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Insulin antibodies in patients with type 2 diabetic receiving recombinant human insulin injection: A report of 12 cases

Anticorps anti-insuline chez les patients diabétiques de type 2 recevant des injections d'insuline humaine recombinante

Abstract

We report 12 cases of patients with type 2 diabetic receiving recombinant human insulin injection, who had uncontrolled hyperglycemia or frequent episodes of hypoglycemia, high levels of serum insulin and positive insulin antibodies. The clinical characteristics and insulin antibodies pharmacokinetics parameters were analyzed. After administration of glucocorticoids, changing insulin formulations or discontinuing the insulin and switching to oral antidiabetic agents, the level of insulin antibodies decreased and the plasma glucose restored. Thus, we recommend to identify the presence of high insulin antibodies in patients with type 2 diabetes who experience unexplained high plasma glucose or frequent reoccurrence of hypoglycemia.

Résumé

Nous rapportons 12 cas de diabète de type 2 traités par injection d'insuline recombinante avec un déséquilibre glycémique et de fréquents épisodes d'hypoglycémies associés à des taux circulants élevés d'insuline et à la présence d'anticorps anti-insuline. Le profil clinique des patients et la cinétique des anticorps anti-insuline sont ici rapportés. Après l'administration de glucocorticoïdes et le changement de type d'insuline ou son arrêt au profit d'hypoglycémiants oraux, les taux circulants d'anticorps anti-insuline ont baissé avec restauration d'un meilleur équilibre glycémique. Nos résultats suggèrent que la présence d'anticorps anti-insuline doit être recherchée en cas de diabète de type 2 déséquilibré avec fréquent épisodes d'hypoglycémies.

1. Introduction

Insulin antibodies are occasionally produced in diabetic patients treated with exogenous insulin [1]. Although the prevalence of insulin antibodies in exogenous insulin-treated patients have decreased since the wide use of purified and recombinant human insulin preparations [2], it has been reported by Fineberg et al. that insulin antibodies still appear in diabetic patients treated with recombinant human insulin [3], especially in the Oriental region [4,5]. Insulin antibodies may be associated with clinical events such as hypersensitivity reactions, pregnancy, glycemic variability, and metabolic control [3], and mainly with insulin resistance/hyperglycemia [5–8] or hypoglycemia [4,9,10].

Here we report 12 cases of patients with type 2 diabetic receiving long-term recombinant human insulin subcutaneous injection, who had either uncontrolled hyperglycemia or frequent episodes of hypoglycemia, higher levels of serum insulin and positive insulin antibodies. After administration of prednisone, changing insulin formulations or discontinuing the insulin and switching to oral antidiabetic agents, the level of insulin antibodies was decreased and the plasma glucose could be well controlled again.

2. Cases report

Of the 12 patients, 5 were man and 7 were women, with a mean age of 69.1 ± 7.7 years (range 62–80 years). The mean

Table 1
Clinical data of the patients with insulin antibodies.

No.	Sex	Age (y)	Duration (y)	Hypoglycemia	HbA1c (%)	Induration and pruritus	Insulin Dosage (unit/d)	Insulin type
1	M	76	11	Y	10.7	Y	28	MPZRHII70/30
2	M	72	15	Y	9.0	Y	34	MPZRHII70/30
3	F	62	13	Y	10.5	Y	32	MPZRHII70/30
4	M	70	19	Y	9.5	Y	34	IPBHII30R
5	M	67	13	N	9.1	Y	44	MPZRHII70/30
6	F	75	15	N	10.2	Y	53	MPZRHII70/30
7	F	68	17	N	9.7	Y	70	MPZRHII70/30
8	M	80	9	N	10.1	N	43	IPBHII + BHII
9	F	78	27	N	12.2	N	68	IPBHII50R
10	F	68	19	N	11.4	Y	64	IPBHII30R
11	F	58	13	N	10.3	N	66	IPBHII + BHII
12	F	56	12	N	9.3	Y	52	IPBHII50R

M: Male; F: Female; N: No; Y: Yes; BHII: biosynthetic human insulin injection; IPBHII: isophane protamine biosynthetic human insulin injection; IPBHII30R: isophane protamine biosynthetic human insulin injection (premixed 30R); IPBHII50R: isophane protamine biosynthetic human insulin injection (pre-mixed 50R); MPZRHII70/30: mixed protamine zinc recombinant human insulin injection (70/30).

