Influenza Immunization in Adults with Diabetes Mellitus

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The antibody responses to influenza vaccination of a group of adult diabetic patients were compared with responses in a healthy group of regular volunteer vaccinees. The initial and final geometric mean hemagglutination-inhibiting antibody titers were lower in the patient group, but the relative increase in titers was greater for each of the vaccine components. The percentage of fourfold rises in individual titers was greater in the diabetic group than in the control group. It was concluded that patients with diabetes mellitus responded normally to influenza vaccination. This was confirmed in an additional study. There was no significant difference in the antibody responses of patients treated with insulin or oral antidiabetic agents. There was no impairment of diabetic control as a result of influenza vaccination when this was evaluated by measuring the concentration of glycosylated hemoglobin, or by random blood glucose estimations. There was no significant change in the serum insulin level after immunization in patients on oral diabetic agents. It was concluded that influenza vaccination was safe and effective in adult diabetic patients. DIABETES CARE 6: 475–478, SEPTEMBER–OCTOBER 1983.

Influenza remains a significant cause of morbidity and mortality despite the lower incidence of epidemic infection in the last few years. Although the major impact of infection occurs in younger age groups, complications and death are most common in the aged and in those with chronic disease. These are the groups for whom annual vaccination is recommended by national authorities in Australia, Britain, and the United States.

In individuals with diabetes mellitus, the risk of complications of influenza is increased.[1] Poorly controlled patients may have an impairment of their immune responses involving both lymphocyte and neutrophil functions.[2,3] Immunity can be also impaired by viral infections, including influenza.[4] In diabetic patients, therefore, there is an increased risk of secondary bacterial infection and this may lead to hyperglycemia and ketoacidosis.[5] For these reasons, influenza immunization has been recommended in patients with diabetes mellitus.

It is important to establish that vaccination is effective and safe in the groups for whom it is recommended. It has been suggested that immunization may impair the metabolism of certain drugs.[6,7] For these reasons a study was designed to evaluate the response to influenza immunization of a group of adult patients with diabetes mellitus. It was also designed to investigate the effect of immunization on the control of diabetes mellitus by insulin and by oral antidiabetic agents.

METHODS

Design. The study was an open controlled trial of the antibody responses to influenza virus subunit vaccine in a group of adult volunteers from the Diabetes Clinic at the Royal Melbourne Hospital (Victoria, Australia). The control group consisted of employees of the Commonwealth Serum Laboratories (Parkville, Victoria, Australia).

Participants. The patient group comprised 49 volunteers whose ages ranged from 22 to 77 yr. The mean age was 52 yr and the median age was 55 yr. There were 27 men and 22 women. Thirty-one patients were stabilized on insulin, 16 were on oral antidiabetic agents, and 2 were on diet alone.

The control group consisted of 38 adults whose ages ranged from 21 to 61 yr. The mean age was 41 yr. There were 24 men and 14 women in this group.

Vaccine. The vaccine was a commercially available influenza virus vaccine (Commonwealth Serum Laboratories) prepared from virus grown in the allantoic cavity of embryonated

TABLE 1
Hemagglutinin antibody responses*

Group	HI antigen	Reciprocal geometric mean titer			Percentage with antibody increase		Percentage with postvaccination titers	
		Before vaccination	After vaccination	Fold increase	≥2 fold	≥4 fold	≥20	≥40
Diabetic	A/Brazil/11/78	12.5	70.6	5.6	82	63	84	65
	A/Bangkok/1/79	9.2	41.4	4.5	77	57	65	43
	B/Singapore/222/79	8.1	22.7	2.8	57	43	45	27
CSL	A/Brazil/11/78	54	83	1.5	34	13	95	82
	A/Bangkok/1/79	22	93	4.2	79	42	92	76
	B/Singapore/222/79	17	46	2.7	71	32	84	61

*All geometric mean titers are calculated on the assumption that a reciprocal titer of <10 is equal to 5.

eggs, inactivated by β-propiolactone, purified by zonal centrifugation, and disrupted by sodium deoxycholate.

Each one-milliliter dose of the vaccine contained antigens representative of the following types: A/Brazil/11/78, 7 μg hemagglutinin; A/Bangkok/1/79, 7 μg hemagglutinin; and B/Singapore/222/79, 7 μg hemagglutinin. The final vaccine contained thiomersal 0.01% wt/vol as a preservative.

Dosage and administration. A single dose of vaccine was given by deep subcutaneous or intramuscular injection to each participant. Blood samples were collected on the day of vaccination, and 1 wk and 4 wk later. Fasting blood samples were collected from patients on insulin, but samples were collected after breakfast from patients on oral agents.

Blood and serum assays. Serum antibody titers were measured by the hemagglutination inhibition (HI) test using standard laboratory techniques.[8] Titers were measured against the vaccine type strains A/Brazil/11/78, A/Bangkok/1/79, and B/Singapore/222/79.

In the diabetic group, blood glucose levels were measured by the glucose-oxidase method in an autoanalyzer. Glycosylated hemoglobin (HbA_1) estimations were measured by glyco-spin kits supplied by Clinical Research Laboratory (Croydon, Victoria, Australia). The normal range for HbA_1 is 4.0–8.0%.

Serum insulin measurements were completed in patients on oral therapy. Serum insulin estimations were undertaken by double antibody radio immunoassay.

Urine tests. Routine urinary glucose tests were carried out by the patients using Diastix (Ames, Mulgrave, Victoria, Australia). A daily record was maintained by each patient.

