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Prevalence and 15-year incidence of retinopathy and associated characteristics in middle-aged and elderly diabetic men

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SUMMARY We examined 178 men for the presence of diabetic retinopathy during 1978–80. They had been part of a group of 205 men from the Jerusalem area, diagnosed as being diabetic or having an abnormal glucose tolerance test in the Israel Ischaemic Heart Disease Project, a 5-year epidemiological investigation of Israeli male government employees. Seventy-four (42%) had diabetic retinopathy as determined by direct and indirect ophthalmoscopy, 3-mirror contact lens examination, and fundus photography. Those with and without retinopathy were compared for clinical, biochemical, behavioural, and biographical variables measured subsequently in 1963, 1965, and 1968. We found no significant differences between the 2 groups with respect to antecedent Quetelet index, blood pressure, peripheral vascular disease, blood lipids, haematocrits, smoking habits, area of birth, and education. Statistically significant differences between men with and without retinopathy were found for severity of carbohydrate metabolic intolerance at identification, duration of the metabolic abnormality, age, casual glucose values, and serum uric acid levels. Low serum uric acid appears to precede the incidence of diabetic retinopathy and to decline further as the disease progresses.

Diabetic retinopathy is a major cause of visual impairment and blindness in economically advanced countries. It is the commonest cause of newly reported blindness in the 41–60 age group,[1] accounting for at least 12% of all new cases of blindness yearly. Considerable differences in rates of retinopathy among diabetics have been reported,[2–5] but studies attempting to evaluate the possible causes of these differences are inconclusive.

This follow-up study was undertaken (*a*) to investigate the prevalence and incidence of retinopathy in a group of men diagnosed as having diabetes or an abnormal glucose tolerance test (GTT) during the Israel Ischemic Heart Disease Project (IIHDP) survey, and (*b*) compare diabetics with retinopathy to diabetics without retinopathy for clinical, biochemical, behavioural, and sociodemographic variables measured during 3 previous successive examinations.

By studying diabetics with and without retinopathy who were examined repeatedly many years ago we attempt to support the hypothesis that a factor associated with the development of retinopathy may be present before any signs of the disease occur. These may even disappear after the retinopathy develops.

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Materials and methods

A prospective epidemiological investigation was carried out on 10059 men aged 40 to 65 by the IIHDP during 1963–8.[6] Inhabitants of the Jerusalem, Tel Aviv, and Haifa areas, civil servants and municipal employees, underwent 3 examinations in 1963, 1965, and 1968. The participants were born in 6 predefined geographical areas: Israel, Eastern Europe, the

Table 1 *Criteria for diagnosis of diabetes based on a scoring system for glucose tolerance tests*

Method	*Fasting value*		*1-hour value*		*2-hour value*	
	(mg/100 ml)	*(Score)*	*(mg/100 ml)*	*(Score)*	*(mg/100 ml)*	*(Score)*
Glucose oxidase or Somogyi-Nelson	≥110	1	≥170	½	≥120	½
	100 to 109	½	160 to 169	0 (Abnormal)	100 to 119	0 (Abnormal)
	≤99	0	≤159	0	≤99	0
Autoanalyzer (Hoffman)	≥120	1	≥180	½	≥130	½
	110 to 119	½	170 to 179	0 (Abnormal)	110 to 129	0 (Abnormal)
	≤109	0	≤169	0	≤109	0
Hagedorn-Jensen	≥130	1	≥200	½	≥140	½
	120 to 129	½	180 to 199	0 (Abnormal)	120 to 139	0 (Abnormal)
	≤119	0	≤179	0	≤119	0

Scores are obtained by addition: a score of 1, 1½, or 2 indicates diabetes; a score of 0 (abnormal) or ½ indicates abnormal glucose tolerance; a score of 0 without the designation (abnormal) is normal (no diabetes).
SI conversion: glucose mg/100 ml×0·0555=mmol/l.

Middle East (excluding Israel), Central Europe, South Eastern Europe, and North Africa. This investigation provided us with approximately 120 variables for analysis.

The diagnostic procedure for and the severity classification of carbohydrate intolerance have been reported.[7 8] A diagnosis of diabetes was based on a scoring system for GTT (Table 1) or, when GTT data were not available, on 3 diabetic abnormalities—usually 3 abnormal glucose values while fasting (Table 2). The criteria for classification of the severity of the diabetes are summarised in Table 3.

