Diabetologia (1984) 27: 198–202

Diabetologia

Retinopathy is associated with higher glycaemia in maturity-onset type diabetes

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Summary. In a group of 149 maturity-onset type diabetic patients followed from diagnosis, 55 (37%) had retinopathy on colour photography 7 years later. Those patients with retinopathy had significantly greater glycaemia, as shown by higher fasting plasma glucose levels at diagnosis, larger mean values for fasting glucose 1, 3 and 5 years later, and higher random glucose and haemoglobin A_{1c} at ophthalmic review ($p = 0.001$, 0.002, 0.007 and 0.001, respectively). Substantial retinopathy, as measured by >5 microaneurysms, also correlated significantly with each index of glycaemic control.

Key words: Background retinopathy, maturity-onset type diabetes, glycosylated haemoglobin, prospective study, colour photography.

The importance of glycaemic control to the development and progression of retinopathy remains uncertain [1, 2]. In this study, the metabolic and ophthalmic progress of 150 maturity-onset type diabetic patients has been followed from diagnosis so as to relate glycaemic levels to the development of retinopathy about 7 years later. Glycaemic control in the first years after diagnosis has been claimed to be of particular importance to later development of retinopathy in Type 1 (insulin-dependent) diabetes [3, 4]. This could be so, if the recent hypothesis that diabetic nephropathy runs an irrevocably downhill course once it has developed [5] were to apply to a certain extent also to retinopathy.

Subjects and methods

Subjects

In 1973, a prospective study was initiated of newly diagnosed maturity-onset diabetic patients referred to the Radcliffe Infirmary diabetic clinic [6]. By 1976, 250 patients had been recruited. On entry to the study, all patients were under 66 years old and untreated except for occasional dietary advice. Patients were excluded if on any treatment likely to disturb carbohydrate metabolism markedly, if they had an imminently life-threatening condition, or if they were judged clinically to need insulin in their initial treatment. The presence (or past history) of any other endocrine disease, myocardial infarction or neurological deficit following a cerebrovascular accident precluded admission, as did the presence, but not past history, of liver disease. To enter, patients had to give their informed consent and to show impaired glycaemic control (see below). They were initially randomised between two different types of dietary advice, either a traditional 'low carbohydrate regime' or a diet based on limitation and modification of the fats [6]. Throughout, treatment with diet was supplemented with either oral hypoglycaemic drugs or subcutaneous insulin, as judged necessary on clinical grounds.

All the patients in the original study were invited to return to the Oxford Eye Hospital for an ophthalmic review, and 150 patients attended in 1982.

Ophthalmic assessment

The ophthalmic assessment included tests of visual acuity and colour vision, and ophthalmoscopic examination of the fundus through dilated pupils. This assessment was performed at diagnosis, and again at review in 1982, when retinopathy was also assessed both by comparison of clinical fundus examination to the Hammersmith grading photographs (grade B) [7], and by analysis of seven 30° fundus photographs taken with a Zeiss fundus camera using Ektachrome 64 film. From these photographs, and via a back projection screen, a montage of the fundus was traced onto transparent acetate paper.

Metabolic assessment

At the start of the study, an intravenous glucose tolerance test (20 g/m^2 body surface) was performed after 2 or 3 days on a diet containing at least 200 g carbohydrate daily. Patients were admitted to this study only if there was evidence of impaired glycaemic regulation, as indicated by a K_G rate constant below 1.2 [8]. The patients were re-studied 1, 3 and 5 years after diagnosis, and assessed for glycaemic control and other metabolic features as well as by general clinical examination.

At the ophthalmic review in 1982, a random blood sample was taken for haemoglobin A_{1c} (HbA_{1c}) and plasma glucose. The HbA_{1c} was measured by an isoelectric focussing method with which the upper limit of the range for non-diabetic subjects was 8.0% [9]. Plasma glucose was measured on an autoanalyser by a glucose oxidase method.

