Brief Communications

Anti-Insulin Antibody Titers Do Not Influence Control or Insulin Requirements in Early Pregnancy

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IgG antibodies (AB) to insulin have been reported to influence insulin requirements and control in patients who have taken insulin for prolonged periods of time. Nineteen pregnant type I diabetic patients (C-peptide < 0.03 pmol/ml) were studied in their fifth week of gestation after the establishment of normoglycemia. Mean age was 27.5 yr and duration of diabetes, 14.2 yr (range: 1–23 yr). IgG AB to beef and pork insulin were measured. IgG AB to insulin were encountered in all diabetic patients (range: 103–6736 μU/ml). None of the nondiabetic pregnant controls in their fifth week of gestation (N = 17) had detectable (>50 μU/ml) AB levels. The antibody titer did not affect the insulin requirement (P > 0.2, NS) or ability to achieve normoglycemia. AB levels were correlated with years of treatment with conventional insulin preparations (r = 0.73; P < 0.001). At 5 wk postmenstruation the mean AB level in the patients with less than 10 yr duration of diabetes (N = 7) was 727 μU/ml and mean insulin requirement was 0.7 U/kg/24 h. In the group of patients with greater than 10 yr duration of diabetes (N = 12) the mean antibody titer was 3716 μU/ml and the insulin requirement was also 0.7 U/kg/24 h. IgG AB to insulin increase with increasing duration of treatment with beef/pork insulin. IgG AB do not affect the insulin requirement or the ability to achieve normoglycemia during early pregnancy. DIABETES CARE 7: 68–71, JANUARY–FEBRUARY 1984.

Up to 97% of patients with diabetes treated with insulin for more than 10 yr duration have antibodies to insulin.[1] It has been suggested that these antibodies may alter the time course of biologic activity of injected insulin.[2,3] Whether or not the antibody level influences the ability to achieve or maintain glucose "control" or contributes to insulin resistance remains controversial.[4–10] Recently, programs have been devised that enable the maintenance of normoglycemia throughout gestation.[11,12] Therefore, it was possible to readdress the relationship of antibody levels to insulin requirements in a highly motivated group of patients in whom uniformity of metabolic control was achieved.

MATERIALS AND METHODS

Nineteen type I (insulin-dependent) diabetic women (C-peptide < 0.03 pmol/ml) were admitted serially to the study. These women were selected only because they were documented to be pregnant and were in their fifth week from the last menstrual period. Pregnancy was documented by serum hCG radioreceptor assay.[13] All diabetic women were placed on 3–4 injections of insulin as described previously.[14] The diabetic patients were matched to 17 normal control subjects by age and week of gestation. All control subjects had negative glucose challenge tests.[15] The mean age was 27.5 yr in both groups. Duration of insulin treatment in the diabetic group was 14.2 yr (range: 1–23 yr). None of the control subjects was receiving any chronic medication.

All studies of insulin requirements were performed on a metabolic ward. Insulin requirements were calculated as the mean of seven days of insulin doses using the mean insulin dose for 24 h per kilogram of present weight. Diet was calculated at 25 kcal/kg and distributed as three meals and three snacks with 40% carbohydrate, 40% fat, and 20% protein. The diet was documented by a nutritionist to be entirely ingested during the period of hospitalization on the Clinical Research Center. Women were between 80% and 120% ideal body weight.[16] Patients were ambulatory within the confines of the metabolic ward. Maternal blood glucose was documented throughout the day by hourly blood glucose measurements. All women were verified to have "normal" blood

TABLE 1
Profile of diabetic study subjects

Subject no.	White Class (24)	Weight (kg)	Creatinine clearance (ml/min)	IgG (μU/ml)
1	B	63	90	363
2	B	71	120	402
3	B	74	110	345
4	B	69	130	395
5	B	68	120	2578
6	B	86	110	903
7	B	92	105	103
8	C	58	103	3716
9	C	68	98	5400
10	C	67	80	6413
11	C	59	89	1770
12	C	54	100	4511
13	D	81	110	2036
14	D	73	88	766
15	D	76	84	6332
16	D	57	100	1289
17	D	81	100	6736
18	RF	74	50	1120
19	RF	69	60	3209
Mean	—	70.5	102	2546.7
SD	—	10.7	13	2307.05
Normal range	—	—	70–120	<50

glucose levels for at least 2 wk before the study as documented by self blood glucose monitoring seven times per day using solid phase reagent strips.[12] "Normal" was defined as a mean of 84 ± 7 mg/dl with no excursions above 140 mg/dl.[12] Glycosylated hemoglobin was measured by the microcolumn technique (Helena Labs, Beaumont, Texas). No attempt was made to eliminate the labile adduct since all assays were performed within 2 h of venipuncture and the value therefore represents short- and long-term events.[17,18]

IgG antibodies to beef and pork insulin were measured according to Christiansen.[19] In order to avoid the problems noted by Christiansen[19] with interassay variation, all samples were analyzed in the same run. C-peptide levels were measured using antiserum MK 1230 (Novo Laboratories, Princeton, New Jersey) as described previously.[20] The results from these studies were not made available to the investigators until the clinical protocol was completed.

