Association of glucose-6-phosphate dehydrogenase deficiency with diabetes mellitus in ethnic groups of Singapore

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SUMMARY Six hundred and nine male patients suffering from maturity onset diabetes mellitus, comprising 422 Chinese, 66 Malays, and 121 Indians, were investigated to determine the incidence of G6PD deficiency, ABO blood groups, and haemoglobin types, and these were compared with normal healthy controls. A positive association with a higher incidence of G6PD deficiency in diabetics was observed in Chinese and Indian patients. There was no significant difference in the frequencies of ABO blood groups and haemoglobin types between the patients and the controls in any of the ethnic groups studied.

The genetic association of diabetes mellitus has been studied in the past mainly by the relative incidence of blood groups and serum proteins (Craig and Wang, 1955; McConnell *et al.*, 1956; Andersen and Lauritzen, 1960; Macafee, 1964; Berg *et al.*, 1967; Klebe and Nielsen, 1972; Lamba *et al.*, 1974), but the results, far from being in agreement, are rather conflicting. From an epidemiological study into the incidence of cancer and diabetes mellitus and glucose-6-phosphate dehydrogenase (G6PD) deficiency in different populations of the world, Kessler (1970) suggested a negative association of G6PD deficiency in cancer and a positive relationship in diabetes mellitus. Naik and Anderson (1971) observed a negative association of G6PD deficiency in cancer in American Negro patients, but only in the case of females. In an earlier study on a pooled sample of smaller size we failed to observe any association of G6PD deficiency and ABO blood groups in diabetes mellitus (Saha, 1971). The three ethnic groups in Singapore (Chinese, Malays, and Indians), who have different incidences of the disease, with a higher incidence among Indians compared with the other two (Cheah *et al.*, 1972, 1975), provided an excellent opportunity to study the possible association of G6PD deficiency, ABO blood groups, and haemoglobin types in diabetes mellitus.

We present in this report the incidence of G6PD deficiency, ABO blood groups, and haemoglobin types in maturity onset diabetes mellitus compared with healthy controls in the three ethnic groups of Singapore.

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Materials and methods

PATIENTS

Six hundred and nine male patients, comprising 422 Chinese, 66 Malays, and 121 Indians, attending the Diabetic Clinic at the Tan Tock Seng Hospital, Singapore, were investigated for the distribution of G6PD deficiency, ABO blood groups, and haemoglobin types. These were consecutive cases of maturity onset diabetes mellitus as confirmed by standard glucose tolerance tests after oral glucose. Five diabetic patients with G6PD deficiency at the first test were followed up and tested for blood glucose levels and G6PD deficiency on three or four subsequent visits while undergoing treatment.

CONTROLS

For comparison, controls were taken from (a) patients proved to be normal and (b) series in published reports.

- (a) Seven hundred and forty seven male subjects comprising 523 Chinese, 87 Malays, and 137 Indians attending the same diabetic clinic formed the control series. These were consecutive cases confirmed as non-diabetic by standard glucose tolerance tests. They were investigated for the distribution of G6PD deficiency, ABO blood groups, and haemoglobin types.
- (b) Published data. ABO blood groups were compared with the series of Chan (1962), cases of G6PD deficiency with the series of Saha and Banerjee (1971a, b), and for comparison with

abnormal haemoglobins the series of Saha *et al.* (1973) were taken as healthy controls.

ABO blood grouping was carried out by slide tests using commercial antisera. G6PD deficiency was identified by the dye decoloration method of Motulsky and Campbell-Kraut (1961). Haemoglobin phenotypes were screened by paper electrophoresis using barbital buffer pH 8.6, ionic strength 0.025.

Results and discussion

G6PD DEFICIENCY

Table 1 shows the distribution of G6PD deficiency in diabetic patients and healthy controls in the three ethnic groups. The incidence of G6PD deficiency is significantly higher in diabetic Chinese and Indian patients (10.4% and 9.9%) compared to non-diabetic controls attending the diabetic clinic (5.0% and 2.9%) and published series (3.3% and 1.7%). The P values are 0.002 and 0.04, respectively, in the case of the former, and 0.16×10^{-10} and 0.0001 in the case of the latter comparison. The relative risk of getting diabetes in G6PD deficient subjects is 2.2 and 3.4 in Chinese and 3.4 and 6.3 in Indians compared with non-deficient subjects in the diabetic clinic and population controls. This association of G6PD deficiency with diabetes mellitus holds up even when the three ethnic groups are combined ($P = 0.007$). Further, there is no significant heterogeneity between the two comparisons based on the two different controls in Chinese, Indians, and the combined group ($P = 0.08, 0.59$, and 0.15, respectively). There is no apparent significant difference in G6PD deficiency in the ethnic groups studied, and there is no significant difference in the case of Malays, which may be because of the small size of the sample.