Table 1. Comparison of features before treatment, and known liability to retinopathy of those attending and not attending ocular review in 1982

	Patients reviewed ($n=149$)	Patients not reviewed ($n=100$)	p
Age (years)	57.8 ± 0.8	48.7 ± 1.2	0.001
Gender (male : female)	82 : 67	41 : 59	NS
Body mass index (weight ÷ height^2)	29.7 ± 0.5	27.8 ± 0.5	0.02
Months of symptoms before entry	4.3 ± 1.2	8.6 ± 1.6	0.05
Body mass index (Maximum–0)	1.1 ± 0.7	0.7 ± 1.0	NS
Plasma glucose (mmol/l)	11.8 ± 0.3	11.4 ± 0.4	NS
Number with retinopathy at diagnosis	3	14	
Number without retinopathy at diagnosis	136	46	
Number without full ocular examination at diagnosis	10	40	

Results expressed as mean ± SEM

Table 2. General characteristics of 149 diabetic patients with or without retinopathy

	Patients with retinopathy	Patients without retinopathy	Total number
Number of patients	55 (37%)	94 (63%)	149
Gender: male	28 (34%)	54 (66%)	82
female	27 (40%)	40 (60%)	67
Age (years)	55.2 ± 10.4[a]	59.3 ± 10.1	57.8 ± 10.4
Time since diagnosis of diabetes (months)	90 ± 10	87 ± 12	88 ± 12
Body mass index (weight ÷ height^2)			
At diagnosis	30.0 ± 6.8	29.2 ± 5.4	29.5 ± 6.0
At test	30.0 ± 5.7[a]	27.9 ± 4.9	28.6 ± 5.3

Results expressed as mean ± SEM
[a] $p < 0.05$ for comparison between those with and without retinopathy

Table 3. Glycaemic control in 149 diabetic patients with or without retinopathy

	Patients with retinopathy ($n=55$)	Patients without retinopathy ($n=94$)	p
Fasting plasma glucose at diagnosis (mmol/l)	13.2 ± 4.0	10.9 ± 3.8	0.001
Mean fasting plasma glucose at 1, 3, 5 years (mmol/l)	9.0 ± 2.9	7.5 ± 2.3	0.002
Random plasma glucose (mmol/l)	10.8 ± 4.8	8.5 ± 4.2	0.007
HbA_{1c} (% total Hb)	8.9 ± 1.8	7.7 ± 2.0	0.001

Results expressed as mean ± SEM

Statistical analysis

Statistical analysis was performed on an ICL 2988 computer, using the statistical package for the social science program [10]. The significance level of Student's unpaired t-tests and Spearman rank correlation (coefficient r_s) was taken as $2p < 0.05$.

Results

One hundred and fifty patients from the original cohort of 250 patients attended Oxford Eye Hospital for assessment in 1982. One of these had cataracts preventing fundoscopy and photography and was excluded from all analyses. Of the 100 not then attending, 22 had died, 20 had moved away from the area, and 58 declined the invitation to ophthalmic review, including two who had already been treated with retinal photocoagulation and were under regular review at the Eye Hospital for their visual impairment. In Table 1, pre-treatment features are compared between those reviewed in 1982 (group A) and those who did not attend then (group B). The latter differ from the former in the longer history of symptoms they recalled at diagnosis, their younger age and their greater propensity, already, not to attend all recommended examinations. Notably, too, group B patients had a greater frequency of background retinopathy at diagnosis. For all 250, this was 8.5%.

Of the 149 examined in 1982, three had retinopathy at diagnosis and 10 had not attended for ophthalmic examination at entry. Our conclusions do not differ significantly whether all the 149 or the 136 remaining after exclusion of those 13 are analysed.

Retinopathy was found in 55 (37%) of the 149 patients examined in 1982. Of these, 22 had minimal retinopathy (defined as five microaneurysms or less in either eye), and 33 had a more extensive background retinopathy. No patient with proliferative retinopathy was found among the 149, though two group B patients developed this and have received treatment and regular supervision for it, and therefore declined special ophthalmic review in 1982.

Those with retinopathy of any degree were younger than those without (mean ± SD, 55.2 ± 10.4 versus 59.3 ± 10.1 years, $p < 0.05$). The two groups were well matched for gender, duration of diabetic symptoms and body mass index at diagnosis (Table 2). However, the body mass index at test (1982) was significantly greater in those with retinopathy.

Glycaemic control

Four measures of glycaemic control were used: the fasting plasma glucose at diagnosis, the mean of three fasting plasma glucose samples (1–5 years), and both a random plasma glucose and HbA_{1c} at ophthalmic review. All four values were significantly higher in those with retinopathy ($p < 0.001$, 0.002, 0.007 and 0.001, respectively; Table 3).

