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Retinal microangiopathy and pigment epithelial lesions in subjects with normal, borderline, and decreased oral glucose tolerance

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SUMMARY Retinal fluorescein angiography was performed in 150 subjects: 64 with normal fasting blood glucose and normal oral glucose tolerance test (OGTT), 49 with borderline, and 37 with decreased OGTT. Microaneurysms were noted in only two subjects, both with decreased OGTT. Minute changes in the retinal pigment epithelium (RPE) were seen in 23% of the 64 normal persons, in 35% of those with borderline, and 49% of those with decreased OGTT ($p<0.05$). The impact of glucose intolerance was more pronounced in subjects under the age of 50 years, RPE changes being rare (7%) in those with normal OGTT but occurring in 32% of those with borderline or decreased OGTT ($p<0.01$). The corresponding figures among subjects aged 50 or more were 55% and 57%, respectively. We conclude that at least half of the subjects above 50 years show RPE alterations, and that minimal changes in glucose metabolism may precipitate the development of such changes at an earlier age.

The presence of microaneurysms and more advanced signs of diabetic retinopathy at the time of diagnosis of manifest diabetes mellitus has long been recognised and has been reported to occur in 4–15% of such patients.[1] Changes compatible with diabetic retinopathy have also been observed in some subjects with decreased oral glucose tolerance (OGTT) only,[2] as well as in a few with normal OGTT but with renal lesions of the diabetic type.[3]

It has recently been reported that minute changes in the retinal pigment epithelium (RPE), visible both on fluorescein angiograms and colour photographs, occur in about 30% of normal subjects.[4] Since RPE has a high metabolic activity and great phagocytic capacity, the question arises whether alterations of RPE precede apparent diabetic vascular changes in the retina. We have therefore investigated the prevalence of RPE changes in younger (<50 years of age) and older (≥50 years) subjects with and without minor impairment of glucose metabolism.

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Material and methods

SUBJECTS

The study included 150 subjects (54 females, 96 males), 64 of whom had normal fasting blood glucose and normal OGTT (Table 1). Forty-nine of the subjects had borderline and 37 decreased OGTT. Their age ranged from 23 to 72 years. Those with borderline or decreased OGTT were matched with normal controls for age, sex, and body weight.

All subjects participating in the study were apparently healthy. On the basis of detailed case histories, physical examinations, and a series of laboratory tests, the following diseases could be excluded: anaemia, heart failure, hypertension, liver and kidney disease, malabsorption, and endocrine disorders. In addition in all subjects the insulin response to oral glucose and glucose infusion was measured, and estimates were obtained for insulin secretory capacity and insulin sensitivity.[5]

METHODS

Oral glucose tolerance test (OGTT). Glucose was given orally in 300 ml of water in a dose of 1·75 g per kg body weight, and venous blood samples were

collected from an indwelling catheter before and at 15, 30, 45, 60, 90, and 120 min. OGTT was assessed according to the criteria in Table 1, which were adopted from those of Reaven *et al.*[6] *Glucose* in whole blood was measured with glucose oxidase.

The *ophthalmological examination* included measurements of visual acuity and intraocular pressure, as well as slit-lamp biomicroscopy and ophthalmoscopy.

Fluorescein angiography of the fundi was performed with a Zeiss fundus camera (Oberkocken, West Germany) equipped for angiography (excitation filter: Schott BG 12; barrier filter: Schott GG 14). 5 ml of a 10% solution of sodium fluorescein was injected into an antecubital vein. A standard 30% view of the posterior pole of the fundus (centring the macular area) was photographed in both eyes at 1–2 s intervals during the first 30 s and later at about 15 s intervals for 3 min. Mydriasis was induced by topical tropicamide (Mydriacyl) and cyclopentolate (Cyclogyl). Fundus photographs in colour were taken from both eyes. The colour slides were projected on a screen and examined under magnification (X 8). The black and white prints of the angiograms (8×8 cm) were assessed without further magnification by three investigators without knowledge of the patients' glucose tolerance.

Table 1 *Criteria for OGTT*

Groups	*Venous blood glucose, mmol/l*		
	Fasting	*1 hr*	*2 hr*
Normal	<5·2	<7·8	<6·4
Borderline	<5·2	≥7·8 or	≥6·4
Decreased	<5·2	≥8·9 and	≥6·7

Table 2 *Prevalence of retinal changes and age of subjects*

	No. of subjects	*Retinal changes*	*Age, years (mean ± SEM)*
A. Normal controls	64	15 (23%)	43±1
B. Borderline OGTT	49	17 (35%)	43±2
C. Decreased OGTT	37	18 (49%)*	46±2

*The difference between groups A and C is significant ($p<0·05$), that between groups A and B is not.

