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REVIEW

Allergic reactions to human insulin: a review of current knowledge and treatment options

Baris Akinci · Serkan Yener · Firat Bayraktar · Sena Yesil

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Abstract Although the incidence of insulin allergy decreased after the introduction of recombinant human insulin preparations, it is still a major problem which may be life-threatening in some cases. In this article, we attempted to review current knowledge concerning allergic reactions to human insulin and discuss the available treatment options of insulin allergy.

Keywords Allergic reactions · Diabetes · Insulin treatment

Introduction

Insulin allergy is a rare complication of insulin treatment [1]. It includes a wide range of clinical pictures from local injection reactions to severe generalized anaphylaxis [2]. The frequency of insulin allergy has been decreased with the use of human insulin; however, it is still a major problem which may be life threatening in some cases [3]. Allergic reactions to human insulin include immediate type IgE-mediated reactions (type I), immune complex type which is characterized with localized Arthus reaction and/or generalized serum sickness (type III) and delayed-type hypersensitivity reactions (type IV) [1, 3]. Additionally, delayed reactions with histological signs of leukocytoclastic vasculitis have been reported [4]. In this article, we reviewed recent knowledge on allergic reactions to human insulin and discussed the available treatment options of insulin allergy. We also briefly overviewed immunologic reactions against human insulin and its receptor.

B. Akinci (✉) · S. Yener · F. Bayraktar · S. Yesil
Division of Endocrinology of Metabolism, Department of Internal Medicine, Dokuz Eylul University Medical School, Inciralti, 35340 Izmir, Turkey
e-mail: baris.akinci@deu.edu.tr

Types of allergic reaction to human insulin

Type I allergic reaction is the most common type of insulin allergy characterized with rapid onset and IgE-mediated reactions [1, 3]. This IgE-dependent reaction is mediated by the release of vasoactive substances mainly from basophiles and mast cells. Local symptoms typically start immediately after injection of insulin as swelling, erythema, and itching at the injection site. Flare reactions may develop at the former injection sites upon insulin injection [5]. Type I allergic reaction to human insulin may confine itself and resolve; however, in a minority of cases it may progress to a generalized reaction, ranging in severity from simple urticaria to anaphylaxis [6]. Biphasic allergic reactions with a late phase, which may have a peak 4–6 h after the first reaction, may occur [3, 6]. Delayed-type hypersensitivity reactions due to insulin have also been reported [3]. In that case, induration at the injection site may last up to several days. It is believed that an IgG-mediated and cell-mediated reactions resulting in mononuclear infiltration are responsible for the delayed-type hypersensitivity to human insulin [6]. Type I insulin allergy typically occurs within several weeks after initiation of insulin therapy and, more frequently, when it is resumed after a delay [7]. However, unusual cases developing insulin allergy after treatment with insulin for years have been reported [3].

Type III insulin allergy is very rare, but reported in few cases [8, 9]. Serum sickness associated with human insulin is extremely rare. Type III insulin allergy is characterized with localized Arthus reaction [10]. It represents insulin-antibody

complexes that cause basophile degranulation and local release of histamine and other mediators of hypersensitivity. It involves complement fixation, leukocyte attraction, and an inflammatory response to antigen–antibody complex formation [1]. Localized Arthus reaction due to human insulin is characterized with the development of subdermal, small, tender, and non-erythematous or mildly erythematous nodules at injection sites which occur 4–8 h after insulin injection, lasting up to 48 h [8, 9]. Serum sickness like reactions to human insulin is mediated by IgG antibodies [6]. Simultaneous type I and III reactions to insulin have been also reported [9].

Type IV insulin allergy is also rare. It is characterized by T-cell-mediated delayed reaction that appears at least 8–12 h after insulin injection, lasting for 4–7 days [6]. Cutaneous nodules due to type IV insulin allergy usually develop usually 24 h or more after the insulin injection. Mononuclear infiltration is present histopathologically [1].

