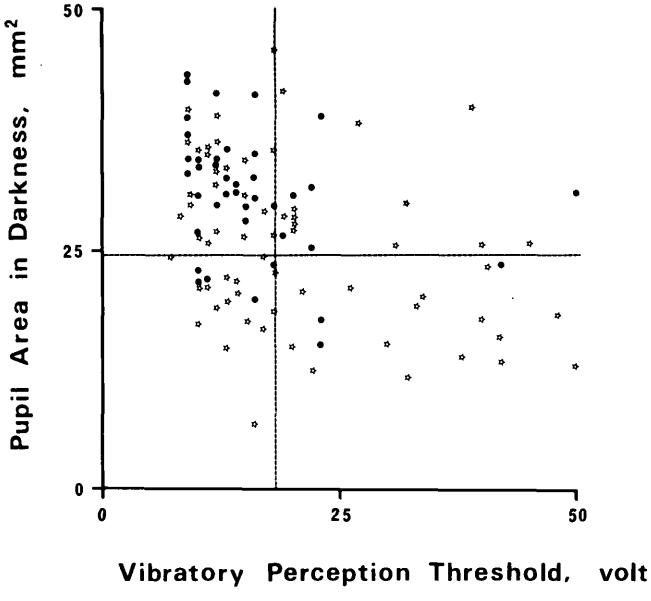
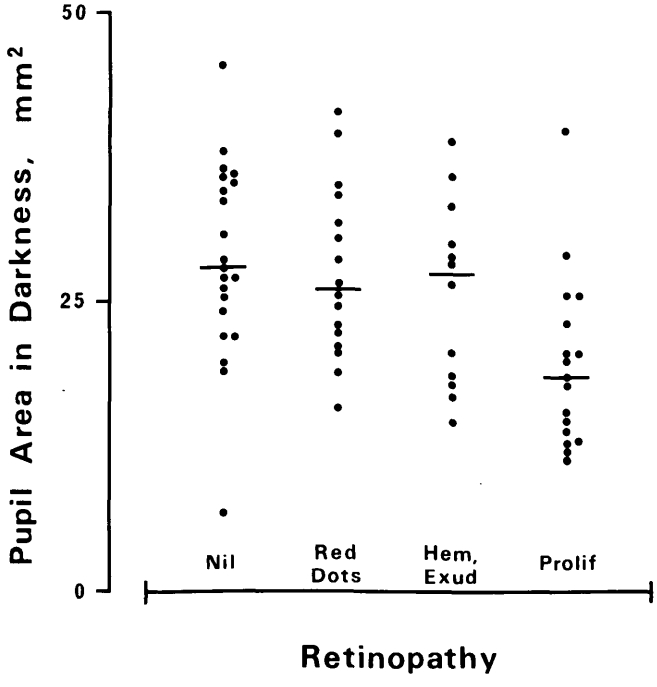


FIGURE 6. The relationship between pupil size in darkness and retinopathy in long-term diabetics (duration ≥ 15 yr).



measuring long-range mean annual blood glucose (diabetes duration longer than 15 yr and more than 5-yr attendance to the clinic). There was no relationship between duration of diabetes and mean annual blood glucose. As shown in Table 2, patients with higher mean blood glucose level had a smaller pupil area ($\tau = -0.49$, $2P < 10^{-3}$), more severe retinopathy ($\tau = 0.43$, $2P < 10^{-3}$), and relatively more often nephropathy ($\tau = 0.30$, $2P = 0.024$). A tendency in the same direction was seen for the VPT, but that relationship fell just short of statistical significance. Of the 15 long-term diabetics within the best control group (mean annual blood glucose < 150 mg/dl) only 1 had a pupil area in the smallest quartile, only 1 had proliferative retinopathy, and only 1 had proteinuria.

Change in pupil area during 4 yr. In the group of 24 patients reexamined after 4 yr, the mean pupil area in darkness had fallen by 9% ± 2 (SEM) ($2P = 0.0011$) (Figure 7).