Informed consent was obtained from all patients before the study and approval was obtained from the appropriate institutional committees.

RESULTS

Table 1 characterizes the study subjects by White Class, weight, creatinine clearance, and IgG titer at time of referral. Relationships between insulin dosage, IgG antibody titers, and glycemic control as documented by glycosylated hemoglobin levels are shown in Table 2. Before the study, all patients were injecting either NPH, lente, or regular insulin. Dose and frequency of administration are given in Table 2. None of the patients had taken PZI insulin. At the time of the study, all patients in the diabetic group were injecting beef/pork Iletin I insulin (Eli Lilly, Indianapolis, Indiana). IgG antibodies to insulin (Table 1) were encountered in all diabetic women (range: 103–6736 μU/ml). None of the nondiabetic controls had detectable antibody levels (>50 μU/ml). Antibody levels were positively correlated with years of treatment with conventional insulin preparations (Figure 1: $r = 0.73$; $P < 0.001$).

Table 2 reveals that despite a wide range of antibody levels, insulin requirements were remarkably uniform at 0.7 U/kg/24 h (range 0.68–0.81 U/kg/24 h). The three patients with the highest antibody titers (6413, 6332, and 6736 μU/ml) had insulin requirements of 0.79, 0.69, and 0.69 U/kg, respectively. The three patients with the lowest titers (363, 345, and 103 mU/ml) had similar insulin requirements of 0.70, 0.70, and 0.69 U/kg, respectively. Likewise, there was no difference between the three subjects with the highest and lowest antibody titers in number of hypoglycemic episodes (three versus two) or proportion of referral dose given as an intermediate insulin (Table 2). There was no correlation between insulin antibodies and insulin requirements in the 19 diabetic patients ($r = 0.29$, P = NS).

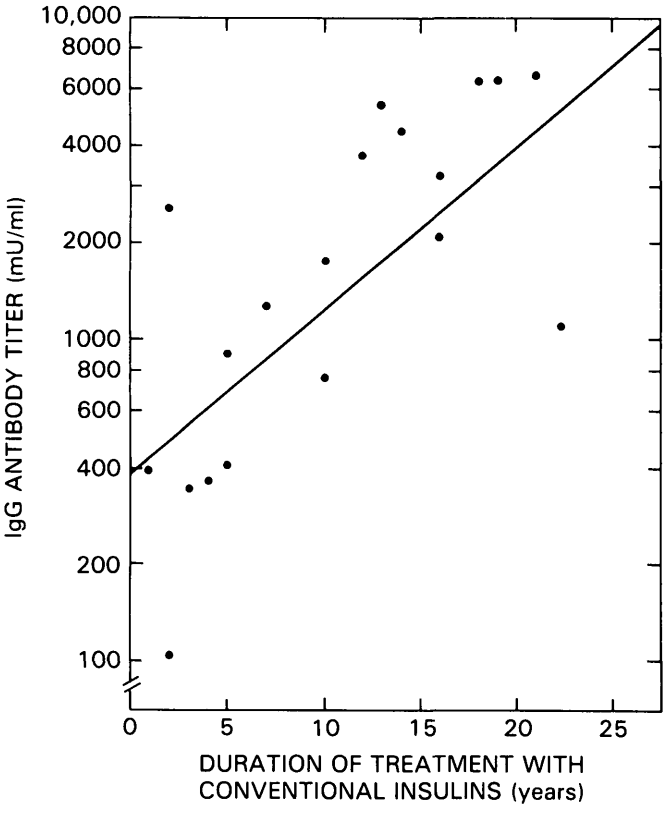

FIG. 1. Serum insulin IgG antibody level (Y) compared with years of treatment with conventional insulin (X). N = 19. Log Y = 0.05X + 2.59; r = 0.73, P < 0.001.