Figure 1 shows that the number of patients with retinopathy 7 years after diagnosis can be related to either their fasting blood glucose at diagnosis or their mean fasting plasma glucose levels at 1, 3 and 5 years. From Figure 2, it can be seen that the risk of developing retinopathy is increased from 23% to 52% if the fasting plasma glucose exceeds 12 mmol/l at presentation, and

also that the risk of retinopathy gradually increases as the mean fasting glucose under treatment increases. Only 18% of 22 patients with a mean fasting plasma glucose of <6 mmol/l showed retinopathy 7 years after diagnosis compared with seven of eight patients (88%) with a mean fasting glucose of 14 mmol/l or more. The percentage with retinopathy at 7 years was also related to the HbA_{1c} and random plasma glucose level taken at ophthalmic assessment, with a gradual increase in risk of retinopathy as HbA_{1c} increased, especially above 8%. A random plasma glucose >10 mmol/l was also associated with a marked increase in risk of retinopathy.

The mean fasting plasma glucose from 1 to 5 years correlated with the random plasma glucose and HbA_{1c} (coefficient $r_s < 0.001$). As examined in a sample of 100 patients, the mean of random plasma glucose values at visits to an afternoon diabetic clinic showed highly significant correlations with the fasting glucose values, except for the fasting value before treatment. Thus, the mean random glucose for the period 1 to 5 years after diagnosis had a correlation coefficient (r_s) of 0.63 ($p < 0.001$) with the mean fasting glucose at the 3-year review (A Schidlmeier, V Beckett, TDR Hockaday, personal observations). But the same mean random value had a coefficient of only 0.24 against the pre-treatment fasting glucose (NS).

Treatment

By definition, patients entering this study were judged clinically not to require insulin treatment initially, but subsequently 22 (15%) have been prescribed insulin, and another 72 patients (48%) oral hypoglycaemic tablets; 55 (37%) have been managed by diet alone. Such therapeutic decisions were made in the routine out-patient clinic, and without reference to observations gathered for the prospective study. The incidence of retinopathy was higher in those treated with insulin or tablets compared with those on diet alone ($p < 0.025$; Table 4). This was presumably because of significantly higher glucose values in both insulin and tablet groups (Table 4).

Analysis allowing for interaction between various factors

The results can be analysed by multiple linear regression analysis for factors associated with (1) whether or not retinopathy of any degree is present, (2) whether or not substantial background retinopathy is present (more than five microaneurysms in either eye), or (3) the difference between substantial retinopathy and no detectable retinopathy. In each case, the only significant associate of developed retinopathy is the glycaemic control, having allowed for interactions with age, gender, whether or not insulin-treated, the type of dietary advice to which the patients were randomised [6], time in months between diagnosis and ophthalmic review, and duration of symptoms before diagnosis (as recalled then by the patient). The link with HbA_{1c} was always at a significance level of $p < 0.005$, but with mean fasting plasma glucose (1–5 years) this varied between $p < 0.05$ for comparison (1) and $p < 0.025$ for comparisons (2) or (3). The gradient of risk was such that a 1 mmol/l change in mean glycaemic level shifted 4% of the 149 patients from one category to the other. In these analyses, the glycaemic level (with zero order correlation coefficient around 0.3) contributed some 10% of the total variance for development of retinopathy, while only about 25% of this total could be attributed to recognised factors.

