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Clinical Letter

Diagnosis and treatment of IgE-mediated insulin hypersensitivity: two case reports

DOI: 10.1111/ddg.13832

Dear Editors,

The introduction of insulin therapy in the 1920s was a major breakthrough in the treatment of diabetes. At that time, insulins were extracted from bovine and porcine pancreases. Unlike human insulin, the heterologous protein structures often caused local injection site reactions. Systemic hypersensitivity reactions were also common. Additives such as protamine and zinc provided beneficial therapeutic effects by prolonging absorption and duration of action (long-acting insulins). In the late 1970s, researchers were first able to produce recombinant insulin with a human amino acid sequence, using genetically modified plasmids in *Escherichia coli*. This has resulted in a decrease in allergic reactions from 5 % to < 1 % [1, 2] in recent decades. Thus, IgE-mediated insulin allergy is currently very uncommon in routine clinical practice.

Case 1

A 79-year-old patient with a three-year history of insulin-dependent type 2 diabetes was referred to us for evaluation of chronic urticaria. Other comorbidities included heart failure, mitral valve insufficiency, atrial fibrillation, coronary heart disease, arterial hypertension, chronic kidney disease, and prostate cancer. The patient reported that he had experienced pruritus as well as two episodes of generalized urticaria in recent months; urticarial lesions had also occurred at the injection sites of insulin isophane (Protaphane®). Insulin glulisine (Apidra®) had been tolerated only in certain areas of the abdominal skin; a switch to insulin glargine (Lantus®) 40 IU once daily (in the evening) had led to contact urticaria at the injection sites. Prick testing revealed positive reactions to virtually all tested short/intermediate- and long-acting insulins available in Germany (Table 1).

Blood tests showed specific IgE antibodies against human insulin, bovine insulin and porcine insulin yet not against protamine (Table 2). Basophil activation testing (using insulin glargine, human insulin and isophane insulin) was subsequently used to further assess the potential tolerability of insulin glargine, to which the patient had shown no reaction on prick testing. The test revealed cellular sensitization to all three insulins tested, including insulin glargine. Based on the aforementioned clinical and laboratory findings, the patient was diagnosed with IgE-mediated immediate-type hypersensitivity to insulin.

Treatment with insulin glargine was continued, as the patient seemed to tolerate this agent reasonably well. The regimen was switched to four daily injections, with individual doses depending on blood glucose levels. On this treatment, fasting blood glucose levels of < 140 mg/dL were achieved, which were acceptable given the patient's age. He was prescribed (but subsequently never had to use) an anaphylaxis emergency kit consisting of dimetindene drops, betamethasone drops and an epinephrine autoinjector. In addition, he was prescribed cetirizine 10 mg PO to be taken as regular antiallergic medication. On this treatment, there was a decrease in contact urticaria lesions, and neither generalized urticaria nor other systemic reactions subsequently occurred. Thus, the patient was free of symptoms one month after the above-mentioned adjustments had been initiated.

Table 1 Summary of prick test results. Testing was performed using various insulins approved for therapeutic use in Germany. A wheal size of ≥ 3 mm was considered to be a positive test result

		Patient 1	Patient 2
Normal insulin	Human insulin, metacresol (Actrapid®)	+	+
Short-acting insulin analogs	Insulin glulisine (Apidra®)	+	n.t.
	Insulin lispro (Humalog®)	+	+
	Insulin aspart (NovoRapid®)	+	+
Intermediate-acting/NPH insulins	Isophane insulin/NPH, protamine (Insuman Basal®)	+	+
	Isophane insulin/NPH, protamine (Protaphane®)	+	+
Long-acting insulin analogs	Insulin glargine (Lantus®/Toujeo®)	Ø	+
	Insulin detemir (Levemir®)	+	+

Abbr.: n.t., not tested; Ø, negative result; +, positive result

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Table 2 Measurement of total IgE and specific IgE antibodies against insulin/insulin components using ImmunoCAP

	Patient 1		Patient 2	
	IgE [kU/L]	CAP class	IgE [kU/L]	CAP class
Total IgE	53.6		265	
Human insulin	1.78	2	12.7	3
Insulin (bovine)	1.37	2	16.0	3
Insulin (porcine)	2.05	2	21.1	4
Protamine	< 0.10	0	< 0.1	0

Case 2

A 70-year-old patient with a history of insulin-dependent type 2 diabetes, arterial hypertension and hypercholesterolemia was referred for further evaluation. He reported to have repeatedly developed erythematous lesions and pruritus at the injection sites after administrating human insulin (Insuman basal solostar®), insulin glargine (Toujeo solostar®) or insulin detemir (Levemir®); there was no generalized urticaria or other systemic symptoms. The patient was also taking candesartan, sitagliptin, metformin and a statin.