TABLE 2
Insulin dosage, antibody levels, and glycosylated hemoglobin levels

		At time of referral				First trimester			Third trimester		
Subject no.	IgG titer (μU/ml)	Type	Total units	Injections/day	U/kg/24 h	U/24 h	U/kg/24 h	HbA_1 (%) (week 5)	U/24 h	U/kg/24 h	HbA_1 (%) (week 38)
1	363	Lente	40	1	0.67	44	0.70	8.8	80	0.95	5.2
		Reg	20	1	0.37						
2	402	NPH	30	1	0.42	50	0.70	8.0	84	0.87	4.9
		Reg	15	1	0.21						
3	345	NPH	55	1	0.74	52	0.70	8.2	95	0.96	6.1
4	395	NPH	40	2	0.58	48	0.69	8.8	91	1.00	6.3
		Reg	18	2	0.26						
5	2578	NPH	60	1	0.88	47	0.69	6.7	80	0.88	5.2
		Reg	20	1	0.29						
6	903	NPH	50	1	0.58	60	0.69	7.2	97	0.92	5.7
7	103	NPH	50	2	0.54	64	0.69	7.9	110	0.99	6.1
		Reg	10	1	0.11						
8	3716	Lente	40	2	0.69	41	0.71	7.1	91	1.10	6.9
		Reg	40	2	0.69						
9	5400	NPH	70	2	1.02	49	0.72	8.2	83	0.88	6.3
		Reg	30	2	0.44						
10	6413	NPH	70	1	1.07	53	0.79	8.5	91	0.95	5.8
11	1770	NPH	80	2	1.35	48	0.81	6.9	76	0.90	5.4
12	4511	Lente	50	2	0.93	42	0.77	7.0	72	0.91	5.7
		Reg	25	1	0.46						
13	2036	NPH	50	1	0.62	57	0.70	7.0	99	0.98	6.3
14	766	Lente	50	2	0.68	50	0.68	7.4	96	0.97	6.9
		Reg	20	2	0.27						
15	6332	Lente	30	2	0.39	53	0.69	7.8	113	1.12	6.4
		Reg	16	2	0.21						
16	1289	Lente	50	1	0.88	40	0.70	6.8	91	1.10	6.5
17	6736	NPH	30	2	0.37	56	0.69	6.5	99	0.89	7.0
		Reg	20	2	0.27						
18	1120	Lente	50	2	0.67	53	0.72	6.2	95	0.93	5.8
		Reg	30	2	0.41						
19	3209	NPH	20	2	0.28	47	0.68	6.8	85	0.95	6.1
Mean	2546.7					50	0.71	7.5	91	0.96	6.0
± SD	2307.05					6	0.04	0.8	11	0.08	0.6
Normal range	<50							5–7.5			4.5–7.0

The mean glucose level during the study was 84 ± 7 (1 SD) in the diabetic group and 84 ± 5 (1 SD) in the control group (Table 1). Glycosylated hemoglobin levels remained slightly elevated in the diabetic group as compared with the normal group (7.5 ± 0.8% versus 5.8 ± 1.0%, respectively). There was no influence of antibody levels on the ability of the patients to achieve normoglycemia. There was also no correlation between antibody titers and HbA_1 or mean blood glucose achieved during the study ($P > 0.2$ in both cases, NS).

DISCUSSION

The present study documents that in type I diabetic women at 5 wk gestation euglycemia is achieved at a mean insulin dose of 0.71 U/kg/24 h and that this insulin requirement is not altered to a clinically significant degree by the level of circulating antibodies to beef/pork insulin. Diet, exercise, and ambient glucose levels were held constant for all patients as documented at a clinical research center. Hemoglobin A_1 levels were slightly elevated at the time of study due to the fact that achievement of normoglycemia was a relatively recent event in many of these women. In pregnancy it has been shown that hemoglobin A_1 levels return to normal after the establishment of normoglycemia over a 6-wk period.[12]

Insulin antibodies were present in all the diabetic patients and the titer of antibodies to insulin was directly porportional to the duration of insulin use. The level of antibodies to insulin, however, was not a factor in the insulin dosage necessary to achieve normoglycemia or in the ability of the patient to achieve and maintain normoglycemia.

The trend in the management of the type I diabetic patient has been toward normalization of blood glucose.[11,12,21,22] These

efforts are predicated on the hypothesis that hyperglycemia per se, or some abnormality that occurs secondary to hyperglycemia, is responsible for pregnancy complications encountered in the diabetic population. If circulating antibody levels to insulin were shown to play a role in the ability to achieve normoglycemia or the insulin requirement, then women with high antibody levels to insulin would comprise a subpopulation at risk during pregnancy.[23]

The literature on the relationship of the titer of antibodies to metabolic control is conflicting. Peacock and colleagues[9] reported a worsening in control as evidenced by a rise in HbA_1 levels as the patients were switched from conventional insulins to highly purified insulins. Antibody levels to insulin fell concomitant with the rise in HbA_1 levels. Walford and co-workers[8] were able to maintain comparable levels of "control" with a lower total insulin dose as antibodies declined. The present study demonstrates that IgG antibodies do not increase insulin requirements to a clinically significant degree, nor do they increase the difficulty of maintaining normoglycemia during early pregnancy.

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