Family histories in Asian and European non-insulin-dependent diabetic patients

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Abstract

Family histories of 135 Asian Indian and 146 European NIDD patients attending clinics in Ealing and Hammersmith Hospitals were obtained, using a detailed questionnaire. Forty-five per-cent of Asian and 36% of European patients had a first-degree relative with diabetes. Twenty-eight per-cent of Asians and 20% of Europeans had one diabetic parent. In 10% of Asians and 1% of Europeans, both parents were diabetic ($p<0.01$). Autosomal-dominant inheritance was seen in 14% of Asians and 4% of Europeans ($p<0.01$). The higher frequency of diabetes in parents, and the higher frequency of dominantly-inherited diabetes among Asians compared to European NIDD patients, suggest that genetic mechanisms operating in NIDD are different in different ethnic groups.

Introduction

Diabetes in patients originating from the Indian sub-continent ("Asian") differs from that seen in the European population *(Ref 1)*. Insulin-dependent diabetes (IDD), is less common, and the associations with the genetic markers differ from those seen in European IDD patients *(Refs 2, 3)*. In non-insulin-dependent diabetes (NIDD) differences such as younger age at onset and reversal of sex ratio have been described *(Ref 1)*. The prevalence of diabetes is much higher in immigrant Asian communities in South Africa *(Ref 4)*, Fiji *(Ref 5)*, and Singapore *(Ref 6)*, than in the local populations. A recent study in Southall, West London, has shown that the age-adjusted prevalence rates for "known" diabetes are considerably higher in Asians than in Europeans *(Ref 7)*. Few studies have compared the family histories of different ethnic groups. We undertook this study to look for differences, if any, in the genetic mechanisms operating in Asian and European NIDD patients.

Patients and methods

A total of 299 consecutive Asian and European NIDD patients attending diabetic clinics at Ealing and Hammersmith Hospitals were studied. Eighteen patients (14 Asian and 4 European) were excluded because the patients either had no contact with their families or no knowledge about disease in their families because they lived apart. The remaining 135 Asian and 146 European patients participated in the study. The criteria for diagnosis of diabetes and the classification of NIDD were those of the National Diabetes Data Group *(Ref 8)*. None of the patients had a history of ketosis at any time and all had been treated without insulin for a minimum period of two years from diagnosis, a clinical criterion considered adequate to exclude IDD patients *(Ref 9)*.

The term NIDDY (non-insulin-dependent diabetes of the young) is used in this report instead of the more commonly used MODY (maturity onset of diabetes in the young) to denote patients with age at diagnosis below 35 years *(Ref 10)*. Patients diagnosed when aged 35 years or above were termed "classical NIDDM". Although earlier studies had used a cut-off point below 25 years for diagnosis of NIDDY *(Ref 9)*, recently it has been shown that it is not the age at diagnosis but the mode of inheritance that is important for the diagnosis of NIDDY *(Ref 11)*. Moreover the S. African studies have used age at diagnosis below 35 years. Hence, to compare our finding with the above studies *(Refs 12, 13)*, we chose to classify patients with onset below 35 years as NIDDY. Admittedly, the age at diagnosis has its own limitations because it represents the age when diabetes was actually diagnosed and the possibility exists that many patients could have had the disease for unknown durations of time, due to lack of symptoms. None of the patients in this study were born of a consanguinous marriage. The clinical details of the patients are shown in *Table 1*.

A detailed questionnaire was used to elicit information on the family history of diabetes, and pedigree charts were drawn up to three or more generations. The diagnosis of diabetes in the relative was accepted if he was treated by a physican with insulin, oral hypoglycaemic agents or with diet. All questionnaires were administered by one of us (VM). Viability of the data was confirmed by questioning the proband and, wherever possible, one more member of the family at subsequent visits. The family history was con-

Table 1. Clinical characteristics of subjects studied

	Sex ratio M:F	Age (yrs)	Age at diagnosis (yrs)	BMI (kg/m)	Duration diabetes (yrs)
Asians (n=135)	78:57	50 ± 13	45 ± 12	26.9 ± 4.6	6.5 ± 3.0
Europeans (n=146)	71:75	60 ± 13	54 ± 14	26.8 ± 5.3	8.9 ± 2.0

All values = Mean ± SD

sidered positive if diabetes was present in a first-degree relative (parents, siblings and children). Autosomal-dominant inheritance was defined using the criteria of Roberts *(Ref 14)*, which included the following:

(1) There is vertical transmission of the disease through three or more generations
(2) Diabetic parents give rise to diabetic off-spring, while children of non-diabetic parents are free of the disease
(3) Approximately 50% of the off-spring in a particular generation have the disease
(4) There is equal sex distribution.

Body Mass Index (BMI) was calculated using the formula: *weight (kg)/height (m)*^{2}. Male patients with a BMI>27 and female patients with BMI>25 were categorised as obese, and the remainder as non-obese. Statistical analysis of the differences in frequencies between the two groups was calculated by the 2×3 chi-squared test and differences between means by unpaired t tests.

