

Diabetes Mellitus and the Blood Groups

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SUMMARY

The results of studies of the possible association between the ABO, Rhesus and the MN blood groups and diabetes mellitus and the secretion of blood group substances in the saliva of these patients have been reported. There is evidence of borderline statistical significance suggesting an association between the ABO blood groups and diabetes mellitus characterized by an increased frequency of the disease in persons of blood type B and a decreased frequency in those of blood type AB. However, because of the conflicting findings reported by other investigators, this probably represents a random distribution of the blood types within diabetes mellitus patients or some undetected specious factor rather than a cause and effect association between the ABO blood groups and diabetes mellitus.

There is evidence that heredity plays a role in the etiology of diabetes mellitus. A significantly higher incidence of the disease is found in families of diabetics than in nondiabetic families. Diabetes mellitus occurs more than three times as often in both members of monozygotic as in dizygotic twin pairs. In one study, both members of forty-six identical twin pairs had diabetes after the age of forty-three.¹

The view has been current that a recessive gene present in "double dose" causes diabetes mellitus. On the basis of the recessive gene hypothesis and assuming a known diabetic population of 2.0 per cent, about 22 per cent of the population carries this gene. The known, unknown, and potential diabetic population would be approximately 5 per cent² (see References).

However, much remains unclear concerning the genetic and other factors involved in the etiology of diabetes mellitus. Sometimes the disease is not manifest with the expected frequency in the first or second generation of families in whom one parent is diabetic and the other has a strong family background of the disease. The reverse also occurs, that is, the disease is found in the absence of a positive family history. It is true that a good many of these and other discrepancies with the recessive inheritance concept can be explained on the basis of inaccurate and incomplete histories or non-

genetic factors such as pancreatic failure secondary to infection or neoplasia. Present information does not exclude the possibility that multiple rather than single pairs of genes are involved. Unsolved and controversial questions related to the etiology of diabetes mellitus are discussed by Gunther in his report of a study of 10,000 diabetics.³ The indication for continued study of the etiology and pathogenesis of the disorder is apparent.

The usefulness of blood groups as tools to investigate genetic factors in disease has been demonstrated.⁴ This is a report of a study in which the ABO, Rhesus and MN blood groups have been used to investigate the role of heredity in the genesis of diabetes mellitus.

MATERIAL AND METHODS

All patients in this study were seen at either the University or Veterans Administration Hospitals in Iowa City. Some of the data were obtained by retrospective review of records of patients seen at the two hospitals prior to the beginning of the "prospective" study in 1957. Most of the data were obtained prospectively from currently hospitalized patients. The usual clinical criteria, blood glucose, fractional urine, glucose tolerance tests and the historical and physical findings, were used in establishing the diagnosis of diabetes mellitus. Only those patients who had convincing diagnoses were included in the study. No other factors were used to select patients for inclusion or exclusion in the study. A substantial number of the patients were operated upon for complications of diabetes mellitus. The blood groupings and the isohemagglutination tests used to determine the saliva secretor status of some of the patients were done by the project technician or by a technician under her direction. Blood typing was done according to the slide and tube methods described by the maker of the high titer standardized commercial antisera used in the project.

The blood group and secretor frequencies of the patients were compared with those of the controls. Three different kinds of controls were used in the statistical evaluation of the data. Controls I were blood donors. These were used to evaluate the ABO blood group data. It was not possible to use these controls to evaluate the A and AB blood subgroup or saliva secretion findings

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of the patients since these determinations had not been done in blood donors. Controls II, used for this purpose, were a heterogeneous group of persons consisting 55 per cent of physicians, students and technicians and 45 per cent of spouses of the patients. The third group of controls were the unaffected siblings of the patients. These controls are discussed later in the text.

The differences between the blood group frequencies of the patients and controls were examined for significance; digital computers and suitable programs were employed in the analysis of the data. In previous communications the methods have been described in detail.^{4,5}

RESULTS

The ABO blood group findings in all patients with diabetes mellitus and in the blood donors used as controls are recorded in table 1. The chi square (X^2) values and probabilities are recorded for the differences between the patient and blood donor control blood group frequencies which occur simultaneously for the four blood groups.