Evaluation of suspected insulin allergy

The management of suspected allergic reactions to human insulin is summarized in Fig. 1. A careful medical history should be taken to ascertain whether this is a case for insulin allergy, if so, what kind of an allergic reaction is that, and which agent is the most likely cause of these symptoms. The medical history for other allergies and autoimmune disorders should be questioned. At first, allergic reactions due to human insulin should be distinguished from any lesions due to incorrect injection technique. A possible reaction to alcohol wipes should not be ignored. The presence of an insulin allergy can be proven by the determination of specific IgE or IgG. However, it should be noted that positive antibody titers indicate sensitization only and may occur in diabetic patients being administered with insulin without any clinical relevance [11]. Intradermal skin test would be very helpful to confirm insulin allergy and to determine the type of insulin allergy as the appearance of a lesion within 60 min of injection usually indicates type I allergy to insulin [12]. Skin prick test is also available to help in the diagnosis of insulin allergy; however, it is less sensitive than intradermal skin test [13]. Another point is that pharmaceutical additives in insulin preparations might be the reason for the allergic reactions [14]. While protamine sulphate is the most common additive to be responsible for allergic reactions after insulin injections, possible allergic reactions due to other additives such as zinc or metacresol should be kept in mind [12, 15]. Specific IgE measurements against additives can be performed [16]. Rare cases regarding insulin-injection-site reactions associated with

1. Make sure the patient has insulin allergy

Exclude:
- Incorrect injection technique
- A possible reaction to alcohol wipes
- Latex allergy

Keep in mind that additives may be the reason for the allergic reactions

2. Confirm the allergic nature of lesions, determine the type of insulin allergy (type I, III or IV), and find out which agent is the most likely cause of these symptoms

Intradermal skin test:
- Include the insulin preparations used, alternative insulin preparations and additives.
- Histamine and 0.9 % NaCl can be used as positive and negative controls.
- The reaction is regarded as weakly positive when it is half that of the histamine control (usually at 20th min), and clearly positive when it is the same as that of the histamine control.
- Avoid taking antihistaminic agents for at least 3 days before testing.

Skin prick test (less sensitive than intradermal skin test)

Determination of specific IgE or IgG (against insulin and additives)

Histamine release test can be performed when necessary

3. Switch insulin to oral antidiabetics if possible

Not possible if insulin is an indispensable choice of treatment (type 1 diabetes, concomitant organ dysfunctions etc.)

4. Use alternative insulin preparations (preferentially of ones with negative intradermal testing), and consider to change the route of insulin administration
- Injection sites modification
- Rapid acting analogues
- CSII
- i.v. insulin

5. Local corticosteroids for local allergic reactions

6. Antihistamines for symptomatic therapy

7. Consider specific immunotherapy
- The initial dose is 0.00001 units.
- Increase progressively 10-fold up to 1 unit, then 2, 4, 8, 12, 16, and 20 units.
- If local allergic reactions develop, repeat the last dose until no reaction occurs and then increase the dose.
- If systemic reactions develop decrease the dose to one half.
- In type 2 diabetes, maintain glycemic control by medical nutrition treatment and oral antidiabetics.
- In type 1 diabetes, different insulin preparations than insulin preparations used for immunotherapy can be administered.

8. Consider other alternative treatments
- Systemic steroids
- Immunosuppressive agents
- Targeted biologic agents
- Plasmapheresis
- Pancreas transplantation

Fig. 1 Management of suspected allergic reactions to human insulin

type I latex allergy have also been reported [17, 18]. An intradermal skin test reaction would be useful to find out whether the case is a true insulin allergy or not [19]. However, some patients under insulin treatment may have already developed insulin antibodies without having any clinical symptoms. In that case, a positive intradermal skin test may have no diagnostic relevance. Nevertheless, a negative intradermal skin test can exclude an allergic reaction against the injected type of insulin or additive [19, 20]. Intradermal skin test should include the insulin preparations used, alternative insulin preparations, and additives. Histamine and 0.9% NaCl can be served as positive and negative controls, respectively, [3]. Intradermal skin test reaction can be regarded as weakly positive when it is half that of the histamine control (usually at 20th min), and clearly positive when it is the same as that of the histamine control [21]. Patients should be asked to avoid taking antihistaminic agents for at least 3 days before testing [19].

The amounts of histamine released from peripheral blood basophiles can be evaluated by histamine release test. For this purpose, basophiles should be purified from peripheral blood of the patient with suspected insulin allergy. Anti-basophile monoclonal antibody-coated magnetic beads can be used for purification. Different concentrations of human recombinant insulin are used to stimulate the basophiles, and the amounts of released histamine are measured by an enzyme-linked immunosorbent assay [21, 22].

