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Fat Atrophy in Human Insulin Therapy

Fat atrophy is generally considered to be an immunologic reaction to impurities contained in insulin preparations.[1] It was seen fairly frequently before the introduction of highly purified insulins, but in recent years the incidence seems to have decreased markedly, probably due to the increased purity of currently available insulins. To my knowledge, fat atrophy has never previously been reported in patients receiving human insulin.

A 24-yr-old woman developed insulin-dependent diabetes in April 1983. She was subsequently stabilized on a single morning injection of porcine monocomponent insulin (6 U Actrapid insulin and 15 U Monotard insulin, Novo, Johannesburg, South Africa) before breakfast with excellent diabetes control, as evidenced by intensive self-monitoring of blood glucose. She subsequently married and moved to another city but returned to see me in January 1985 when she was experiencing problems with staphylococcal skin infections. Her insulin regimen was unchanged and her diabetes control remained good, with a glycosylated HbA_{Ic} level of 6.9% (normal range 5.8–8.8%). At that stage she had noted small areas of fat atrophy on both thighs in areas distant from the skin infections. Examination revealed two shallow indentations, 1–2 cm in diameter, on the anterior aspect of both thighs. She was changed to the identical dose of semisynthetic human insulin (Novo Actrapid-HM and Monotard-HM).

She returned to see me in September 1985 and reported that the areas of fat atrophy had enlarged. Examination showed a large area up to 5 cm diameter and 1 cm deep on each thigh. Her diabetes control had remained good, with a glycosylated HbA_{Ic} of 5.9%. She was then changed to biosynthetic human insulin (Humulin-R and Humulin-N, Eli Lilly, Indianapolis, IN) and has returned home to see whether the areas of fat atrophy will continue to progress or start regressing. I am awaiting follow-up when she next visits Cape Town.

This must presumably be an extremely rare complication of human insulin therapy, and it would be interesting to know whether this has been noted elsewhere.

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HLA and NIDDM in the Young

In the South African Indian the presentation of diabetes in the young is atypical in that insulin-dependent diabetes mellitus (IDDM) is rare, whereas non-insulin-dependent diabetes mellitus (NIDDM) in the young is common.[1–3] This syndrome of NIDDM in the young is uniformly accepted to be a subset of NIDDM with the strongest genetic component and appears to segregate in an autosomal dominant fashion.[4] In the previous studies in which the HLA status of Caucasoid patients with NIDDM in the young were investigated, this syndrome does not appear to be associated or linked to the HLA system.[5–8] In an attempt to ascertain whether the HLA system was involved in a non-Caucasian population, the HLA antigens of four Indian families with NIDDM in the young (25 members) were determined.

Twelve patients belonged to families in which NIDDM was transmitted via one parent through three successive generations. NIDDM in the young was categorized according to the following criteria: age <30 yr at diagnosis, duration of diabetes >2 yr (as defined by WHO criteria[9]), aketonuric but symptomatic presentation, and prevention of ketonuria and control of symptoms without insulin therapy.

HLA-A, -B, and -C antigens of all family members were determined by the standard two-stage microlymphocytotoxicity test,[10] by use of 180 local and exchanged sera to define the specificities. HLA-DR antigens were defined by the long-incubation technique (Ninth International Histocompatibility Workshop) with 120 local and exchange sera. Lymphocytes were isolated on a Ficoll-Hypaque density gradient,[11] and T- and B-cells were separated by means of straws containing nylon wool.[12]

The HLA haplotypes, ages, 2-h plasma glucose levels (after 75 g oral glucose), and body mass indices of the families are shown in Table 1. It is evident that in none of the families did the diabetic state segregate with an HLA haplotype or a combination of haplotypes. In addition, it appears that no HLA type is more frequent in the diabetic than in the nondiabetic family members.

In 1976, Nelson and Pyke[5] studied 13 diabetic and 9 nondiabetic members of families with NIDDM in the young. They reported that the gene involved is not linked to the HLA-B locus. During the same year Barbosa[13] suggested that there was an association between the HLA haplotypes A3 and BW15 and the hyperglycemic trait. He later confirmed this suggestion.[14]

Faber et al.[6] HLA-typed a family with NIDDM in the young for A, B, C, and D antigens. They demonstrated that there was no association between specific HLA antigens and NIDDM in the young, whereas Platz et al.[7] performed HLA typing for A, B, and C antigens on 53 members of one family. They also concluded that there was no significant positive linkage of HLA type with NIDDM in the young. More recently, Barbosa[8] studied 10 large families with NIDDM in the young and found that the disorder was neither associated nor linked