In an earlier study we failed to observe any significant difference in the incidence of G6PD deficiency between diabetics and controls (Saha, 1971). This was probably because this was a pooled sample of all ethnic groups together. The present report suggests that there is an association of G6PD deficiency with diabetes mellitus which is in agreement with the hypothesis put forward by Kessler

Table 1b Data for association and relative risk*

		Chinese	Malays	Indians
Diabetic clinic controls	χ^2	10.13	0.37	5.40
	P	0.0022	0.79	0.03
	Relative risk	2.20	0.69	3.39
Population controls	χ^2	47.10	1.90	17.24
	P	0.16×10^{-10}	0.34	0.0001
	Relative risk	3.38	2.60	6.26

*Relative risk of getting diabetes of G6PD deficient compared with non-deficient.

χ^2 for association, three ethnic groups combined using the diabetic clinic controls = 11.45, $P = 0.007$.

χ^2 for heterogeneity between controls, 3.44, 0.8, and 3.75, respectively, for Chinese, Indians, and combined groups ($P = 0.08, 0.59$, and 0.15, respectively).

(1970). The higher incidence of G6PD deficiency among non-diabetics of the diabetic clinic compared to the published series (Vella, 1961; Saha and Banerjee, 1971a, b) may be the result of the presence of prediabetics in the series.

It has been reported that glucose tolerance is altered in subjects with G6PD deficiency (Chamugam and Frumin, 1964) and the level of reduced glutathione in blood of diabetics is decreased (Illing *et al.*, 1951). In view of the above findings one needs to guard against the possible inhibitory effect of diabetes on G6PD levels of red cells, indicating the screening test as deficient. However, Belfrage *et al.* (1974) reported an increase of G6PD activity in the liver of maturity onset diabetic subjects. Five of the diabetic patients of the present series showing G6PD deficiency on the first visit were followed up and they were found to be G6PD deficient on subsequent tests, even when their disease was under control. Therefore, it seems very unlikely that diabetes *per se* produces G6PD deficiency as detected by screening tests with brilliant cresyl blue dye. Because of the empirical nature of the dye decoloration test, it needs to be confirmed by parallel G6PD assay that diabetes by itself does not lower the activity of G6PD in red cells.

The present diabetic series is representative of the population of Singapore, as shown by the higher incidence of diabetes among Indians, which corroborates the findings of Cheah *et al.* (1972, 1975). In

Table 1a Distribution of G6PD deficiency in diabetes mellitus

Ethnic origin	Diabetes mellitus			Diabetic clinic controls			Population controls		
	No tested	No deficient	% deficient	No tested	No deficient	% deficient	No tested	No deficient	% deficient
Chinese	422	44	10.42	523	26	4.97	3312*	111	3.35
Malays	66	3	4.55	87	6	6.89	1384*	28	2.02
Indians	121	12	9.92	137	4	2.92	362†	6	1.66
Total	609	59	9.69	747	36	4.82	5058	145	2.87

*Saha and Banerjee (1971a); †Saha and Banerjee (1971b).

view of the lack of association of G6PD deficiency with diabetes in Malay patients in the present series and in our earlier series (Saha, 1971), further investigations with larger samples are advisable to reach a definite conclusion. Further, it will be interesting to look into the phenotypic distribution of G6PD in diabetes mellitus in different populations, as there are many populations with a high incidence of diabetes but with low frequency of G6PD deficiency or none at all. The underlying significance of the association of G6PD deficiency with diabetes mellitus is not clear at the moment.

ABO BLOOD GROUPS

Table 2 shows the distribution of ABO blood groups in Chinese, Malay, and Indian patients compared to normal controls. There was no significant difference in the distribution of ABO blood groups between the patient and control series in any of the ethnic groups. There seems to be no real association present. The conflicting reports in the various published series may be because of the heterogeneity between patient and control series. The present study is unique in the sense that Singapore is served by only one blood bank and a parallel control series has been investigated blindly using non-diabetic patients attending the same clinic.

HAEMOGLOBIN TYPES

The incidence of abnormal haemoglobins in diabetic patients was: 0.24% in Chinese, 4.54% in Malays, and 0.83% in Indians, compared to 0.00% in Chinese, 3.45% in Malays, and 0.73% in Indians in the control series of the diabetic clinic, and 0.64% in Chinese, 5.52% in Malays, and 1.10% in Indians in the published series of Saha *et al.* (1973). All the abnormal haemoglobins were of phenotype AE. In the present series there was no significant difference in the incidence of abnormal haemoglobins between the patient and control series.

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Table 2 Distribution of ABO blood groups in diabetes mellitus

Blood groups	Chinese						Malays						Indians					
	Diabetes		Diabetic clinic controls		Controls*		Diabetes		Diabetic clinic controls		Controls*		Diabetes		Diabetic clinic controls		Controls*	
	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%
O	208	43.06	227	43.16	6644	43.53	27	40.91	30	34.48	2098	38.42	51	42.15	56	40.88	1951	39.02
A	136	28.16	144	27.38	3967	25.99	23	34.85	25	28.74	1369	25.07	27	22.31	29	21.17	1051	21.02
B	117	24.22	125	23.76	3814	24.99	12	18.18	23	26.44	1596	29.23	37	30.58	44	32.12	1680	33.60
AB	22	4.55	30	5.70	837	5.48	4	6.06	9	10.34	398	7.29	6	4.96	8	5.84	318	6.36
Total	483		526		15262		66		87		5461		121		137		5000	

*Chan (1962)

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