Results

Forty-five per cent of Asians and 36% of Europeans had a positive family history of diabetes *(Table 2)*. The frequency of parental diabetes was higher among Asians ($p<0.001$). Twenty-eight per cent of Asians and 20% of Europeans had one diabetic parent. In 10% of Asians and 1% of Europeans both parents were diabetic. Thus in 38% of Asians and 21% of Europeans one or both parents were diabetic ($p<0.01$). Autosomal-dominant inheritance was present in 14% of Asians and 4% of Europeans ($p<0.01$). The frequency of diabetes among siblings of the proband was not significantly different in Asians and Europeans. However, 157 (30%) of 519 siblings of Asian patients were below the age of 40 years, whereas only 5% of siblings of European patients were below this age.

Twenty-nine Asians (21%) and 13 Europeans (9%) were classified as NIDDY ($p<0.01$). In both ethnic groups, a positive family history of diabetes and dominantly-inherited diabetes was more common in the NIDDY than in classical NIDD *(Table 3)*. Dominantly-inherited diabetes was more common in Asian patients than in European patients, even in patients with classical NIDD ($p<0.05$). The relationship between obesity and a positive family history of diabetes is shown in *Table 4*. The frequency of positive family history was similar in both non-obese and obese groups.

Discussion

This study shows significant differences in the genetic pattern of NIDD in Asian and European patients. Diabetes in parents and dominantly-inherited diabetes are significantly more common in the Asians than in the Europeans. The high frequency of diabetes amongst parents of Asian diabetics is consistent with a previous report from South Africa *(Ref 12)*, in which 61% of Asian diabetics who were aged less than 35 years at diagnosis had one diabetic parent, and in which 20% had two diabetic parents. The present study confirms that the incidence of both parents with diabetes is significantly more common in Asians than in Europeans with NIDD. Other studies have shown that the prevalence of diabetes amongst the offspring of Asian conjugal diabetic couples is considerably higher than in any European series *(Ref 15)*. These findings point to a stronger genetic mechanism operating in Asian diabetes. This might be one of the reasons for the high prevalence of diabetes in migrant Asian populations in the UK *(Ref 7)* and elsewhere *(Refs 4-6)*.

This study confirms previous reports from South India *(Ref 16)* that autosomal-dominant inheritance is very common in Asian diabetic subjects. Our patients were mostly Punjabis and Gujarathis, ie North Indians, who form the majority of Asians living in Southall. This suggests that similar genetic mechanisms may be operating in NIDD in North and South Asians. This is in contrast to IDD patients, in whom the association with genetic factors such as HLA and properdin system (BF) are different in North and South Indian patients *(Refs 17-19)*. The fact that dominantly-inherited diabetes is more common in Asians with "classical" NIDD, as well as NIDDY patients, suggests this mode of inheritance is common to Asian NIDD regardless of age of onset.

The frequency of a positive family history was not significantly different in Asians and Europeans. In practice, however, it was more common to have several family members affected by diabetes among the Asians. In this study, a positive family history is given the same weight, irrespective of the number of family members affected.

We did not find any difference in family history frequencies between obese and non-obese patients. This is at variance with some earlier studies *(Refs 20, 21)*. The reason for this is not clear, but may be related to differences in selection of patients and/or ethnic differences. One of the limitations of this study is that it is based on family histories and not by testing of family members. This however, applies to both groups. Moreover, since the families of Asian patients were in many instances not living in the UK, the observed frequency in Asians, as determined by family histories, may well be an under-estimate. Complex segregation analysis would be necessary to determine the exact mode of inheritance of diabetes in this ethnic group. Such studies are being planned.

Aknowledgements

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Table 2. *Details of family history of Asian & European diabetics*

	Positive family history	Two non-diabetic parents	One diabetic parent	Both parents diabetic	Autosomal dominant inheritance	Diabetic siblings
Asians	61 (45%)	83 (62%)	38 (28%)	14 (10%)	19 (14%)	51 (10%)
Europeans	53 (36%)	115 (79%)	29 (20%)	2 (1%)	6 (4%)	49 (10%)
Significance	NS		* p<0.001		p<0.01	NS

* 2×3 chi-squared test

Table 3. *Family history in NIDDY & classical NIDD*

	Total number	Positive family history	Autosomal-dominant inheritance
NIDDY			
Asian	29	20	8
European	13	7	1
Significance	p<0.01	NS	NS
Classical NIDD			
Asian	106	41	11
European	133	46	5
Significance	-	NS	p<0.05

Table 4. *Obesity & family history of diabetes*

	ASIANS		EUROPEANS	
	Total	Positive family history	Total	Positive family history
Non-Obese	60	26 (44%)	69	26 (38%)
Obese	75	35 (47%)	77	27 (35%)