Management of insulin allergy

The easiest way to treat insulin allergy is switching insulin preparation to oral anti-diabetics. In the same way, immunological insulin resistance against exogenously administered human insulin can be treated by ceasing insulin administration [14, 23]. In daily practice, however, vast majority of patients with insulin allergy need insulin as an indispensable choice of treatment for diabetes, as their endogenous insulin secretion is not preserved or they have concomitant organ dysfunctions.

Standard clinical approach to human insulin allergy includes exclusion of poor injection technique and reaction to alcohol wipes, use of alternative insulins, antihistamines, local and systemic steroid therapies, and desensitization. Local reactions to insulin may resolve spontaneously without any need to discontinue insulin [12]. However, local reactions persisting longer than weeks and generalized reactions to insulin need to be treated. It should be noted that worsening of local symptoms may be a sign for developing generalized insulin allergy [3].

The use of alternative insulin preparations is the first line management of human insulin allergy. In particular, this intervention works if the reason for the allergic reaction is pharmaceutical additives used in the insulin preparations [1]. Even in the case of human insulin allergy, the use of alternative insulin preparations, preferentially of ones with negative intradermal testing, may solve the clinical problem [24]. Local injection of corticosteroids may be beneficial in patients with local allergic reactions. Injection sites modification can be proposed along with subcutaneous injection of 1 μg dexamethasone per unit of insulin [25]. The use of simultaneous infusion of corticosteroids in small amounts by CSII has been reported to be associated with an improvement of local insulin hypersensitivity [26]. Besides, antihistamines can be used for symptomatic therapy [20].

Specific immunotherapy has been used successfully to treat insulin allergy [27–29]. It has been associated with a decrease in IgE antibodies titers, although the reduction in serum IgE levels does not always prevent from the development of allergic symptoms [17]. In addition, the induction of insulin IgG antibodies leading to insulin resistance has been very rarely described as a complication of immunotherapy for insulin allergy [18]. As immunotherapy consists of injections of insulin at increasing concentrations, allergic reactions may develop during the procedure. Therefore, specific immunotherapy should be performed under close monitoring with preparation for emergency intervention in an in-patient setting [3]. It may be combined with systemic steroid treatment, in particular to treat patients with generalized insulin allergy [27]. Specific immunotherapy is usually effective; however recurrence of allergic reactions after successful desensitization may occur [28]. Although specific immunotherapy is usually efficient for type I allergy, patients with type III or type IV allergies can be partially or totally refractory to the immunotherapy [9, 30]. An algorithm of specific immunotherapy for patients with severe symptoms of insulin allergy has been suggested by Heinzerling et al. [3] as below. The initial dose is 0.00001 units, with subsequent doses progressively increasing 10-fold up to 1 unit, then 2, 4, 8, 12, 16, and 20 units. In case of local allergic reactions, the last dose is repeated until no reaction occurs and then the dose increases are continued. If systemic reactions occur the dose is reduced to one half. Glycemic control can be maintained by medical nutrition treatment and oral anti-diabetics in patient with type 2 diabetes. However, type 1 diabetics usually needs insulin treatment during immunotherapy, as it can last up to 2 days. In that case, different insulin preparations than insulin preparations used for immunotherapy can be administered. CSII can be also used. Glucose solutions can be given to control hypoglycemias due to increased insulin doses administered to patients.

The type and route of insulin administration

Adachi et al. [21] described a patient who had reactions to regular and NPH insulin but not to long-acting insulin (Humulin-U). Interestingly, histamine release tests revealed that rapid-acting insulin analogues (insulin lispro and aspart) induced higher amounts of histamine release than Humulin U. The authors concluded that long-acting crystallized insulin may rather slowly release insulin monomers, which may have lower antigenicity. A recent paper by Asai et al. [31] concerning the induction of immunologic tolerance with the use of intravenously injected insulin in a severely insulin-allergic patient with type 1 diabetes raised the question whether identical insulin molecules can behave in markedly different ways depending on the route of injection. The authors mentioned that the formation of anti-human insulin IgG might be caused only by insulin molecules that are in contact with subcutaneous tissue. They assumed that some modification of insulin, such as aggregation, might lead to the allergic reactions [23, 31]. It is also known that subcutaneous tissue is rich in mast cells [7]. In the same way, Neville et al. [32] reported two pediatric cases with type 1 diabetes and insulin allergy. Failing rapid desensitization to insulin delivered by either subcutaneous injection or CSII, the concurrent use of i.v. insulin allowed desensitization to CSII over 5–6 days in those patients.