Table 2
Serum insulin concentrations, levels and pharmacokinetics parameters of the insulin antibodies.

No.	Insulin antibody (%)	Total serum insulin (mU/L)	Free serum insulin (mU/L)	Bound serum insulin (mU/L)	High-affinity antibody		Low-affinity antibody	
					k1 (10^{-10} M)	b1 (pM)	k2 (10^{-8} M)	b2 (pM)
1	38.59	1125.3	199.0	926.3	2.86	58.60	2.22	829.17
2	60.80	1848.0	48.9	1799.1	0.85	407.30	7.69	37907.38
3	60.21	1281.7	15.0	1266.7	3.03	1017.97	1.09	7798.60
4	56.97	1118.6	52.5	1066.1	1.59	643.59	1.18	10311.19
5	50.68	1050.7	32.1	1018.6	1.86	417.56	1.39	8304.96
6	47.06	1085.3	98.9	986.4	4.29	539.87	8.33	19785.42
7	51.74	1055.7	47.3	1008.4	1.56	218.41	1.32	3686.92
8	40.51	1012.3	46.4	965.9	5.08	449.80	3.33	12752.57
9	49.69	1153.3	54.9	1098.4	3.70	303.48	1.56	4188.73
10	47.27	1429.8	57.1	1372.7	2.44	352.80	1.52	3327.37
11	31.16	1189.8	71.1	1118.7	1.72	84.66	5.26	2039.05
12	29.48	1575.3	117.0	1458.3	4.84	91.04	2.08	1281.04

k: affinity constant; b: binding capacity.

duration of the diabetes was 15.3 ± 4.8 years. All of the patients had not taken any thiol-containing drugs, and their past medical histories were unremarkable. Physical examination upon admission found that the patients were conscious with stable vital signs, and none of them had a history of other agents used or heart, lung, abdominal or other abnormalities, which might affect glycemic control or induce insulin autoimmune syndrome (IAS). Abdominal computerized tomography (CT) or ultrasonography revealed no pancreatic abnormalities. The insulin preparations of the patients used before admission were recombinant human insulin including biosynthetic human insulin injection, isophane protamine biosynthetic human insulin injection, isophane protamine biosynthetic human insulin injection (premixed 30R, premixed 50R) and mixed protamine zinc recombinant human insulin injection (70/30). Four patients (patients No. 1–4) exhibited frequent episodes of hypoglycemia and unstable blood glucose levels, the average dosage of their insulin preparation was 32.0 ± 2.8 U/day; the rest eight patients (patients No. 5–12) had no recurrent hypoglycemia but unexpected

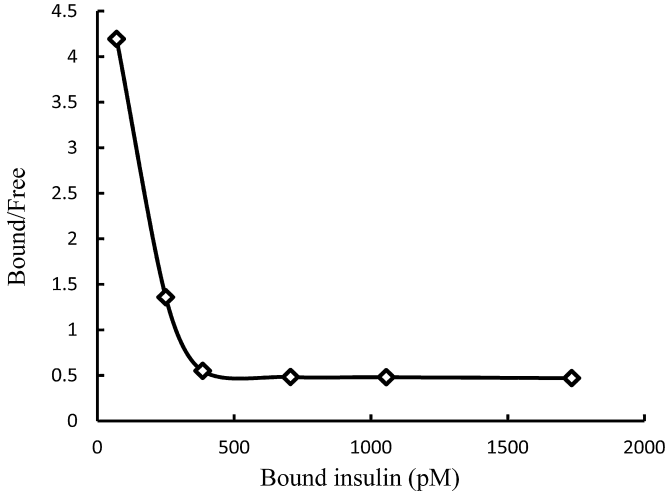

Fig. 1. Representative images of Scatchard plots of insulin antibodies (Case 2). Bound: bound insulin, Free: free insulin.