In 1965 an ophthalmological study was carried out among the 2220 participants of the Jerusalem area.[9] This study included a fundus photograph of 6 standard fields of one eye offered to all subjects who came for examination during a 6-month period. Of the 1200 subjects examined 1092 had fundus photography. The slides of 874 are available and suitable for analysis. Owing to an unfortunate mailing accident the slides of 188 subjects were lost. There is no reason to suspect bias due to this loss. Another 30 were unsuitable for analysis.[10]

Our diabetic retinopathy study was confined to the

Table 2 *Criteria for diagnosis of diabetes based on 3 diabetic abnormalities**

Method	*2 Fasting values (mg/100 ml)*	*Other criteria*		
		1 Fasting value (mg/100 ml)	*1 Casual value (mg/100 ml)*	*History and/or treatment*
Glucose oxidase or Somogyi-Nelson	≥110	≥130	≥160	Positive
Autoanalyzer (Hoffman)	≥120	≥140	≥170	Positive
Hagedron-Jensen	≥130	≥150	≥180	Positive

*Diabetes was diagnosed if there were 2 fasting values equal to or greater than those indicated, plus any one of the other criteria.
SI conversion: glucose mg/100 ml×0·0555=mmol/l.

Table 3 *Criteria for the classification of severity of diabetes*

Categories of diabetic severity	*Glucose tolerance test*	*Other criteria**			
		Fasting (H-J)	*Additional requirements*		
			Fasting (H-J)	*Casual (S-N)*	*History and/or treatment*
Definite diabetes	2 points	≥130×2 +	≥150	or ≥200	or Tablets insulin
Probable diabetes	1½ points	≥130×2 +	≥130	or ≥160	or positive history
Possible diabetes	1 point	≥130×1 +	≥130	or ≥160	or positive history
Abnormal GTT	½ or abnormal				
Normal	Normal at all levels	≤120×3			

*Alternative criteria in the event of a glucose tolerance test being unavailable. H-J=Hagedorn-Jensen method. S-N=Somogy-Nelson method.

Table 4 *1965 prevalence of retinopathy in photographed men of the diabetic study group*

Diabetic study group	*Total (a)*	*Photographed in 1965*			
		Total		*With retinopathy*	
		No. (b)	*% of (a)*	*No.*	*% of (b)*
Examined in 1978–1980	178	77	43	7	9
Alive-not examined 1978–80	27	13	48	1	8
Deceased during follow-up	85	22	26	6	27
Total	290	112	39	14	12

participants of the IIHDP living in the Jerusalem area, both at the time of the initial survey and in 1978–80. All the patients were aged 40 years and over in 1963. They were diagnosed as diabetic or showed an abnormal GTT during any of the subsequent examinations. 112 of the 290 participants conforming with these criteria were photographed during the ophthalmological study in 1965. The colour slides of the retina were examined during the present study to determine if retinopathy had existed at the time (Table 4).

A significant issue in interpreting the results of this paper is the possibility of segregating the diabetic retinopathy cases already present at the beginning of the IIHDP from those developing subsequently through 1978–80. We observed that approximately 1 in 11 (9%) men of those examined during this study had already developed retinopathy in 1965 (Table 4). As the prevalence for those examined in 1978–80 (Table 5) is about 42% (Table 6), it would appear that roughly a fifth of those cases were already present in 1965. Therefore the relationship of the different variables to diabetic retinopathy is an association with a group of cases that consists of approximately 80% incident cases in a 15-year time span. Thus in a high percentage the various measurements taken have preceded the onset of retinopathy, although the associations are not fully equivalent to those computed in a classical prospective design where only measurements in persons free of the disease are considered for identification of risk factors.

Each of the 290 IIHDP participants still living in the Jerusalem area was invited for an interview and examination. Ocular examinations included visual acuity, applanation tonometry, and slit-lamp biomicroscopy of the anterior segment. Direct and indirect ophthalmoscopy were performed after full dilatation of the pupils. In those cases where fundus

Table 5 *The diabetic study group by age and examination status*

Age in 1963	*No.*	*%*	*Alive throughout follow-up*		*Examined in 1978–80*	
			No.	*%*	*No.*	*% (of those alive 1978–80)*
40–49	94	100·0	85	90·4	76	89·4
50–59	147	100·0	99	67·3	88	88·9
60+	49	100·0	21	42·9	14	66·7
Total	290	100·0	205	70·7	178	86·8