Table 3 *Distribution of 150 subjects with or without retinal changes according to age (<50 and ≥50 years)*

	Age of subjects (years)	
	<50	*≥50*
Normal controls		
No changes (n=49)	40	9
Retinal changes (n=15)	3 (7%)	12 (57%)
Borderline or decreased OGTT		
No changes (n=51)	36	15
Retinal changes (n=35)	17 (32%)*	18 (55%)

*$p<0·01$.

Results

Ophthalmological examination in all subjects disclosed normal visual acuity (0·7–1·0) and intraocular pressure and clear ocular media. Retinal vascular changes were limited to slight attenuation of arterioli and pathological arteriovenous crossings in 18 subjects over 50 years of age, equally distributed between the subgroups and controls. No apparent retinal disease was found by ophthalmoscopy except for depigmentation and minor hyperpigmented lesions similar to macular degeneration.

In some subjects, detailed examinations of fluorescein angiograms and fundus colour slides showed changes of the RPE. The prevalence of these alterations—provided they were detected by both methods—is given in Table 2. RPE changes were noted in 23% of subjects with normal OGTT and in 35% of those with borderline OGTT. About half of the subjects with decreased OGTT had RPE changes ($p<0·05$).

These alterations of RPE were characterised on fluorescein angiograms by the following two findings: 'window' defects comprising a variety of alterations ranging from minute dots to multiple or confluent circumscribed areas; and punctate choroidal hyperfluorescence seen as solitary or multiple sharply bordered lesions, some of them looking like drusen (Figs. 1–4). The RPE changes appeared early during angiography, coinciding with the choroidal filling of dye. They showed little change with time and faded with the choroidal fluorescence. On colour fundus photographs these changes corresponded to depigmented, lightly yellow dots or spots and areas with attenuated RPE.

The prevalence of RPE changes in subjects older than 50 years was not related to OGTT (Table 3). On the other hand in the younger groups the prevalence of RPE changes was much higher among those with borderline and decreased OGTT than in normal persons ($p<0·01$).

Retinal microaneurysms were found in only two subjects, both with decreased OGTT.

Discussion

The ocular changes encountered in this study were lesions of RPE, and seen as 'window' defects or drusen-like changes on fluorescein angiograms. The RPE lesions, though limited in size and number, were present in 23% of subjects with a completely

