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Review

Insulin Allergy

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Abstract

At present, hypersensitivity reactions to human insulins and insulin analogs are rare, although these reactions were relatively common when bovine and porcine insulins were used. Clinical presentation can range from local reactions to severe anaphylaxis. Local reactions may decrease insulin absorption, which may disrupt blood glucose regulation. These reactions may be caused by insulin itself or by its additives. Systemic reactions following insulin injection require allergologic work-up. Desensitization therapy is a good option for patients with multiple insulin sensitizations.

Keywords: Insulin, allergy, hypersensitivity, desensitization

Insulin hypersensitivity reactions have been reported in both type 1 and type 2 diabetic patients. Some of these reactions stem from insulin itself, while some result from additive agents. Although reactions to all types of insulin can develop, reactions to human insulin and its analogues are rare. However, vital reactions can be observed. Previously used bovine and porcine insulins are known to be more immunogenic, and reactions to these types of insulin are more commonly observed. Due to the development of the purification process, the rate of these reactions has decreased considerably, from 30%–1% (1, 2). One-third of these reactions are associated with insulin, while the remaining reactions result from different substances that are added to the preparations. The allergic reaction types are named Type I, Type III, and Type IV (1-4). Skin reactions occurring at the injection site reduce the effects of exogenous insulin, stimulate insulin degradation, and/or impair insulin absorption. Thus, diabetes regulation also deteriorates (5).

In addition to human insulins (NPH and regular insulins), analogues (lispro, aspart, glargine, detemir, glulisine, and degludec) may also induce allergic reactions. Stimulants may be an epitope of insulin itself and may also be changed by an antigenic epitope during production and purification. During subcutaneous degradation of insulin, different antigenic structures may be formed. Zinc and protamine are added to insulin to extend the duration of action, while metacresol and various contaminants are added as preservatives; these may cause reactions (1, 2). The commercially available insulin types and the additives they contain are presented in Table 1. Protamine is a cationic substance found in fish sperm; it is added to delay the release of insulin from the injection site. Exposure to protamine is a risk factor for allergy. Although fish allergies and vasectomy are believed to create risks in this regard, this situation was found to be only partly significant; no other relationships with other insulin types were observed, and no risk was found in a prospective study (3). However, protamine allergies and long-time use of insulin create risk for the production of insulin antibodies. In poorly controlled diabetes, this possibility should be considered. Although autoantibodies against protamine-heparin complex have been found, the relationship between insulin antibodies and protamine is not clear. This relationship is particularly significant in intermediate and rapid-acting insulins; the relationship between analogue insulins and autoantibodies was found to be contradictory. The time of insulin use, not the duration of diabetes, is significant. Protamine causes the formation of autoantibodies, probably by causing a change in the conformation of insulin. Also, cross-reactivity between human protamine and salmon protamine in insulin or the development of an immunologic response to salmon protamine can cause an allergic reaction. The amount of protamine found in NPH and insulin aspart is greater than that found in insulin lispro (6).

Hypersensitivity reactions

Early reactions: Clinical manifestations can vary from IgE- or IgG-mediated local reactions to Life-threatening anaphylaxis. Early reactions may take place within an hour, sometimes minutes after injection. Rapidly developing erythema at the injection site or local or generalized urticaria in the form of itchy blisters, rash, angioedema, itching, diarrhea, or cardiovascular symptoms can appear in the form of a general reaction with hypotension and anaphylaxis. Unlike the classic

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Table 1. Insulin types and the additives they contain