Table 6 *1978–80 prevalence of retinopathy by age and duration of diabetes*

Total				*Duration*								
Age	*No.*	*With retinopathy*		*11–13 Years*			*14–16 Years*			>16 Years		
		No.	*%*	*No.*	*With retinopathy*		*No.*	*With retinopathy*		*No.*	*With retinopathy*	
					No.	*%*		*No.*	*%*		*No.*	*%*
55–64	76	37	49	34	11	32	13	7	54	29	19	66
65–74	88	32	36	34	5	15	21	7	33	33	20	61
75+	14	5	36	5	1		3	2		6	2	
Total	178	74	42	73	17	23	37	16	43	68	41	60

photographs could not be taken because of opaque media or for technical reasons, a 3-mirror contacts lens examination was performed. Whenever possible, information on the ocular condition of the persons who did not respond to the third invitation was obtained from the Eye Clinics and Internal Departments records of 2 main hospitals and the Sick Fund Diabetic Follow-up Clinic in Jerusalem.

The patients were classified in the following way. The severity of the diabetes was divided into 4 categories: definite diabetes, probable diabetes, possible diabetes, and abnormal GTT (Table 3). Duration of diabetes was calculated from the date of diagnosis of diabetes or abnormal GTT to the date of the last ophthalmological examination in 1978–80. The patients were divided into 3 groups: 11–13 years (those diagnosed in 1968, having been negative in 1963 and 1965), 14–16 (those diagnosed in 1965, having been negative in 1963), and over 16 years (newly diagnosed or with a known history in 1963).

As a result of the fundal examination the patients were classified in 3 groups: O (absent), indicating no retinal lesions on the fundus photographs and/or the retinal examination; Q (questionable), indicating the presence of something resembling a lesion which could not be positively identified; P (present), if one or more lesions were identified. L.Y. and I.C.M. classified the subjects independently and found no obvious discrepancies in their results. Only those subjects classified P for one or both eyes were considered to have diabetic retinopathy.

The severity of diabetic retinopathy was graded in 3 categories: I, in which one or more microaneurysms in either eye was the only diabetic retinal lesion; II, in which retinal haemorrhages, soft and/or hard exudates, venous calibre abnormalities or intraretinal microvascular abnormalities along with microaneurysms were present; III, in which lesions characteristic of proliferative retinopathy such as neovascularisation, retinal elevation, preretinal haemorrhage, or vitreous haemorrhages were present.

We compared the mean values of several clinical, biochemical, behavioural, and sociodemographic variables in men with and without retinopathy, using measurements performed in 1968 when all the study participants were diabetic or had an abnormal GTT. Analysis of measurements from 1963 and 1965 revealed similar findings and are not reported. Retinopathy/nonretinopathy comparisons for serum uric acid were made with measurements from 1963, 1965, and 1968, since a trend relating the serum uric acid level to the duration of diabetes was observed.[11]

Results

Of the 290 participants of the IIHDP Jerusalem group diagnosed as having diabetes or an abnormal GTT in 1963–8, 205 (71%) were alive during the present 1978–80 diabetic retinopathy follow-up study. 178 (87%) of those alive were examined at that time (Table 5).

The prevalence of retinopathy in the subjects examined in this study was 9% in 1965 (Table 4) and 42% in 1978–80 (Table 6). The fact that we have these data for both the examination periods offers us a unique opportunity to extrapolate the nearly 80% incidence of retinopathy among these patients over a 15-year time span. The distribution of retinopathy by age and duration of diabetes in 1978–80 is also shown in Table 6. The prevalence of retinopathy has increased from 23% in 11–13 years of metabolic abnormality to 43% in the 14–16 years category and 60% in those of more than 16 years. The rate of retinopathy decreased with age, dropping from 49% in the 55–64 age group to 36% in the 2 groups of men over 65 years old. The decrease with age was apparent in each duration group whenever the numbers were large enough to compare. There was little difference in the prevalence of retinopathy among men having diabetes for more than 16 years, between the 55–64 and 65–74 age groups.