TABLE 1
HLA haplotypes in families with three generations of NIDDM in the young

Glucose (mmol/L)	BMI (kg/m^{-2})	Age (yr)	Generation	Family member	Condition of subject				
Family 1									
			1.1	Grandmother	NIDDM*				
21,0	22	48	2.1	Mother	NIDDM	a	A2	C−	B51	DR−
						b	A28	C−	B8	DR3
7,9	25	52	2.2	Father	Normal	c	A2	Cw1	B37	DR10
						d	A1	Cw6	B57	DR7
7,6	22	23	3.1	Child 1 (M)	Normal	b	A28	Cw−	B8	DR3
						c	A2	Cw1	B37	DR10
5,7	20	21	3.2	Child 2 (M)	Normal	a	A28	Cw−	B8	DR3
						d	A1	Cw6	B57	DR7
14,0	21	17	3.3	Child 3 (F)	NIDDM	b	A28	Cw−	B8	DR3
						c	A2	Cw1	B37	DR10
4,9	19	13	3.4	Child 4 (M)	Normal	b	A28	Cw−	B8	DR3
						c	A2	Cw1	B37	DR10
3,9	19	12	3.5	Child 5 (M)	Normal	a	A2	Cw−	B51	DR−
						d	A1	Cw6	B57	DR7
5,9	20	10	3.6	Child 6 (F)	Normal	b	A28	Ce−	B8	DR3
						d	A1	Cw6	B547	DR7
Family 2										
			1.1	Grandmother	NIDDM*					
13,5	29	49	2.1	Mother	NIDDM	a	A1	Cw−	B62	DR−
						b	A1	Cw−	B57	DR7
14,2	25	46	2.2	Aunt	NIDDM	e	A33	Cw−	B61	DR2
						f	A−	Cw−	B−	DR−
4,6	26	56	2.3	Father	Normal	c	A33	Cw−	B61	DR2
						d	A1	Cw−	B17	DR7
4,9	22	24	3.1	Child 1 (F)	Normal	b	A1	Cw−	B57	DR7
						c	A33	Cw−	B61	DR2
12,8	29	23	3.2	Child 2 (F)	NIDDM	a	A1	Cw−	B62	DR−
						c	A33	Cw−	B61	DR2
5,7	22	21	3.3	Child 3 (F)	Normal	b	A1	Cw−	B57	DR7
						c	A33	Cw−	B61	DR2
5,8	22	15	3.4	Child 4 (M)	Normal	b	A1	Cw−	B57	DR7
						c	A33	Cw−	B61	DR2
Family 3										
20,0	24	65	1.1	Grandmother	NIDDM	a	A2	Cw−	B60	DR2
						e	A−	Cw−	B44	DR7
18,0	27	38	2.1	Mother	NIDDM	a	A2	Cw−	B60	DR2
						b	A1	Cw1	B55	DR1
6,9	22	36	2.2	Aunt	Normal	a	A2	Cw−	B60	DR2
						f	A−	Cw−	B44	DR7
5,8	26	45	2.3	Father	Normal	c	A24	Cw−	B35	DR4
						d	A−	Cw−	B58	DR−
13,0	39	15	3.1	Child 1 (F)	NIDDM	b	A1	Cw1	B55	DR1
						d	A24	Cw−	B35	DR4
Family 4										
			1.1	Grandmother	NIDDM*					
20,2	23	45	2.1	Mother	NIDDM	a	A28	Cw−	B52	DR2
						b	A31	Cw−	B51	DR2
7,4	25	48	2.2	Father	Normal	c	A1	Cw−	B60	DR2
						d	A1	Cw−	B60	DR10
18,2	25	29	3.1	Child 1 (F)	NIDDM	a	A28	Cw−	B52	DR2
						c	A1	Cw−	B60	DR2
15,8	19	19	3.2	Child 2 (M)	NIDDM	b	A31	Cw−	B51	DR2
						c	A1	Cw−	B60	DR2
13,6	22	18	3.3	Child 3 (F)	NIDDM	b	A31	Cw−	B51	DR2
						d	A1	Cw−	B60	DR10

M, male; F, female; BMI, body mass index.
*Not tested (died).

to HLA types. Thus far all the studies were confined to Caucasoid patients. In an attempt to determine whether a similar situation pertained in a non-Caucasoid population, we studied a migrant Asian group. In our study, a further antigen HLA-DR was also measured. Similar findings were observed in this group of Indian patients. It thus appears that with respect to HLA status, NIDDM in the young in Indians is in no way different from that which manifests itself in Caucasoids.

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Multiple Herpetic Whitlows in a Child Performing Self-Monitoring of Blood Glucose

Self-monitoring of blood glucose (SMBG) has become the recommended tool for management of type I diabetes. In our diabetes clinic we have noted no bacterial infections of any significance in the 400 patients using this procedure 2–4 times daily over a period of 4 yr. Ryan et al.[1] described two cases of digital sepsis with osteomyelitis and gangrene eventually requiring amputation in immunocompromised hosts undergoing dialysis or renal transplantation. Knezevic and Mastaslia[2] reported a similar case. This communication concerns a proven case of multiple digital herpes simplex whitlows in a boy performing SMBG on a regular basis for 3 yr.

J.F., a 9-yr-old boy requiring insulin since the age of 20 mo and also mildly asthmatic, developed painful erythematous, indurated, and vesicular lesions on the tips of the middle three fingers of each hand (Figure 1). There was moderate bilateral enlargement of the epitroclear and axillary lymph nodes, general malaise, anorexia, and low-grade fever. A crusted herpetic lesion was noted on the lower lip and the patient had a history of recurrent labial herpes for 1 yr before this event. On admission the child's blood glucose was 416 mg/dl and he required intensified insulin treatment. There was no ketosis or acidosis.

TABLE 1
Immunologic investigations on patient and mother

Tests	Patient	Mother	Normal range
IgG (mg/dl)	1225	1400	700–1600
IgM (mg/dl)	105	74	36–260
IgA (mg/dl)	295	155	46–490
IgD (mg/dl)	0.6	1.0	0–41
IgE (U/ml)	800	65	0.3–215
C3 (mg/dl)	135	129	88–252
C4 (mg/dl)	25.5	36	13–72
CH5O classic (U/ml)	141	158	90–160
CH5O alternative (U/ml)	17	27	13–30
Rheumatoid factor	Positive	Negative	Negative
Antinuclear antibody	Negative	Negative	Negative
E rosettes (%)	78	81	65–88
OKT3 (%)	67	64	51–87
OKT4 (%)	38	28	15–52
OKT8 (%)	21	14	13–44
B cells (%)	16	12	6–14
PHA response (cpm)	184,233	171,766	>150,000