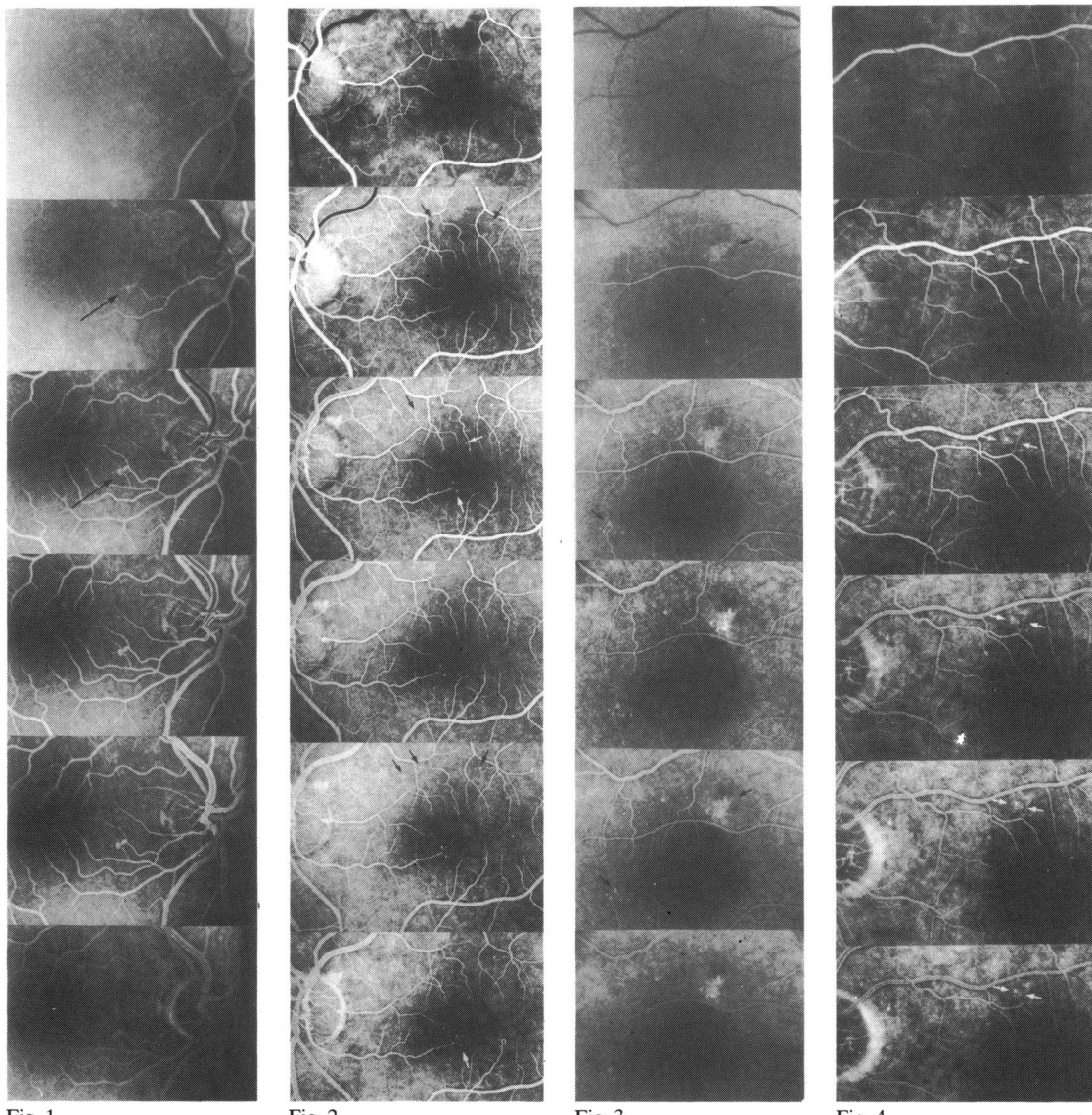

Fig. 1 Fig. 2 Fig. 3 Fig. 4

Figs. 1–4. *Fluorescein angiograms in early, arteriovenous, and late phase (about 2 minutes), depicting alterations at the RPE level (arrows).* Fig. 1 *Hyperfluorescent lesion in papillo-macular area; female aged 54, borderline OGTT.* Fig. 2 *Multiple tiny drusen-like changes; female aged 40, borderline OGTT.* Fig. 3 *Hyperfluorescent spots and a confluent area of attenuated RPE above fovea; male aged 42, decreased OGTT.* Fig. 4 *Indistinctly bordered hyperfluorescent spots; male aged 47, decreased OGTT.*

normal fasting blood glucose and OGTT. This figure underestimates the incidence of these lesions, since only a 30° view of the fundus was assessed. Recently, subtle morphological elements visible both on fluorescein angiograms and colour photographs were reported in about 30% of normal subjects when a 45° view of the fundus was examined.[4] This figure, when extrapolated to a 30° view, would correspond to the 23% in our normal controls.

In subjects with borderline OGTT the incidence of RPE lesions increased to about 35% and in those with decreased OGTT to 49%. Such a trend towards a higher incidence of retinal lesions parallel with increased disturbances of glucose tolerance is sup-

ported by observations of such changes in insulin-dependent diabetics with an onset of the disease prior to the age of 40 years; patients younger than 50 years showed RPE lesions in 53%, and those who were older in 70%.[7] In a similar study the incidence of RPE lesions in juvenile diabetics was as high as 80%.[8]

In general, RPE lesions increase with age and probably proceed to senile macular degeneration.[9] However, electron microscopy has revealed initial RPE changes as early as the age of 30.[10] In the angiographic 'window' defects the RPE is attenuated, with partial or complete loss of melanin granules, and may be associated with sclerosis of the subjacent choriocapillaries.[11] RPE lesions are often accompanied by drusen, which are regarded as residual products of insufficient phagocytosis by the RPE of photoreceptor outer segments, and recognised as basal lamina deposits on Bruch's membrane.[12] Drusen are often found in diabetics[13]

The scantiness of microaneurysms (found in only two subjects) and the absence of other vascular abnormalities indicate that morphological retinal microangiopathy is rare in conditions prior to manifest diabetes.

In human diabetics increased accumulation of fluorescein into the vitreous, as shown by fluorophotometry, is an early finding which may precede angiographically detectable retinal microangiopathy.[14] In streptozotocin diabetic rats, also, an enhanced intravitreal concentration of this dye is seen very early during the disease.[15] The reason for the increased fluorescein accumulation is not clear. Fluorescein is probably eliminated from the vitreous by an active transport mechanism,[16] and several observations suggest that the RPE may be involved in this process.

Early morphological alterations of the RPE were reported in Streptozotocin-induced[17] and spontaneously diabetic rats.[18]

The fluorescein extrusion from eyes of normal and diabetic rats can be inhibited by sodium iodate, a substance that results in damage to the RPE.[19 20]

Although conclusive evidence is lacking, impaired function of the RPE may be an early change in experimental diabetes and possibly in human diabetes as well. An interesting question is whether the changes described here constitute an early retinal alteration which goes on to the microangiopathy characteristic of diabetic retinopathy. If so, the RPE changes might possibly be used as an early marker for this type of retinopathy. Only prospective studies can solve this problem. For this reason the subjects with impaired glucose tolerance with or without RPE alterations are being re-examined with regard to glucose tolerance and RPE changes.

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