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Human insulin allergy: four case reports

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Summary

Insulin allergy was not uncommon in the past, but has lowered with the introduction of human recombinant insulin. Human recombinant insulin allergy is a rare condition, now reported in less than 1% of treated patients. However, it is a serious condition that requires an immediate allergological work-up. In this study, we describe 4 cases of IgE-mediated reaction to human recombinant insulin, emphasizing some practical aspects in diagnosis and treatment.

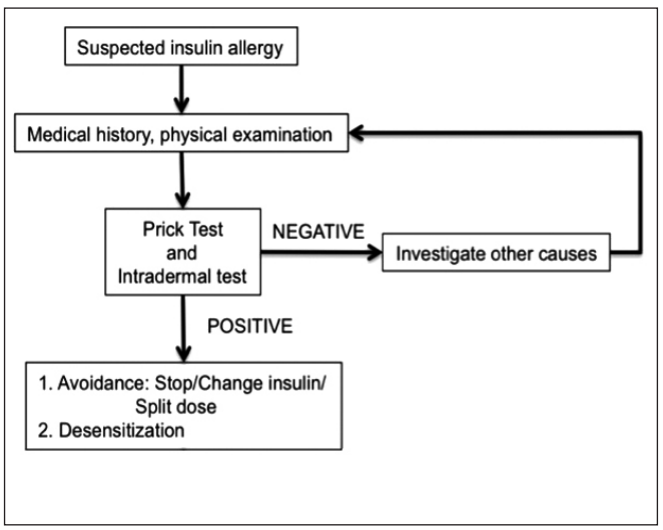
Insulin has been used for the treatment of diabetes since 1920. Primarily, bovine and swine insulin have been available for human use. Due to the marked differences with human insulin allergic reactions to these types of insulin were frequent (1). During the 1980's, different types of recombinant human insulin were introduced in clinical practice: regular insulin (rapid onset of action) and Neutral Protamine Hagerdorn insulin (NPH insulin – intermediate onset of action). The introduction of human recombinant insulin has lowered, but not eliminated, allergic reactions, which now occur in <1% of treated patients (2).

Recently, two insulin analogues, lispro insulin (LI – very rapid onset of action) and glargine insulin (GI – prolonged action), were introduced and caused less reactions because of differences in their amino acid sequences and a rapid dissociation of its monomers. This has led to use them as alternatives to recombinant human insulin.

The clinical presentation of insulin allergy may range from minor local symptoms to a severe generalized allergic reaction. IgE-mediated symptoms occur immediately after an insulin injection and include urticaria, angioedema and anaphylaxis (3). In this study, we describe 4 cases of IgE-mediated reaction to human recombinant insulin, emphasizing some practical aspects in diagnosis and treatment.

Patient 1 is a 67-year-old woman with non insulin-dependent diabetes for 12 years. Her disease was controlled with sulfonylureas until 2007 when human recombinant regular insulin (RI) was added to the treatment. Shortly after initiating the treatment, she developed local hives at the injection sites and generalized urticaria three hours after each injection. NPH human insulin was introduced, but urticaria persisted and was associated with dyspnoea and angioedema. The patient had to be treated with 5 mg of prednisone daily and 120 mg of fexofenadine twice a day to control the aller-

Figure 1 - Insulin allergy investigation chart



gic symptoms. The shift from insulin to oral anti-diabetics led to a complete resolution of allergic symptoms.

Patient 2 is a 55-year-old man with type II diabetes who had been using human insulins for several years. At a certain time point, while taking RI and NPH, he started having self-limited, generalized pruritus, papules and erythema. Treatment with oral-hypoglycemic agents was associated with the disappearance of cutaneous symptoms but was unsuccessful, and urticaria relapsed upon subsequent introduction of RI. Currently, this patient tolerates LI.

Patient 3, a 65-year-old woman, had been treated for 2 years with oral-hypoglycemic agents. Fifteen days after starting daily doses of both NPH human insulin and RI, she developed local reactions and generalized urticaria, which subsided after stopping insulin. LI was then introduced and was well tolerated for a prolonged period of time. However, since she did not have the financial possibility to buy LI, the woman underwent successful desensitisation with NPH insulin.

The last case is a 47-year-old man who was diagnosed as having diabetes at the age of 33 after taking corticosteroids for acute tireoiditis. After 7 years with glibenclamide NPH insulin was added 2 years ago. After 1 year, the patient started having a local reaction associated with abdominal pain and sweating that progressed into cutaneous rash and dyspnoea that appeared one hour after each injection and improved spontaneously in two hours. NPH insulin was stopped and the allergic symptoms disappeared. The patient presently tolerates RI well.

The presence of insulin sensitization can be proven both by cutaneous tests and serum specific IgE detection (4) (Figure 1). Prick tests were performed in all four patients with different human insulins (40 U/mL): regular, lispro, NPH and glargine. Protamin (1 mg/mL) and latex (at a commercial concentration) were tested as well. Intradermal tests were carried out if the prick tests were negative. Intradermal tests with insulins (5 U/mL) were performed at a 1:100 dilution. All the patients had positive tests for RI, NPH insulin and glargine insulin, with the exception of one patient that scored negative for RI (Tale 1). Protamin and latex allergies were excluded. Furthermore, the first patient levels of IgE specific for human insulin were 5.61 kU/l (ImunnoCAP, Phadia).

Tests were also performed in10 insulin–users diabetics that did not react to insulin as control, and all of them scored negative.

Skin test results must be carefully evaluated as non-allergic diabetic subjects may show positive skin prick tests for protamine and, less frequently, for human insulin (4). In our study, all sensitized patients experienced symptom relief when specific insulin avoidance was initiated.

A switch to a different insulin preparation represents the mainstay of insulin allergy management (3).

In most insulin-allergic patients lispro insulin (a genetically engineered insulin analogue) is well tolerated due to its rapid dissociation in monomers (5).

Table 1 - Skin tests results

Type of insulin	Regular		NPH		Glargine		Lispro	
Patient	Prick	ID	Prick	ID	Prick	ID	Prick	ID
1	P	X	P	X	P	X	N	X
2	N	P	N	P	N	P	N	N
3	N	P	N	P	N	P	N	N
4	N	N	P	P	X	X	X	X

Prick: prick test; ID: intradermal test; P: positive; N: negative; X: not performed

Table 2 - Insulin allergy desensitization protocol

1st day	0.004 U
	0.01 U
	0.02 U
	0.04 U
	0.1 U
	1 U
2nd day	1 U
	2 U
	3 U
	5 U
3rd day	6 U
	6 U

Desensitization is based upon successive subcutaneous injections of insulin in an in-patient setting with close patient monitoring and a team prepared for an emergency intervention. The starting dose used depends on the grade of sensitisation, and the procedure lasts approximately three days (Table 2). The mechanism underlying desensitisation has not been fully elucidated; the induction of anergy, depletion of specific T cells, induction of T-regulatory cells and modulation of antibody production by cytokines have been suggested to play a role. Although desensitization has been associated with a decrease in IgE antibodies, this does not prevent the appearance of allergic reactions (3).

In conclusion, allergy to human recombinant insulin is a rare but serious condition that requires an immediate allergological work-up. It can be managed with close cooperation between the allergologist and endocrinologist. Desensitization is efficient and should be considered.

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