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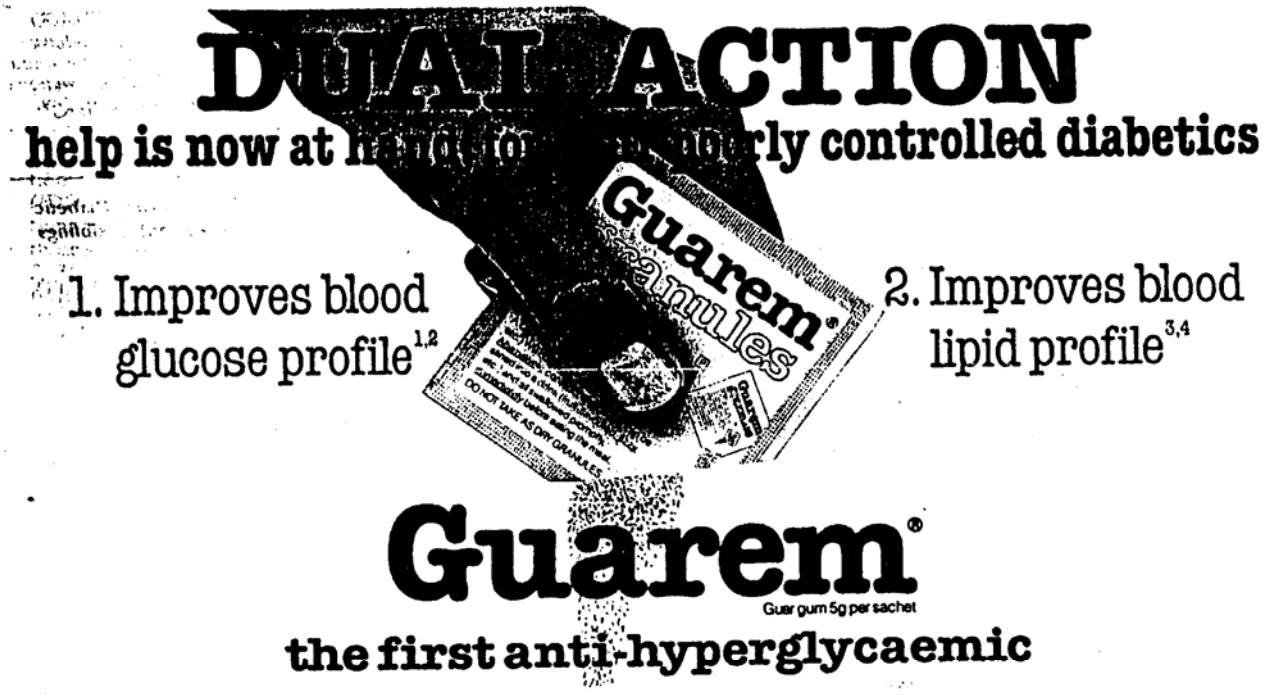

Prescribing Information
Presentation. Sachets, each containing guar gum granules 5 grams. The fine pale cream granules, which are tasteless, are readily water-miscible.
Indications. For use in diabetes to help control post-prandial blood glucose levels, thereby facilitating control, and where appropriate, allowing reduction of insulin or oral hypoglycaemic dosage levels. Action. Guar gum which is derived from natural sources is a high molecular weight polysaccharide galactomannan. In solution it slows the rate of absorption of other carbohydrates leading to a reduction in post-prandial hyperglycaemia and insulin secretion. Guar gum is not absorbed and remains chemically unchanged until it reaches the colon where it is broken down before excretion. Reduction in plasma cholesterol (LDL) levels and symptomatic improvement in dumping syndrome have also been reported. Dosage & Administration. Adults - One 5g sachet to be taken three times daily with each main meal. The contents of a sachet may be stirred into a fruit flavoured drink (Lemsip full) and swallowed promptly before each main meal. Alternatively, it may be sprinkled evenly over a meal on the plate or stirred into suitable foods (e.g. tomato puce, yoghurt, muesli, etc), in which case the food must be accompanied by a drink of 200 ml (orange, tea, etc).
Children (12 and over) - As for adults. Children (under 12) - Not recommended at present. Contra-indications, Warnings, etc. To avoid any risk of oesophageal obstruction or rupture, this product should not be given to patients with a history of oesophageal disease or difficulty in swallowing. Guarem should not be ingested as dry granules. During initial therapy, blood glucose levels should be monitored and concurrent treatment adjusted where necessary, to minimise the possibility of hypoglycaemia. Side Effects. Gastro-intestinal symptoms (flatulence, diarrhoea) are quite common at the commencement of treatment. These can be reduced or avoided by initiating treatment gradually, in accordance with advice on the pack.
Pharmaceutical Precautions. Guarem should be stored in a dry place. Legal Category. P (Pharmacy only). Further information. Each sachet is individually printed with simple and clear administration instructions. Cartons of 50 and 100 sachets. Product Licence Number. PL 23/0023. PA 346/1. Date of Preparation. December 1985. Product Licence Holder. Rybar Laboratories Limited, Hill Avenue, Amersham, Bucks. HP6 5BX.
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