		Additives				Action time
Name	**Type**	**Zn**	**Protamine**	**Cresol**	**Other**	**2-8 hours**
		Short-acting insulins				
Actrapid	Human regular	x		x	Glycerole	
Humulin R	Human regular					
Humalog	Lispro Analog					
Novorapid	Aspart r-DNA ins					
Apidra	Glulisin					
		Intermediate-Long acting insulins				
Humulin N	NPH					
Insulatard HM	NPH					
Lantus	Glargin analog	x		x	Glycerole	More than 24 hours
Levemir	Detemir	x		x	Fenol	Up to 24 hours
		Insulin combinations				
Humulin M	NPH/regular					
Mixtard	NPH/regular					
Novomix 30	Protamine aspart/aspart 70/30	x	x	x	Fenol	Up to 24 hours
Humalog mix 25	Protamine lispro /lispro 75/25	x	x	x	Fenol, Glycerole	
Humalog mix 50	Protamine lispro /lispro 50/50	x	x	x	Fenol, Glycerole	Up to 24 hours

symptoms, anaphylaxis may occur with atypical symptoms such as nausea, vomiting, tremor, blurred vision, and diplopia. Typically, manifestations may be observed several months or years after the patient initiated injection treatment, or immediately after the first injection. In this case, the antigen responsible is probably endogenous insulin or a determinant found in the insulin which was previously used by the patient. Sensitivity that starts with local symptoms may be aggravated over time and may develop systemic reaction characteristics. Early reactions are IgE-mediated and may be caused by insulin or additive agents. Although insulin antibodies are formed, reactions may not be observed. The clinical picture is dependent on released mediators, mainly histamine (1). In the literature, a case was reported of a patient who was allergic to insulin containing fish and protamine; the patient was given protamine in order to antagonize heparin that had been used during spinal surgery and developed fatal anaphylaxis (7). When viewed pathogenetically, Type I reactions usually develop after the first week of treatment. Anaphylaxis may even develop in patients who resumed treatment after a break due to local reactions. Biphasic reactions may reach a peak 4 hours after the injection and disappear within 24 hours (1-3).

Late reactions: Generally, late reactions develop with Type III and Type IV immune reactions. Type III reactions are non-erythematous indurations that develop within 6–8 hours and last until 48 hours after the injection; they are characterized by mononuclear cell infiltration and central hematoma. Type IV reactions, contrastingly, are characterized by nodules that emerge more than 24 hours later and last 4–7 days (1-3). Induration and subcutaneous nodules can be painful or itchy. Granulomatous reactions due to IgG antibodies may also occur. Although anti-insulin G antibodies were positive in some patients, this was not reported to be clinically associated. Localized exanthema or eczema-like lesions may develop at the injection site. In some patients, systemic complaints

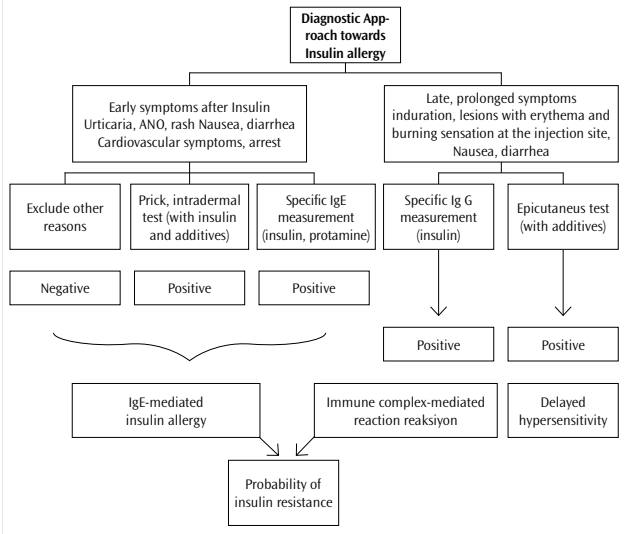

Figure 1. Diagnostic approach toward insulin allergy (1)

such as exanthema, headache, vomiting, and diarrhea may occur. Delayed reactions develop via T-lymphocytes or eosinophils and are often caused by additives. The zinc that is added to the preparation may cause changes in the structure of insulin and may alter its immunogenicity (1).

Insulin-related reactions may manifest as clinically localized reactions, generalized reactions, or insulin resistance. Localized reactions occur in about 5% of patients and may be due to accidentally performed intradermal (ID) injections instead of subcutaneous (SC) injections. Thus, lesions and urticaria characterized by multiple scars and pigmentation may occur. Antigen-presenting Langerhans cells, which are abundant in the dermis, may aggravate immune reactions by increasing the presentation of the antigenic compo-

nent of insulin (8). When the symptoms and signs are related to the skin only, they may result from insulin hypersensitivity or may also be connected with irritation or other dermatologic conditions (prurigo simplex, atopic dermatitis, etc.) (9).