In this case too, prick testing showed sensitizations to commonly used insulins (Table 1) and blood tests revealed specific IgE antibodies against human and animal insulins (Table 2). The patient declined both inpatient challenge testing and desensitization treatment. He was prescribed an anaphylaxis emergency kit consisting of dimetindene drops, betamethasone drops and an epinephrine autoinjector; furthermore, the antidiabetic treatment was switched to the glucagon-like peptide 1(GLP-1) analog liraglutide (Victoza®).

Discussion

Immediate-type hypersensitivity to insulin is a diagnostic and therapeutic challenge. The terminal end of the β chain likely plays a key role in terms of the allergenic potency of insulin. Differences in that particular sequence among the various insulin analogs accounts for differences in their absorption [1, 2]. Late-type hypersensitivity to insulin has likewise been reported in the literature. The latter typically presents as local injection site reactions and is usually caused by additives such as phenol, cresol, protamine sulfate and zinc [3].

Immediate-type hypersensitivity to insulin is characterized by generalized systemic reactions that may increase in severity over the course of treatment. Anaphylactic signs and symptoms may include urticaria, angioedema, shortness of breath, hypotension, shock and even cardiac arrest [4]. While diagnosis is facilitated by the detection of specific IgE antibodies against insulins or protamine, this should always be complemented by targeted diagnostic tests such as prick testing with all insulins currently approved (Table 1). This is the only way to determine whether the clinically relevant epitope is either the basic insulin structure, a specific terminal sequence or possibly an additive such as metacresol or protamine. Ideally, this will already allow for an insulin preparation to be identified that is likely to be tolerated. A recent review recommends supplementary prick testing with protamine, cresol and latex, or alternatively, intradermal testing with diluted protamine and cresol (10–100-fold dilutions) [4]. Given that in Germany said allergens are quite difficult to procure as individual and sufficiently pure substances, this diagnostic approach seems to be unfeasible in everyday clinical practice.

As our first patient showed no reaction to insulin glargine (Lantus®) on prick testing, he was immediately switched to Lantus® monotherapy. Only after the basophil activation test did it become apparent that his hypersensitivity also included insulin glargine. There have been previous reports of negative prick test results using insulin glargine in insulin-allergic patients. This can be attributed either to the smaller proportion of free insulin due to complexation of insulin glargine or, alternatively, to its lower allergenic potential [5].

Pan-insulin hypersensitivity is a major therapeutic challenge as continuation of adequate diabetes treatment is required. The approach most frequently described in the literature, specifically for type 1 diabetics, is desensitization (tolerance induction). The concept of tolerance induction involves repeated exposure of the immune system to allergens in order to achieve a state of unresponsiveness that will prevent anaphylactic reactions. The goal is to maintain this state by continuous administration of the respective allergen [6]. In the majority of reported cases, insulin glargine or insulin aspart were used for this purpose. Following an updosing regimen, these insulins were given either as continuous subcutaneous infusion, as intradermal injection or as intravenous injection [1, 5, 7, 8]. After subcutaneous administration, insulin glargine forms precipitates that, in turn, dissolve slowly and continuously. This allows for a level of antigen presentation comparable to continuous subcutaneous infusion [8]. Furthermore, it is believed that the specific amino acid sequence of insulin glargine might be able to inhibit the immune response [8]. The case of our first patient shows that switching the dosing of insulin glargine to four times daily may be a pragmatic therapeutic concept.

For allergic type 2 diabetics who decline to undergo desensitization treatment, there is potentially an insulin-free therapeutic approach, as demonstrated by our second patient. Here, the diabetologists were able to maintain adequate diabetes treatment by prescribing liraglutide. This agent acts as a GLP-1 analog through the incretin effect (orally administered

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glucose results in greater insulin secretion than glucose given intravenously), thus enhancing the glucose-dependent release of insulin from pancreatic β cells. At the same time, it promotes weight loss and reduces the risk of cardiovascular disease [9].

Conclusion

Patients with insulin-dependent diabetes and confirmed insulin hypersensitivity pose a particular therapeutic challenge as they continuously require insulin. Tolerance induction through monotherapy with insulin glargine is a useful option for the treatment of IgE-mediated insulin sensitization. In some cases, treatment with GLP-1 receptor agonists might be an alternative therapeutic option.

Conflicts of interest

None.

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