TABLE 1

The ABO blood groups of controls and diabetes mellitus patients with statistical significance of the differences which occur simultaneously between the four blood groups of the controls and patients

Blood group	Controls		Patients		Percentage difference between controls and patients
	Number	Per cent of total	Number	Per cent of total	
O	22,392	44.8	656	44.0	-0.8
A	21,144	42.3	634	42.6	+0.3
B	4,695	9.4	164	11.0	+1.6
AB	1,748	3.5	35	2.4	-1.1
Total	49,979	100.0	1,489	100.0	

Chi Square 3 d.f. 9.72
.02 < P < .025

TABLE 2

The ABO blood groups of controls, male and female diabetes mellitus patients with the statistical significance of the differences which occur simultaneously between the four blood groups of the controls and patients

Blood group	Controls		Male patients		Difference (per cent) controls and patients	Female patients		Percentage difference between controls and patients
	Number	Per cent of total	Number	Per cent of total		Number	Per cent of total	
O	22,392	44.8	265	43.3	-1.5	391	44.6	-0.2
A	21,144	42.3	261	42.6	+0.3	373	42.5	+0.2
B	4,695	9.4	72	11.8	+2.4	92	10.5	+1.1
AB	1,748	3.5	14	2.3	-1.2	21	2.4	-1.1
Total	49,979	100.0	612	100.0		877	100.0	

Chi Square 3 d.f. 6.61
.05 < P

Chi Square 3 d.f. 3.95
.05 < P

TABLE 3

The ABO subgroups of controls and diabetes mellitus patients with the statistical significance of the differences which occur simultaneously between the four blood groups of the controls and patients

Blood group	Controls		Patients		Percentage difference between controls and patients
	Number	Per cent of total	Number	Per cent of total	
O	589	43.5	501	43.4	-0.1
A-1	471	34.8	411	35.6	+0.8
A-2	88	6.5	82	7.1	+0.6
B	156	11.5	134	11.6	+0.1
A-1-B	38	2.8	16	1.4	-1.4
A-2-B	13	0.9	10	0.9	0
Total	1,355	100.0	1,154	100.0	
	Chi Square		5 d.f.	6.36	
	.05 < P				

An important criticism of the use of blood donors as controls for the blood group disease studies is that blood donors may inadvertently be selected from a stratum of the population that differs ethnically and anthropologically from the patients. If this occurred, the data might suggest specious blood group disease associations while failing to indicate the valid associations which are present. This question has been discussed in detail in earlier communications.^{7,8} When unaffected siblings of the patients are used as controls instead of blood donors, this possibility is eliminated. The relevant data obtained from the siblings of the diabetes mellitus patients are recorded in table 4. Observe that the

blood type frequencies of the unaffected siblings of the patients agree more closely with the blood donor controls than with the patients. However, the differences between the unaffected sibs and the patients are not statistically significant. C. A. Smith⁹ described a method which examines each family separately which segregates for the blood groups in question. When these data are examined by this method, the results again are not statistically significant; however, they are consistent with the diabetes mellitus ABO blood group association suggested by our data. The largest differences between the patients and their unaffected siblings were in groups B and AB. There were seventy-two families segregating for type B and twenty-five for AB. For the group B analysis (Smith) the total number of patients expected with group B determined from the unaffected siblings, was 30.7; 32.0 were observed giving a variance of ± 0.30 for the group AB analysis. The total number of patients expected with group AB determined from the unaffected siblings, was 9.5; 8.0 were observed giving a variance of ± 0.13 .

Associations have been found between the secretion of the ABO(H) mucopolysaccharide blood group substances in saliva and duodenal ulcer¹⁰ and rheumatic fever.¹¹ The mechanisms responsible for these associations remain to be disclosed. Table 5 records the results of the studies of the secretion of ABO(H) blood group substances in the saliva of patients with diabetes mellitus. The controls were composed chiefly of hospital personnel. No differences of statistical significance were

TABLE 4
Siblings and diabetes mellitus

Blood group	Controls (blood donors)		Patients (with siblings)		Siblings (affected)		Siblings (unaffected)	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
O	22,392	44.8	203	43.3	46	44.7	403	44.4
A	21,144	42.3	205	43.8	48	46.6	388	42.7
B	4,695	9.4	48	10.3	7	6.8	87	9.6
AB	1,748	3.5	12	2.6	2	1.9	30	3.3
Total	49,979	100.0	468	100.0	103	100.0	908	100.0

TABLE 5
Diabetes mellitus, ABO (H) blood group substance saliva secretion

Blood group	Controls				Patients				Percentage difference between controls and patients	
	Secretors		Nonsecretors		Secretors		Nonsecretors		Secretors	Nonsecretors
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent		
O	447	79.4	116	20.6	280	80.7	67	19.3	+1.3	-1.3
A	387	75.6	125	24.4	268	78.6	73	21.4	+3.0	-3.0
B	107	74.3	37	25.7	40	63.5	23	36.5	-10.8	+10.8
AB	30	71.4	12	28.6	13	76.5	4	23.5	+5.1	-5.1
Total	971		290		601		167			

found between the frequencies of secretion of ABO(H) blood group substances in the saliva of the patients and the controls.