Diagnosis

The clinical approach toward insulin allergy is shown in Figure 1. Early reaction diagnosis for insulin is primarily based on the patient's history. Skin tests should then be conducted, and insulin antibodies should be investigated by means of specific IgE measurement in the blood. During history taking, the specific symptoms following injection, the length of time required for these symptoms to emerge after injection, whether these lesions are at the injection site or generalized, whether these symptoms are systemic, whether other drugs are being taken concurrently, the presence of chronic urticaria, the presence of ANO, and whether previously used insulin preparations were tolerated should be questioned. For IgE-mediated reactions, a skin prick test and IgE antibody measurements are required. However, erythema developing at the injection site and induration are associated with IgG-mediated allergy and require measurement of anti-insulin IgG titers (9).

Skin tests may show false positive reactions. Prior to the skin test, the patient should fill out a form, and the insulin type the patient reacts to, other probably used insulin types, and the additives in the preparation must be specified. Negative and positive controls should be performed. Following the prick with undiluted insulin, an intradermal test with 1/100 saline dilutions must be performed. In commercial solution preparations (100 unit/mL), 1/100 dilution is equivalent to 1 unit/ml. Prick test>3 mm bubble or ID test>3 mm bubble is acknowledged as (+). In order to evaluate Type III and Type IV reactions, a control for the tests is required after 12–48 hours. If induration is present, the test is acknowledged as (+). False positive skin tests can occur without allergic symptoms. Even if the allergy is observed clinically, because very small doses of insulin are probably used, the skin test result may be (-) (1-3).

If test material for protamine and other additives is not available, an insulin preparation test can be used with various dilutions. Although the clinical relationship is not clear, conducting a skin test using protamine may be useful in determining the presence of protamine sensitivity. When protamine sulfate (10 mg/mL) is diluted 30 times, NPH is obtained in insulin concentration (350 micrograms/mL). For an intradermal test, the prick solution should be diluted 10–100 times. If the patient has a history of anaphylaxis, further dilution is required. In patients who have experienced anaphylaxis, a positive response with 0.03 nanogram/mL protamine is reported. Cresol is an additive that can be found in many insulin preparations and can cause a premature reaction. It may cause pain at the injection site, erythema, induration, and urticaria with local skin erosions. A (+) skin reaction may be observed with cresol in saline. 1.5 mg/mL solution is suitable for the prick test, and solutions diluted 10–100 times are suitable for intradermal tests (1, 3).

For late reactions, a patch test should be performed with different types of undiluted insulin. Furthermore, metacresol in glycerol should be tested with glycerol as a comparison (2, 3).

For *in vitro* tests, measurements of latex, insulin, and protamine-specific IgE may be useful. The lymphocyte transformation test (LTT) may also be useful in determining T lymphocyte-mediated late reactions. Latex from the membranes of bottles may be responsible for allergic reactions in rare cases. Bottles that do not contain latex are available. If there is a suspicion of latex allergy in the patient's history, a skin test and specific IgE measurements can be conducted (1).

Endogenous insulin rarely causes allergic reactions. For exogenous insulin, sensitivity is possible; a case was reported of an allergic reaction when exogenous insulin was only given with oral sulfonylurea at the time of insulin peak. While a skin test with exogenous insulin was (+), the oral antidiabetic (OAD) result was (-), and the patient could tolerate insulin treatment with steroids (10).

At subcutaneous injection sites, urticaria-like lesions, pain, erythema, and desquamation may occur within minutes (11, 12). However, these may disappear in a few minutes to a few hours. A positive response may be obtained with provocation using a small dose, such as 2 U. Compared to insulins of animal origin, insulins produced by recombinant DNA technology have a lower risk of reaction (11).