Statistical analyses. Statistical analyses were completed by using various rank tests and chi-square tests where necessary.

RESULTS

The results of antibody studies in the group of patients with diabetes mellitus and in the control group are shown in Table 1.

The initial titers reflect the differing experiences in the two groups to the influenza strains in the vaccine. It can be seen that the geometric mean titers in the patient group were two- to fourfold lower than those in the control group. In the diabetic group, 45% of the individuals had HI antibody titers less than 1 in 10 to the A/Brazil/11/78 strain, 75% had titers less than 1 in 10 to the A/Bangkok/1/79 strain, and 90% had titers less than 1 in 10 to the B/Singapore/222/79 strain, but in the control group there were only 3%, 29%, and 30%, respectively, with titers less than 1 in 10 to these strains.

The relative increase in the geometric mean titers after vaccination was greater in the diabetic group for each of the three vaccine components. In addition, the percentage of individuals responding to vaccination with fourfold increases in titer was greater in the diabetic group for each component, but this difference was significant only for the A/Brazil/11/78 component ($P < 0.01$). The final geometric mean titers, however, and the percentage with postvaccination titers >20 and >40 were lower in the diabetes group than in the control group for all vaccine components.

These results indicate that regular vaccinees, i.e., those having a history of annual or repeated vaccination, in general

TABLE 2
Data on diabetes mellitus patients

	Group on insulin treatment		Group on oral agents	
	Mean	±SD	Mean	±SD
Age in years	50.75	16.87	55.22	13.52
Duration of diabetes mellitus (yr)	15.06	11.31	8.5	7.19
Hemoglobin A_1(%)				
Preimmunization	10.36	1.96	9.18	2.36
Postimmunization	10.81	1.66	9.59	1.56
Blood sugar assays (mmol/L)				
Preimmunization	14.54	5.38	10.05	2.36
Postimmunization	14.67	5.54	10.25	2.74
Serum insulin assays (mU/L)	ND*			
Preimmunization			17.14	7.95
At 1 wk			18.66	9.98
At 4 wk			19.42	9.15

*ND = not done.

have higher initial and final titers than persons without such experience. The diabetic group responded to vaccination with a greater increase in titer.

A comparison between the initial titers, final titers, increases in titer, and percentage of individuals with HI titers >40 in the diabetic group showed no significant differences between those on treatment with insulin and those on oral therapy. There was also no correlation between antibody responses and the duration of the disease, the dose of insulin, or the concentration of glycosylated hemoglobin.

Within the diabetic group, control was evaluated by blood glucose levels, by the measurement of glycosylated hemoglobin, and by routine urinary glucose tests. In addition, serum insulin levels were measured in patients on oral treatment. In Table 2, the mean values and standard deviation of the test results are shown. From this table it can be seen that there were no significant changes in the mean values of the group. There were also no clinically significant changes in the results of these tests in individual patients.

DISCUSSION

The two aims of the study were to evaluate the response to influenza vaccination in patients with diabetes mellitus and to determine whether vaccination impaired the control of diabetes.

The antibody response of the diabetic group to vaccination was greater than that of the control group but the initial and final antibody titers were lower. In the control group, the majority were regular vaccinees, but in the diabetic group, a small minority had received vaccine in recent years. In Melbourne between 1976 and 1981, there had been little epidemic influenza in adults in these age groups; therefore, the influence of regular vaccination was manifested in the initial titers of the control group.

In order to further evaluate these findings, a comparison of the antibody responses of the diabetic group was made with antibody responses of another healthy adult group involved in influenza studies in 1981 (Tannock et al., personal communication). This adult group was of similar age distribution, and also had minimal experience with influenza immunization in the past. The initial and final geometric mean titers and the increases in titer in the diabetic group and in this adult group were comparable for the A/Bangkok/1/79 and A/Brazil/11/78 components of the vaccine, and the responses of the diabetic group to the B/Singapore/222/79 component were slightly better. These results were confirmed in assays at the Commonwealth Serum Laboratories.

From these studies it was reasonable to conclude that patients with diabetes mellitus under good control respond normally to influenza immunization. This conclusion is consistent with findings recently published on studies with pneumococcal immunization.[9] It is also in agreement with earlier studies that showed that diabetic children under good control respond with antibody rises like normal children, whereas those whose diabetes was poorly controlled, or who were hypoproteinemic showed a retarded and diminished response.[10,11]

The effect of influenza vaccination on the control of diabetes mellitus was investigated by blood glucose assays and by measuring the concentration of glycosylated hemoglobin before and after immunization. In addition, serum insulin assays were undertaken on patients who were on oral diabetic therapy with sulfonylureas and biguanides. There was no evidence of any impairment of diabetic control as a consequence of influenza vaccination. This is an important observation because some recent studies have shown that immunization may impair the metabolism of certain drugs such as theophylline, warfarin, or phenytoin.[6,7]

One final aspect of this study is noteworthy. Despite the normal responses, the final geometric mean titers of the control group and of the diabetes group were lower than would have been expected from historical comparisons. Similar observations of unexpectedly low titers after influenza immunization have been reported from overseas[12] and have been noted in unpublished studies in Australia. These findings have been attributed to a lower immunogenicity of recently circulating influenza virus strains. As protection against influenzal infection has been correlated with circulating antibody levels,[13] it was recommended by the World Health Organization and by authorities in the United States, Britain, and Australia that the potency of vaccines be increased at least twofold in vaccines for the years 1982–83 in order that higher antibody levels be attained after vaccination.

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