The Rhesus and MN blood groups have been determined in some of the patients with diabetes mellitus. The controls used to evaluate these data consisted of patients with diagnoses previously found to have no association to these blood groups, spouses of the patients and healthy hospital personnel. These data which have been published suggest no statistically significant differences exist between the Rhesus and MN blood group frequencies of the diabetes mellitus patients and the controls.¹² As in the ABO findings, these data were examined for differences related to sex, surgical versus nonsurgical treatment and age; no statistically significant differences were found.

DISCUSSION

In 1955, McConnell reported data suggesting an increased frequency of blood group A in young diabetics.¹³ In 1956, this same author and colleagues published the results of a more elaborate study of 1,333 patients in Liverpool and Oxford showing a statistically significant excess of group A in men with diabetes mellitus as compared with the controls.¹⁴ There was no evidence of a blood group association in female diabetics. These authors also found no differences of significance between the Rhesus and MN blood group frequencies of controls and 500 patients with diabetes mellitus. Craig and Wang,¹⁵ in 1955, reported results of a study of 817 diabetes mellitus patients in Scotland indicating a statistically significant decrease in group O in older overweight patients with a family history of diabetes mellitus or obesity. There was no evidence of significant differences between the ABO and Rh (D) blood group distribution of the patients in general and the controls. In 1960, Andersen and Lauritzen¹⁶ reported the results of a study of 992 diabetics in Denmark. They found a statistically significant excess of group O among male diabetics compared with the controls; there was an excess of O in the females which was not statistically significant. The Rhesus blood groups of these patients did not differ significantly from the controls. However, a significant excess of group Le (a+) was found in male as well as female diabetics. The authors suggest that nonsecretors of ABO(H) blood group substances may have an increased susceptibility to diabetes. This is based on the concept that persons of blood group Le (a+) are nonsecretors of blood group substances. In 1961, Buckwalter et al.¹⁷ reported the findings of a study of Bantu and Indian diabetics conducted

in the Union of South Africa which were inconclusive because of the small volume of the data.

The most important positive finding which emerges from the present study is the suggestion of an ABO blood group association in diabetes mellitus characterized by an increased incidence of the disorder in persons of blood type B and a decreased incidence in those of blood type AB. These findings, although of some statistical significance, suggest only tentatively a blood group association and should be cautiously interpreted. Caution is in order in view of the conflicting findings of others. Of particular interest to our findings are those reported by Bibawi and Khatwa¹⁸ who found the frequency of blood groups A and AB increased in 951 diabetes mellitus patients.

The results of the family studies provide little evidence of the ABO blood group association to diabetes mellitus. When the findings are examined by age and sex of the patients and the severity of the diabetes, no evidence of an ABO blood group association related to these factors emerge. Likewise the findings do not suggest an association between the A and AB subgroups, MN and Rhesus blood groups or the secretion of ABO(H) blood group substances in saliva, to diabetes mellitus.

Our findings in view of those reported by other investigators can be best explained on the basis of the random distribution of the ABO blood groups in diabetes mellitus. The possibility of subtle factors related to ethnic or racial factors in the several studies with conflicting results, can not be categorically ruled out. The conservative and probably correct view is that, as of the present, there is no convincing evidence of an association between diabetes mellitus and the ABO blood groups or between this disease and ABO(H) blood group substance secretion in saliva, the Rhesus and the MN blood groups. In conclusion, the findings of these investigations indicate that the blood groups are not-useful as tools to investigate genetic factors operating in the etiology of diabetes mellitus.

SUMMARIO IN INTERLINGUA

Diabete Mellite e le Grupos de Sanguine

Es reportate le resultatatos de studios concernite con le possibilitate que il existe un association inter le grupos de sanguine ABO, Rhesus, e MN e diabete mellite e le secretion de substantias de gruppo sanguinee in le saliva de tal patientes. Il existe evidentia de marginal signification statistic suggestionante un association inter le grupos de sanguine ABO e diabete mellite, characterisate per un augmentate incidentia del morbo

in personas con le typo B de sanguine e un reduce incidentia in personas con le typo AB. Tamen, viste le conflictos inter le constataciones reportate per altere investigadores, isto representa probabilemente un distribution aleatori del typos de sanguine in patientes con diabete mellite o un non ancora detegite factor deceptive plus tosto que un nexo de causa e effecto inter le gruppos de sanguine ABO e diabete mellite.

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