While insulin allergy test kits were once provided by insulin companies (metacresol, protamine sulfate, zinc, acid-base buffers, glycerol), these agents are no longer provided. It is recommended to perform additional tests using the additives provided by the suppliers (12).

Insulin allergy should be suspected in patients with nonspecific skin and systemic symptoms; these may be underlying symptoms of an autoimmune disease (9).

Differential diagnosis

Differential diagnosis should mostly be used for acute and chronic urticaria. Also, concomitant medications, infections, and physical stimuli should be questioned. Additionally, many diseases, such as psoriasis, atopic dermatitis, and prurigo nodularis, should be considered. Other reactions caused by insulin-related immunological mechanisms are lipodystrophy, lipoatrophy, and insulin resistance.

Treatment

If anaphylaxis occurs during insulin therapy, the patient must be referred for allergological examination. Many non-serious reactions may regress over time. If the skin manifestations cannot be identified, dermatology consultation should be requested. If the patient is suspected to have an allergic reaction to the insulin preparation, the medication should be stopped; symptomatic therapy and an empirical approach are recommended, and the patient should switch to a different preparation. In cases of anaphylaxis, the patient should be hospitalized. For symptomatic treatment, antihistamines may be used; if antihistamines are not sufficient, steroids may be used. However, attention should be paid to blood sugar regulation. In terms of changing the patient's insulin, if human insulin is used, proceeding with analog insulins would be suitable (1). In general, the recommended method is replacement of the patient's insulin preparation. Sometimes, new medication is not tolerated. The patient's condition becomes more serious, with deterioration in both allergic symptoms and glycemic regulation (9).

For late reactions, deep injections, antihistamines, topical steroid ointments (such as mometasone), and antipruritic creams are suit-

Table 2. Desensitization protocol (4)

Number of the solution	Insulin dose	0.9% NaCl	Concentration (/0.1 mL)
2	0.1 mL (10 U)	100 mL	0.01 U
3	0.1 mL (10 U)	9.9 mL	0.1 U
4	Original insulin	-	-

Table 3. Rapid desensitization protocol with insulin

Day	Insulin type	Insulin dose (U)	Route	Dose interval
	Short-acting	0.004	subcutaneous	30 minutes
	Short-acting	0.01	subcutaneous	30 minutes
	Short-acting	0.02	subcutaneous	30 minutes
	Short-acting	0.04	subcutaneous	30 minutes
	Short-acting	0.1	subcutaneous	30 minutes
	Short-acting	0.2	subcutaneous	30 minutes
	Short-acting	0.5	subcutaneous	30 minutes
	Short-acting	1	subcutaneous	30 minutes

Day	Number of doses	Insulin dose (U)	Total daily dose (U)
1	1	0.0001	0.0001
1	2	0.001	0.0011
1	2	0.01	0.0111
1	4	0.1	0.1111
1	5	1	1.1111
1	6	2	3.1111
2	7	1	1
2	8	2	3
2	9	4	7
3	10	6	6

Day	Route	Insulin dose (U)	Dilution
1	intradermal	0.001	1/1000
1	intradermal	0.002	1/1000
1	intradermal	0.005	1/1000
1	subcutaneous	0.01	1/100
1	subcutaneous	0.02	1/100
1	subcutaneous	0.05	1/100
2	subcutaneous	0.1	1/10
2	subcutaneous	0.2	1/10
2	subcutaneous	0.5	1/10
3	subcutaneous	1	1/1

able. If the lesions do not disappear within a few weeks, dermatology consultation should be requested. A patch test or biopsy may be necessary. If drug-induced contact dermatitis is considered, the preparation should be replaced (1). Primarily, the most frequent factors that cause local reactions, such as latex allergy, injection technique, the substances used for skin preparation, and the type of needle, should be considered.

If injection site irritation is considered:

- The injection technique of the patient should be observed.
- Cleaning solution should be used.
- The injection site should be changed.
- Deep injection should be administered.
- The areas on which belts and straps are used should be avoided as injection sites.
- The injection site should be slightly cooled.
- Smaller needles should be used.
- Some massage should be applied on the injection site after the injection is administered.
- The injection should be administered in a warm setting (1).