The relationship between the prevalence of retinopathy found in 1978–80 and the severity of antecedent diabetes in 1963–68 according to the duration

Table 7 *Prevalence of retinopathy by diabetic category and duration in 1978–80*

Total				*Duration (years)*								
Original diabetic category (defined 1963, 1965 and 1968)	*No.*	*With retinopathy*		*11–13*			*14–16*			*>16*		
		No.	*%*	*No.*	*With retinopathy*		*No.*	*With retinopathy*		*No.*	*With retinopathy*	
					No.	*%*		*No.*	*%*		*No.*	*%*
Definite diabetes	86	48	56	17	8	48	18	8	48	51	32	63
Probable diabetes	12	7	58	4	2		5	3		3	2	
Possible diabetes	32	10	31	14	2	13	10	4	36	8	4	50
Abnormal GTT	48	9	19	38	5		4	1		6	3	
Total	178	74	42	73	17	23	37	16	43	68	41	60

Table 8 *Distribution of types of retinopathy by diabetic category*

Type of retinopathy	*Diabetic category*							
	Definite diabetes		*Probable diabetes*		*Possible diabetes*		*Abnormal GTT*	
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
I	20	41·7	4	57·1	9	90·0	8	88·9
II	23	47·9	2		1		1	
III	5	10·4	1					
Total	48	100·0	7	100·0	10	100·0	9	100·0

of diabetes is shown in Table 7. The rates of retinopathy decreased significantly from 56% and 58% in the first 2 categories of severity of disease (definite and probable diabetes), to 31% in the third category (possible diabetes), and 19% in the abnormal glucose tolerance test group ($p<0·01$ by a test for linear trend in proportions). These differences were more noticeable in cases of short duration than in those of 14–16 years or more than 16 years.

Advanced retinopathy was more prevalent among subjects with more severe metabolic abnormalities (Table 8). Diabetic retinopathy II was found in 25 out of 55 (45·5%) subjects with definite or probable diabetes and in only 2 of 19 (10·5%) of those with possible diabetes and abnormal GTT. Diabetic retinopathy III was present only in subjects with definite and probable diabetes.

The IIHDP data enable us to examine additional variables measured in 1963–8 for subjects followed up and examined in this survey. None of the following variables were found to be significantly related to retinopathy: area of birth, education, smoking habits, Quetelet index, peripheral vascular disease, blood pressure, total serum cholestrol, and high density lipoprotein (HDL) cholestrol. However, we did find that casual glucose values and serum uric acid values are related to retinopathy.

Table 9 shows mean casual blood glucose values by duration as found on the IIHDP examination performed in 1968. The mean of casual blood glucose values was significantly higher ($p<0·001$) among men with retinopathy at that time or who subsequently developed it than among those still free of this complication by 1978–80. The relationship appears to be stable for all duration periods.

The mean serum uric acid values in 1963, 1965, and 1968 according to diabetic duration and retinopathy are shown in Table 10. The mean serum uric acid level was lower among retinopathic diabetics for each duration period. The pooled differences between patients who developed retinopathy and those who did not are statistically significant ($p<0·01$). This suggests that the development of retinopathy is preceded by a relatively low uric acid level which decreases progressively as the duration of diabetes increases.

Discussion

The IIHDP survey enables us to examine the occurrence of retinopathy among diabetic subjects identified in the study. The interpretation of the data on incidence and prevalence of diabetic retinopathy pertains to men of diverse ethnic groups aged 40 to 65 when they entered the survey. The conclusions based on the results of this study are limited by the death of 29% of the participants and by the dropping out of another 13% (Table 5).

This study has the advantage of the availability of many variables measured during the IIHDP in assessing the relationship of diabetic retinopathy to the other factors as a logical step in providing clues to the aetiology of this diabetic complication. While most of the surveys on the incidence and prevalence

Table 9 *Casual blood glucose in 1968 in diabetic men with and without retinopathy in 1978–80*

Onset of diabetes (duration and year)	*With retinopathy*			*Without retinopathy*		
	No.	*Mean blood glucose (mg/100 ml)*	*SD*	*No.*	*Mean blood glucose (mg/100 ml)*	*SD*
Known before 1963 (>16)	18	186	63	13	133	47
Discovered 1963 (≥16)	13	161	51	14	129	33
Discovered 1965 (14–16)	16	168	72	21	132	48
Discovered 1968 (11–13)	17	194	67	56	162	24

SI conversion: glucose mg/100 ml×0·0555=mmol/l.

of retinopathy have been performed in selected diabetic cases, this is a population based study and not of patients specifically referred for medical care. Under the circumstances it was possible to compute the duration of diabetes by using the time of diagnosis as an accurate starting point. Such conditions are also pertinent in the studies of the Pima Indians,[4] and they are essential in decreasing the disparity between known and actual duration of diabetes.