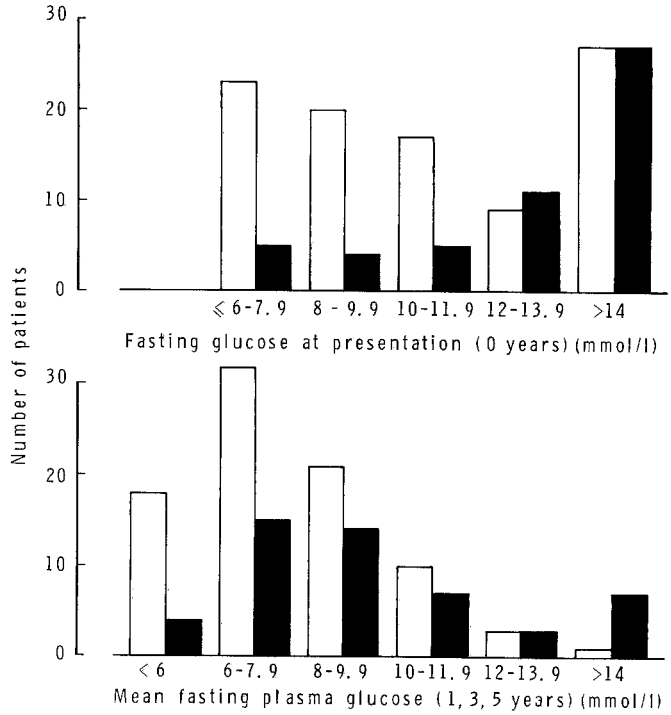

Fig. 1. Number of patients who have developed retinopathy at 7 years according to (a) their fasting plasma glucose at diagnosis, and (b) their mean fasting plasma glucose (1, 3 and 5 years). ■ = with retinopathy; □ = without retinopathy

If duration of symptoms was excluded, then pre-treatment fasting blood glucose was an independent predictor of development of retinopathy alongside glycaemia under treatment ($p < 0.025$). If only values ascertained at diagnosis were considered, the K_G rate constant in the intravenous glucose tolerance test was an independent ($p < 0.01$) factor for development of substantial (but not any) retinopathy alongside fasting blood glucose.

Discussion

Although the relationship between retinopathy and glycaemic control continues to be debated, most reviews conclude that good glycaemic control is beneficial [11–13]. In the present study, the risk of developing retinopathy was clearly directly related to glycaemic control as measured by the mean of three fasting plasma glucose values over 5 years, or by random HbA_{1c} or blood glucose values at the final ophthalmic review. The fasting glucose at diagnosis, if considered alone, was a predictor for the development of retinopathy in this group of maturity-onset type diabetic patients

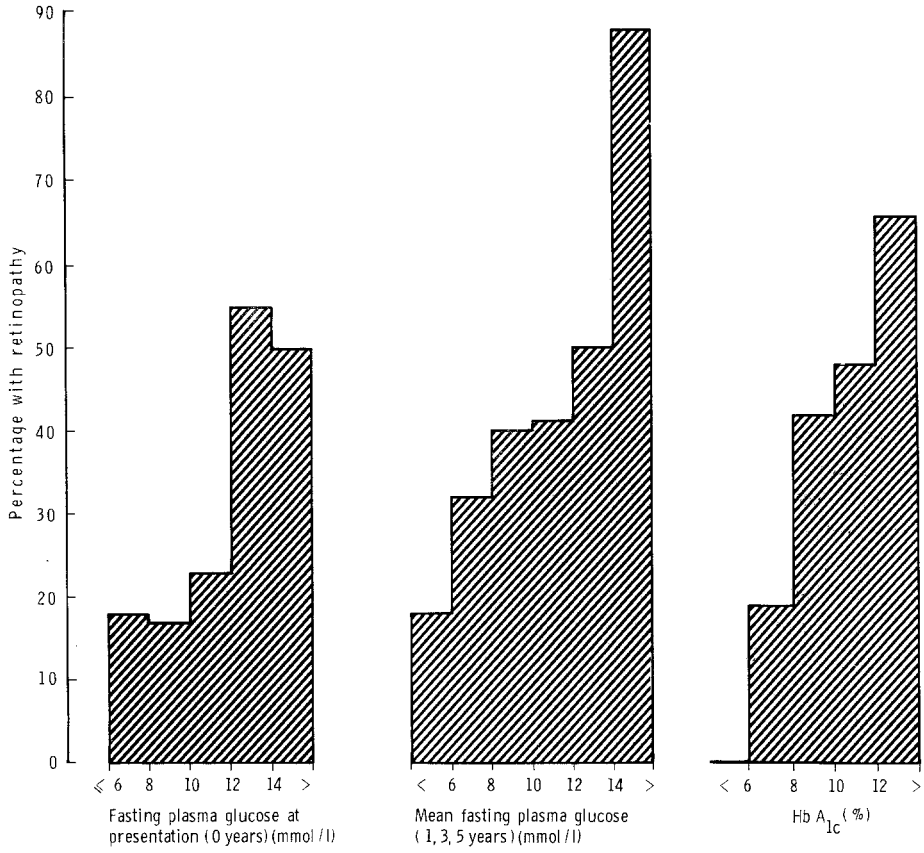

Fig. 2. Percentage of patients with retinopathy at 7 years according to (a) their fasting plasma glucose at diagnosis, (b) their mean fasting plasma glucose (1, 3 and 5 years), and (c) their haemoglobin A_{1c} value at review

