

THE INCIDENCE OF SKIN REACTIVITY TO INSULIN IN DIABETIC PATIENTS

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CRYSTALLINE insulin derived from alien species has antigenic properties when repeatedly injected into animals or human subjects; however, clinically significant allergic reactions to insulin are unusual. While the development of insulin-binding antibody appears to be an invariable response to insulin therapy,^{1,2} the frequency of occurrence of skin reactivity to insulin is not known. Skin reactivity to insulin has usually been found during the course of study of patients with overt insulin allergy, such as generalized urticaria. Since the demonstration of skin reactivity has been used as evidence that insulin was the offending antigen, it would seem important to know the incidence of skin reactions to crystalline insulin in a population of diabetic subjects. Although Tuft³ was unable to demonstrate skin reactivity to crystalline insulin in diabetics who had no history of allergic reactions (10 insulin-treated diabetics; 10 managed by diet alone), the results of the present study would indicate that skin reactivity is present in over 50 per cent of insulin-treated diabetics.

METHODS AND MATERIALS

Subjects were studied as they appeared for routine clinic visits in the Metabolic Clinic of the Milwaukee County Hospital. Four groups were tested. Group I consisted of 76 diabetics who had been treated with insulin for at least 6 months at the time of study. Group II consisted of 43 diabetic subjects who had been treated with insulin in the past, but not within the last year, and were currently managed by diet alone or diet plus one of the oral hypoglycemic agents. Group III consisted of 29 diabetics who, so far as could be ascertained, had never received insulin. Group IV consisted of 20 nondiabetic hospital personnel (confirmed in each case by normal post-prandial blood sugar determinations).

Control of diabetes was graded as follows: excellent—fasting blood sugar between 80 and 150 mg. per cent (Folin-Wu) with zero to trace glucosuria (Clinitest); good—fasting blood sugar between 151 and 200 mg. per cent with zero to trace glucosuria; poor—fasting blood sugar over 200 mg. per cent or greater than 1+ glucosuria.

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Subjects were tested with a solution of regular insulin* (U.80) diluted to a concentration of 8 units per milliliter with a diluent containing sodium chloride 0.5 per cent, potassium acid phosphate 0.0364 per cent, disodium phosphate 0.1431 per cent, and phenol 0.4 per cent as a preservative. Sites on the forearm were tested with 0.02 ml. of the diluent plus insulin and 0.02 ml. of diluent alone as a control injected intracutaneously. Sites were read at 20 minutes by one examiner (J. A. A.) and graded 0 to 4+ depending on the degree of erythema and whealing. For reporting purposes, results are given simply as "positive" or "negative." A positive skin test correlates with a 2+ or more, i.e., definite erythema and whealing. All control tests with the diluent were negative.

EXPERIMENTAL RESULTS

Table I compares the distribution of positive and negative skin tests within the four groups of subjects. Mean ages were comparable with the exception of the nondiabetic group which was somewhat younger. The insulin-treated diabetics had had their disease for a longer time and tended to be more poorly controlled, possibly reflecting the selection of better controlled subjects for oral therapy. Although only 11 per cent of insulin-treated diabetics recalled local reactions at injection sites, observation of new diabetics suggests that this figure should be higher and may reflect the tendency to forget transient and not particularly troublesome symptoms. The incidence of history of allergic ("atopic") diseases in each group was comparable to that reported for the general population.⁴ Results of testing showed no positive correlation with age, duration of diabetes, degree of control, insulin dosage, history of local reactions, or history of allergic disease.

TABLE I. COMPARISON OF RESULTS OF SKIN TESTS IN RELATION TO THE VARIOUS FACTORS LISTED

	GROUP I (76) DIABETICS CURRENTLY ON INSULIN		GROUP II (43) DIABETICS FORMERLY ON INSULIN		GROUP III (29) DIABETICS NEVER ON INSULIN		GROUP IV (20) NONDIABETICS	
	SKIN REACTION		SKIN REACTION		SKIN REACTION		SKIN REACTION	
	+	-	+	-	+	-	+	-
Number	40	36	8	35	3	26	0	20
Mean age	56.5	57.8	60.1	62.3	74.3	58.7		49.6
Duration of diabetes (yr.)	10.3	11.8	2.9	7.1	1.0	2.9		
Insulin dose (units/day)	41.5	38.2						
Time since last insulin dose (yr.)			1.5	2.2				
Control								
Poor	23	17	0	8	1	8		
Good	8	10	5	16	2	12		
Excellent	9	9	3	11	0	6		
History of local reaction	6	2	0	2				
History of allergic ("atopic") disease	6	5	1	4	0	4		

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Positive skin tests were obtained in 40 (53 per cent) of the 76 insulin-treated diabetics (Group I). Only 8 (18.6 per cent) of 43 subjects in Group II, who had received no insulin for over a year, had positive skin tests. Those reacting positively had had diabetes for a somewhat shorter period of time and had been off of insulin therapy for a slightly shorter period.

Of particular interest, 3 of 29 subjects in Group III in whom no history of insulin therapy could be found had positive skin tests. All of these patients had been followed in the outpatient clinics for a number of years preceding the diagnosis of diabetes mellitus and during the entire duration of diabetic therapy. While it is difficult to rule out exposure to insulin, exhaustive review of inpatient and outpatient records and repeated questioning of the patients disclosed no evidence that this had occurred. Of the 20 nondiabetic subjects studied, one had an equivocal response which was clearly negative when repeated. By contrast, the tests reported as positive in other groups were more marked and caused no confusion in interpretation.

COMMENTS

Skin reactivity to insulin has been presumed to imply the presence of skin-sensitizing antibody. Since no attempt was made in this study to verify this presumption, comments can be made only about the ability of the skin to react to insulin.

The demonstration of skin reactivity to crystalline insulin in 53 per cent of insulin-treated diabetics is of interest in view of the apparent universal induction of insulin-binding antibody. It is clear that skin reactivity may develop with equal facility in subjects with and without an "atopic" history. The data presented also suggest that there is no difference in the incidence of allergic (atopic) diseases in diabetic subjects when compared with the general population.⁴ Instances of skin reactivity occurred in subjects who had received insulin for periods as short as 6 months and persisted for as long as 3 years after insulin injections were stopped. No difference in the occurrence of skin reactivity was found between subjects who recalled local reactions and those who did not, but doubt exists as to the accuracy with which these reactions were remembered. The discovery of 3 patients out of 29 with positive skin reactions but in whom no record of exposure to insulin could be obtained is of particular interest. It is cautiously suggested that endogenous insulin might on occasion incite an autoimmune response, but this can be confirmed or denied only by more exhaustive studies.

SUMMARY

Skin tests for the presence of skin reactivity to insulin were done on 168 diabetics and 20 nondiabetic individuals. The individuals were divided into 4 groups. Group I consisted of diabetics on insulin, Group II consisted of diabetics formerly on insulin, Group III consisted of diabetics who had never received insulin, and Group IV consisted of nondiabetic controls. Group I

demonstrated 53 per cent with skin reactivity; Group II, 18.6 per cent; Group III, 10 per cent; and Group IV, none. There was no positive correlation with age, duration of diabetes, control, or history of allergic disease.

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