There was an increasing prevalence of retinopathy in the 178 diabetics examined in this study with increased duration of diabetes. These findings are consistent with previous studies[12 13] in showing the strong effect of duration in the development of diabetic retinopathy.

We noted that the prevalence of retinopathy declined from 49% in the 55–64 year old age group to a plateau of 36% in the 2 older age groups. One possible explanation of this decline is the high death rates among patients with retinopathy.[14] This is partly supported by the fact that 3 times as many of the subjects who died during the follow-up period in our study already had retinopathy when examined in 1965 as compared with those who survived (Table 4).

Another variable that deserves high priority in the epidemiological research on diabetic retinopathy is hyperglycaemia or severity of diabetes, classified in our study in diabetic categories (Table 3). In order to assess the effect of severity of diabetes on the development of retinopathy we tabulated the prevalence of retinopathy by diabetic categories and duration (Table 7) and the type of retinopathy by diabetic categories (Table 8). In all duration groups the rate of retinopathy was relatively low among those with a low degree of diabetic severity at the time of diagnosis and high in those with an increased one. The disparity between the groups gradually diminished as duration increased. Advanced retinopathy was more prevalent in diabetic categories with severe metabolic abnormalities. It was also observed that the mean of casual blood glucose values was significantly higher among retinopathy subjects than in those free of retinopathy (Table 9).

Many clinical studies have reported a positive relationship between a high degree of glycaemia and risk of retinopathy.[2 14–16] There were also suggestions that mitigation of hyperglycaemia has a protective effect against the development of retinopathy.[17] However, other studies found no relationship between the level of glycaemia and the incidence of retinopathy.[18 19] Our findings support the view that the severity of diabetes and the degree of hyperglycaemia influence susceptibility to the development of retinopathy and its severity.

We have found no relationship between retinopathy and factors that have been implicated in the pre-

Table 10 *Serum uric acid levels on 3 measurements (1963, 1965, and 1968) in diabetic men with and without retinopathy in 1978–80*

Onset of diabetes (duration in yrs)	*1963 Values*						*1965 Values*						*1968 Values*					
	With retinopathy			*Without retinopathy*			*With retinopathy*			*Without retinopathy*			*With retinopathy*			*Without retinopathy*		
	No.	*Mean (mg/100 ml)*	*SD*	*No.*	*Mean (mg/100 ml)*	*SD*	*No.*	*Mean (mg/100 ml)*	*SD*	*No.*	*Mean (mg/100 ml)*	*SD*	*No.*	*Mean (mg/100 ml)*	*SD*	*No.*	*Mean (mg/100 ml)*	*SD*
Known before 1963 (>16)	23	3·91	0·74	13	4·36	0·66	20	4·40	0·92	13	5·08	0·93	18	4·35	0·89	13	4·92	1·08
Discovered 1963 (≥16)	17	4·63	1·33	14	4·89	0·76	14	4·91	0·98	14	5·36	0·90	13	4·57	0·75	14	5·26	1·07
Discovered 1965 (14–16)							16	5·10	1·28	20	5·58	0·97	16	5·06	1·03	21	5·52	0·78
Discovered 1968 (11–13)													17	5·20	1·54	56	5·49	1·20

SI conversion: uric acid (urate) mg/100 ml×0·0595=mmol/l.

diction of coronary heart disease and/or diabetic vascular complications such as areas of birth, level of education, smoking habits, overweight, peripheral vascular disease, total serum cholestrol, HDL cholestrol, or blood pressure.

Probably the most significant finding of this study is the clear trend towards lower values of antecedent serum uric acid in men with retinopathy in 1978–80 as compared with those not suffering from retinopathy. This was most distinctive in the diabetics of a long duration.

All the diabetics examined in the IIHDP had lower uric acid values than the nondiabetic subjects.[8] Other studies have cited similar findings.[20 21] This relationship was interpreted as resulting from a competitive inhibition of uric acid reabsorbtion in the proximal renal tubules by glucose in persons with hyperglycaemia and glycosuria.[11] Whether such increases in uric acid excretion would cause even lower serum uric acid levels in diabetics prone to retinopathy is intriguing. To the best of our knowledge this report is the first to cite lower mean serum uric acid among diabetics who subsequently developed retinopathy as compared with those who did not. Additional epidemiological studies on this subject should shed light on the validity of our findings.

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