Table 4. Prevalence of retinopathy according to treatment group

	Number of patients			Mean plasma glucose	
	With retinopathy	Without retinopathy	Total	1–5 years (three values) (mmol/l)	*2p*
Insulin	10	12	22	10.9 ± 3.5	$p = 0.001$
Tablets	33	39	72	8.5 ± 2.2	$p = 0.001$
Diet	12	43	55	6.4 ± 1.3	
			149		

Increased prevalence in the insulin and tablet groups was linked to significantly higher glucose values. $p < 0.025$ (χ^2 test) for distribution of retinopathy among treatment groups

p value at right is for comparison of mean glucose of either insulin- or tablet-treated patients with those managed by diet alone

7 years later, and patients with an initial fasting glucose of > 12 mmol/l increased their risk of retinopathy from a one in four to a one in two chance. However, our results give no real support to the concept of an absolute glycaemic threshold for retinopathy, as previously advanced [14, 15].

On multiple linear correlation analysis the pre-treatment plasma glucose level remained a predictor of development of retinopathy independent of glycaemia under treatment and disappeared as a significant index only if the months of pre-treatment symptoms were also in the analysis. It is too early to know whether these results will eventually support the hypothesis of Caird [3] and Constam [4] that during the first 5 years after diagnosis good control is crucial for reduction of 'complications' in the long term. Burditt et al. [16] found a significant relationship between the incidence of retinopathy 10–14 years after diagnosis and the glycosuria percentage in the first 5 years. Patients with good initial control, followed by poor control, resembled the group with good control, but those with poor initial control, but subsequent good control, resembled those with poor control throughout. If the first 5 years are specially important, it may explain why some studies have shown glycaemic control to be without effect on the incidence of retinopathy, as patients in these studies may already have developed an irreversible retinopathy during the earlier years of diabetes. This retinopathy may have its own momentum to deterioration, by analogy with the suggestions of Viberti et al. [5] for diabetic nephropathy, namely that early tissue damage is preventable and reversible (or at least capable of arrest) by tight glycaemic control, but that slightly more severe lesions have an inherent tendency to deteriorate, whatever the glycaemic level, even if this contributes something to the rate of deterioration. We would rephrase the Caird-Constam hypothesis as: – 'good' (glycaemic) control is crucial so long as no or very little retinopathy has developed'. This does not mean that the level of glycaemia may not still be important in later management.

This report provides something of a counterweight to the conclusions that might be drawn from the early results of the Steno Memorial Hospital study on insulin-treated patients [2] of the effect on retinopathy of near-normal glycaemia achieved by continuous subcutaneous infusion of insulin. Despite improvement in two indices of retinal function by continuous insulin infusion, the group so treated showed more soft exudates in the retina during the first year (and especially during the first 6 months) than a group continuing on conventional subcutaneous insulin, and mostly at a higher glycaemic level. From the discussion above, one can suspect that the retinopathy in the Steno study patients was already too advanced to be easily improved.

Two other studies have related glucose levels to development of microangiopathic lesions in diabetic patients. Even though one also linked hyperglycaemia with greater tissue damage [17], it cannot be directly compared with the present study, because retinopathy was lumped together with nephropathy and neuropathy in the analyses. In addition, a minority entered the study up to 9 years after diagnosis, while the clinical assessment followed entry over as wide a range as from 5 to 10 years. Much data on the development of retinopathy in non-insulin-dependent diabetics patients was gathered in the University Group Diabetes Programme [18], but this was analysed primarily according to the allocated treatment rather than the glycaemic level.

A prospective cohort study is the most appropriate method for studying the association between glycaemia and retinopathy. The one therapeutic randomisation [6] at entry did not affect the frequency of retinopathy, and our conclusions are undiminished by absence of other randomisations between different therapies or glycaemic targets. Full allowance has been made here for recorded interacting factors. Randomisation at entry or later reduces bias in allocating different procedures to different patients, but we are not here assessing the optimal mode of management. More pertinent is to question the extent to which our conclusions apply to the universality of diabetic patients. One can only believe it likely that they apply widely, while noting the difference between the diabetics for whom we have definite information (Table 1, group A) and those where this is incomplete (group B). We have not examined diabetic patients in other places and of other habits and race. All such cohort studies face the problem of lack of final assessment of those who die during them. In principle, these do not differ from any other final absentees. Calculations of what happens during the study must be confined to those patients assessed throughout. Incomplete final assessment affects only the width of applicability of the conclusions.