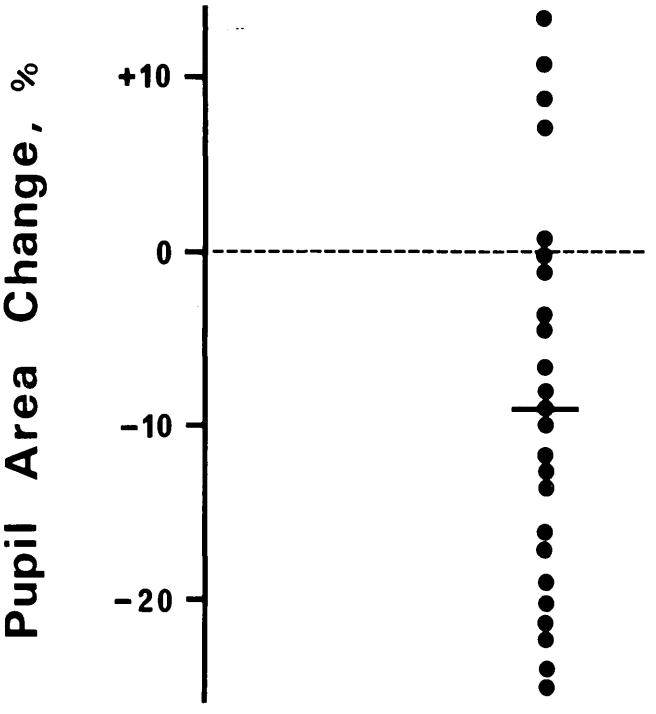


FIGURE 7. The relative change in percent in pupil size in diabetics during a 4-yr period. Bar indicates the mean value of the change.

DISCUSSION

The present investigation of 109 insulin-dependent diabetics, aged 26–43 yr, unselected with regard to long-term complications and without a correlation between age and duration of diabetes, has clearly established that the resting pupil size in darkness decreases with increasing duration of diabetes. These findings, together with the demonstration of a close relationship to the well-known manifestations of microangiopathy and neuropathy, place the abnormally small pupil as an integral part of the long-term diabetic syndrome.[18]

In contrast to the pupil size in darkness, we found that the pupil size in continuous light was not significantly smaller in the diabetic than the control group. Only in the group of long-term diabetics was the difference from normals significant. Although there is a strong relationship between the pupil sizes in darkness and in light in both the diabetic and normal control groups, the reduction in size from darkness to light is less in the former group. This phenomenon may, in part, be explained by the markedly reduced ability in diabetics to maintain miosis in continuous light during metabolic derangement, an abnormality that is seen in both short- and long-term diabetics and one which can be reversed by improved glycemic control.[19] In practical terms, the above findings indicate that the chance of detecting the abnormally small pupil in a diabetic patient would be less under routine clinical conditions than in darkness. The reason why some previous investigators[5–7] have failed to find a smaller pupil size in diabetics than normals could well be that the pupils were studied under illumination.

It is well known that pupil size decreases with advancing age. The lack of such a relationship in the normal control group is undoubtedly explained by the relatively narrow age range studied.

The question of the influence of metabolic control on the development of the long-term manifestations of diabetes has been debated for many years. Strong evidence in favor of the importance of good control has been provided by the large prospective study of Pirart. This study demonstrates a highly significant correlation between the degree of glycemic control and the severity, prevalence, and incidence of diabetic neuropathy and microangiopathy.[20] In the present study, the degree of metabolic control was estimated retrospectively by averaging over a long period of time a number of blood glucose concentrations, one from each year. The results revealed unquestionable relationships between the

TABLE 2
The relationship between mean annual blood glucose (mg/dl) and pupil size (left), retinopathy (middle), and nephropathy (right) among 54 long-term diabetics

Mean annual blood glucose (mg/dl)	Pupil size				Retinopathy				Proteinuria		Σ
	4th	3rd	2nd	1st	0	I	II	III	−	+	
≥ 225	0	1	1	6	0	1	2	5	4	4	8
150 < 225	5	10	9	7	10	9	6	6	27	4	31
< 150	9	3	2	1	9	4	1	1	14	1	15
Σ	14	14	12	14	19	14	9	12	45	9	54
		$2P < 10^{-3}$				$2P < 10^{-3}$			$2P = 0.024$		

The long-term manifestations are arranged in order of increasing severity. The 4th to 1st quartiles are pupil size distribution, and 0 to III are classes of retinopathy ranging from zero to proliferations.
Σ indicates the number of patients in each row or column.

average blood glucose level and the severity of abnormalities in pupil size, retinopathy, and nephropathy.