Administering divided doses at different sites, adding 1 mg dexamethasone for each insulin unit or oral administration of steroids, and application of a pump are methods that can used if local reactions continue (1).

For patients with insulin antibodies:

- Rather than intermediate-acting and premix biphasic insulins, insulins that do not contain protamine are recommended
- Suitable OAD combinations with long-acting insulins
- Long-acting and rapid-acting insulins
- Insulin degludec/insulin aspart
- Long-acting insulin+GLP1 agonist; if the patient's insulin reserve is good, GLP1 agonist can be used (5, 6).

When an allergy to a preparation is detected, if switching to an alternative medicine is not possible, desensitization should be performed. Desensitization can be successfully performed with SC insulin pumps (1).

Desensitization is necessary for patients with Type I reactions who require insulin treatment. Desensitization is based on the loss of allergenic mediators from mast cells and the formation of IgG-type blocking anti-insulin antibodies. To ensure the development of tolerance, continuous and regular medication in increasing doses is applied. Application is performed via continuous SC (CSII) or appropriate SC injections. Because rapid-acting analogues are generally quickly absorbed and degraded at the injection site, their antigenicity decreases. Among the different types of insulin used by the patient, using a preparation that causes a milder reaction during a skin test is appropriate when performing desensitization. Reaction to insulin glargine is also rare. A precipitate is formed after the injection; by implementing SC insulin at a slow and steady pace, and by imitating CSII, abjunction takes place. Again, the amino acid composition of glargine may suppress immune reactions.

Subcutaneous administration for desensitization can be performed as shown in Tables 2, 3.

While continuous insulin should be given, to prevent ketosis and ensure normoglycemia, rapid-acting insulin should be implemented via a peripheral intravenous catheter for about an hour (<3 U). If SC insulin is used, 0.025 units per hour is administered. The dose is increased by 0.05 units every 6 hours. Faster application creates discomfort in the chest. While the dose is not changed in cases of insignificant discomfort, for significant discomfort, the dose is decreased 0.05 units per hour. If more severe pain and urticaria

develop, medication can be stopped, and 20 mg of oral steroids can be given for 3 days.

Sometimes, Type II and Type IV reactions may be experienced by the same patient. Metacresol can be found in many substances, such as soap and adhesives. This is an important substance because it has been reported to cause reactions in many patient histories. The amount of metacresol in insulin is important in terms of the intensity of the reaction (higher in NPH). Because metacresol is present in all insulin types, it requires desensitization. A case with a metacresol allergy was reported for whom insulin desensitization was performed; the patient's basal insulin dose could be increased to the desired level within five days (12).

When performing desensitization with subcutaneous insulin, it is still not known how IV insulin, which is given to prevent ketosis, is tolerated. It is probable that a small volume of insulin enters the circulation via a catheter inserted into a large vein; the application of insulin by different methods causes different immune responses, which induce different reactions. Antihistamines and steroids may be used in the treatment of acute reactions and in desensitization. Performing the desensitization process during the honeymoon period may be more appropriate (13).

In this protocol, SC insulin is applied with 30-minute breaks as 0.1, 0.2, 0.4, and 0.8 mL of 0.001 units. Then, the application is continued with the same volumes of dilution with 0.1/mL concentration. Similar procedures are repeated with other types of insulin that are intended to be administered to the patient, and the desensitization is complete when the required therapeutic dose is reached. Meanwhile, the blood sugar of the patient is monitored and glucose infusions are performed when necessary.

Meanwhile, if a local reaction develops, cold application is performed; after waiting for 30 minutes, the procedure is continued with the same dose that caused the reaction. If systemic reaction develops, after treating the reaction, desensitization is continued with half the dose. With the formation of Ig G antibodies, insulin resistance may develop. Due to ineffective desensitization procedures, omalizumab was used in some cases. A case for whom rituximab, mycophenolate mofetil, and omalizumab were used has been reported. As a rarer condition, a case report in which a pancreas transplant was required can be found in the literature (3).

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