Acknowledgements. These studies have been supported at various stages by the International Sugar Research Fund, the British Diabetic Association, the Oxford Diabetes Trust and the Simon Broome Heart Research Trust, to all of whom we express our gratitude. We appreciate greatly the ready cooperation of the patients described, and of Mrs C. Whitwell and Mrs B. Pim, nursing sisters who supervised many of the observations. We are also very grateful to Mrs D. Renton for careful preparation of the manuscript; to Miss V. Beckett for skilful statistical help; to the Department of Clinical Biochemistry, John Radcliffe Hospital, under supervision of Dr R. H. Wilkinson, for blood glucose measurements, and to Mr R. Jelfs for the glycosylated haemoglobin measurements.

References

1. Job D, Eschwege E, Guyot-Argenton J-P, Aubry J-P, Tchobroutsky G (1976) Effect of multiple daily insulin injections on the course of diabetic retinopathy. Diabetes 25: 463–469
2. Steno Study Group (1982) Effect of 6 months of strict metabolic control on eye and kidney function in insulin-dependent diabetics with background retinopathy. Lancet 1: 121–124
3. Caird FI (1967) Estimation of the long-term control of diabetes. Diabetes 16: 502–503
4. Constam GR (1965) Zur Spätprognose des Diabetes Mellitus. Helv Med Acta 32: 287–306
5. Viberti GC, Hill RD, Jarrett RJ, Argyropoulos A, Mahmud M, Keen H (1982) Microalbuminuria as a predictor of clinical nephropathy in insulin-dependent diabetes mellitus. Lancet 1: 1430–1432
6. Hockaday TDR, Hockaday JM, Mann JI, Turner RC (1978) Prospective comparison of modified fat and low carbohydrate dietary advice in the treatment of diabetes. Br J Nutr 39: 357–362
7. Oakley N, Hill DW, Joplin GF, Kohner E, Fraser TR (1967) Diabetic retinopathy, I. The assessment of severity and progress by comparison with a set of standard fundus photographs. Diabetologia 3: 402–405
8. Conard V, Franckson JRM, Bastenie PA, Kestens J, Kovacs L (1953) Etude critique du triangle d'hyperglycémie d'un coefficient d'assimilation glucidique. Arch Int Pharmacodyn Ther 93: 277–292
9. Jeppsson JO, Franzen B, Gaal AB (1980) Simplified determination of haemoglobin A_{1c} in diabetic patients by use of electro-focussing. In: Radola BJ (ed) Electrophoresis '79. Advanced methods: biochemical and clinical applications. De Gruyter, Berlin New York, pp 655–661
10. Nie NH, Hull CH (1975) Statistical package for the social sciences. McGraw-Hill, New York
11. Stowers JM (1975) Complications in relation to diabetic control: general review. In: Keen H, Jarrett J (eds) Complications of diabetes, 1st edn. Arnold, London, pp 1–5
12. West KM (1982) Hyperglycaemia as a cause of long-term complications. In: Keen H, Jarrett J (eds) Complications of diabetes, 2nd edn. Arnold, London, pp 13–18
13. Tchobroutsky G (1981) Metabolic control and diabetic complications. In: Brownlee J (ed) Current and future therapies, Vol 5. Handbook of diabetes mellitus. Wiley, Chichester, pp. 3–39
14. Jarrett RJ, Keen H (1976) Hyperglycaemia and diabetes mellitus. Lancet 2: 1009–1012
15. Pettitt DJ, Knowler WC, Lisse JR, Bennett PH (1980) Development of retinopathy and proteinuria in relation to plasma glucose concentrations in Pima Indians. Lancet 2: 1050–1052
16. Burditt AF, Caird FI, Draper GJ (1968) The natural history of diabetic retinopathy. Q JMed N.S. 37: 303–317
17. Maneschi F, Cassar J, Lowy C, Kohner EM (1981) Development of diabetic microangiopathy and diabetic control. Diabète Métab 7: 181–187
18. University Group Diabetes Program (1976) A study of the effects of hypoglycaemic agent on vascular complications in patients with adult-onset diabetes. VI. Supplementary report on non-fatal events in patients treated with tolbutamide. Diabetes 25: 1129–1153

Received: 19 October 1983
and in revised form: 9 April 1984

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