The exact mechanism of the pupillary abnormalities in diabetes is not clarified as yet. Intrinsic changes in the iris tissue (e.g., as a part of diabetic microangiopathy) could be suspected, and indeed, the close correlation to retinopathy and nephropathy shown in the present study would suggest such a relationship. However, by applying rhythmic light stimulation we have demonstrated in an earlier report that even the smallest long-term diabetic pupil is able to react with normal motility, making the presence of rigidity of the iris tissue unlikely as the cause of the abnormality in size.[21] In the present study, the diabetics with biomicroscopic changes in the iris had a pupil size that was not less than that of the patients without such changes. These findings are in agreement with the findings of Ohrt, who found no correlations between the presence of degenerative changes or rubeosis in the iris in diabetics and diminished pupillary dilation with parasympathicolytic agents.[5,6]

There are two conceivable nervous mechanisms that could lead to the reduced pupil size in darkness: (1) increased contraction of the parasympathetically innervated pupillary sphincter because of a diminished supranuclear inhibition, and (2) reduced sympathetic nervous activity with relaxation of the pupillary dilator. In the first case, which occurs in states of decreased wakefulness, the decrease in pupil size is accompanied by exaggerated fluctuations (Hippus) of the pupil.[22] Because the diminished pupil size in diabetics is not accompanied by increased fluctuations (they are indeed less than normal),[9,10,13] the latter explanation of decreased sympathetic function is much more likely. Impaired sympathetic nervous function as a part of autonomic nervous abnormalities in long-standing diabetes is well established and has been demonstrated (e.g., by the considerably reduced catecholamine concentration in blood and tissues of diabetics).[23,24] Recently, it has been shown that diabetics have an enhanced mydriatic response to sympathomimetics, indicating the presence of classic denervation supersensitivity of the sympathetically innervated dilator muscle.[25,26] Similarly, pharmacologic studies in normals have indicated that the diminished pupil size in senescence is due to loss of sympathetic tone.[27]

The findings of impaired vibratory perception in the present material and the correlation of this abnormality of peripheral nervous function to the duration of diabetes accords with previous studies.[16,28] The demonstrated association between increasing VPT and decreasing pupil size fits in with the view that both abnormalities may be a part of a generalized nervous dysfunction in diabetes. Nevertheless, as is evident from Figure 4, these changes by no means always accompany each other.

Results from previous investigations of the relationship between various autonomic nervous system abnormalities and the duration of diabetes are conflicting. Several authors have found an association between the duration of the disease and the severity of the abnormalities [Aagenaes (neurovascular response in the feet),[29] Christensen (spontaneous variation in blood flow in the feet).[30] Gundersen and Neubauer (heart rate variation)],[31] while others like Sharpey-Schafer and Taylor (Valsalva maneuver),[32] Ewing et al. (cardiovascular response to sustained handgrip),[33] Murray et al. (heart rate variation),[34] and Smith et al. (pupillary parameters)[10] have not. The failure of Smith et al. to demonstrate a correlation between pupillary abnormalities and duration of diabetes could be related to the wide age range of their patient material (18–69 yr).

There have only been few attempts to study the natural history of autonomic nervous dysfunction in diabetes. Mackay et al.[35] and Ewing et al.[36] employed tests of cardiovascular reflex function to demonstrate progression of the abnormalities over a period of a few years. In the present study we have examined 24 patients within an interval of 4 yr and found a mean rate of diminution in pupil size of about 2% per year, which fits well with the observed relationship between pupil size and duration of diabetes as illustrated in Figure 2.

The significance of the abnormally small pupil in diabetes lies chiefly in its usefulness for research purposes. The importance of taking into account the pupil size when studying the stimulated light reflex in diabetes has been pointed out earlier.[11,21,37]

There is a growing interest in diabetic autonomic neuropathy, which has been shown to be associated with disabling symptoms and also with a grave prognosis quo ad vitam.[36] Measuring the pupil size in darkness is a simple, noninvasive, reproducible method that may yield information about the autonomic nervous system in diabetes.

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