The use of insulin analogues

Although insulin analogues present new epitopes for recognition by the immune system, current evidence revealed that there is no increased risk for allergic reactions associated with insulin analogues [33, 34]. However, several case reports regarding development of local and generalized insulin allergy on insulin analogue treatment have been published [24, 27, 35–37]. On the other hand, it has been shown that persistent cutaneous insulin allergy resulted from high-molecular-weight insulin aggregates [38]. Rapid-acting insulin analogues revealed with an immediate dissociation of hexamer structure to monomers, so that they might be less antigenic [38, 39]. Successful treatment of local and systemic insulin allergy has been reported with switching of insulin treatment to a rapid-acting insulin analogue, namely insulin lispro [40–43], aspart [44, 45] or glulisine [46]. In a series of 22 patients with insulin allergy, Bodtger et al. [12] reported five patients treated with insulin analogues, of those three had full and two had partial remission. Frigerio et al. [30] reported improvement of insulin allergy by using rapid-acting insulin analogue in a patient with insulin allergy who developed insulin allergy when she was on CSII therapy with regular insulin. On the other hand, several papers reported the failure of rapid-acting insulin analogues in the treatment of insulin allergy [27, 47].

Long-acting insulin analogues are a good option to provide basal insulin coverage in patients with diabetes [39]. Insulin glargine was reported to be successful in the management of insulin allergy in a few cases. The first case was a 45-year-old type 1 patient with generalized allergy to human insulin who was successfully treated with insulin glargine [48]. Later on, Kara et al. [49] reported a 1-year-old patient with insulin allergy who was treated successfully by combination of insulin lispro with insulin glargine. In another paper, Pfohler et al. [50] reported a 68-year-old man with type 2 diabetes and insulin allergy that were treated with a desensitization protocol using human insulin and subsequent conversion to therapy with glargine insulin. In a very recent paper, Hara et al. [51] reported successful desensitization by glargine administration in a 56-year-old man with insulin allergy. They proposed that the pattern of antigen presentation after glargine injection resembles that after CSII, as insulin glargine forms precipitates after it is subcutaneously injected, and these precipitates dissolve at a slow and constant rate. On the other hand, allergic reactions due to insulin glargine have also been reported. In the first report of allergic reactions to insulin glargine, Durand-Gonzales et al. [52] described an 81-year-old man with type 2 diabetes who first developed insulin allergy while using regular and NPH insulin in a mix preparation and his skin tests were very positive with glargine insulin. Another report describes a 60-year-old type 2 diabetic patient who showed allergic cutaneous reactions to insulin glargine [53]. Castera et al. [24] described a patient with insulin allergy who had positive reactions to all sorts of available human insulin as well as insulin glargine. In 2005, Darmon et al. [8] published the first report of insulin allergy to insulin detemir in a 31-year-old man with type 1 diabetes who developed type III insulin allergy when his treatment plan was switched for insulin detemir. Severe injection site reactions to insulin detemir have reported [44, 45, 54]. Recently, Sola-Gazagnes et al. [55] reported four cases of type IV allergy (delayed-type hypersensitivity), and two cases of type I allergy to detemir. In another very recent report, Perez et al. [56] described a patient with detemir insulin-induced anaphylaxis.

Continuous subcutaneous insulin infusion (CSII)

CSII has been proposed to reduce insulin allergy possibly associated with small doses of insulin being delivered [6]. Since most desensitization protocols involve starting insulin administration with very small amounts and gradually increasing the amount of insulin to therapeutic levels, the use of CSII in patients with insulin allergy seems to be

conceivable. Several cases with insulin allergy have been reported to be managed by CSII successfully [24, 29, 53, 57–60]. It has been proposed that combining CSII and the use of a rapid-acting insulin analogue would be a valuable strategy in the treatment of insulin allergy [6]. On the other hand, there are few reported cases developing allergic reactions against insulin while being treated with CSII. In a patient with type III allergy to human insulin managed by our group, allergic reactions developed while she was using CSII. Geldof et al. [61] reported a patient who developed hand eczema associated with CSII. In another paper, Beltrand et al. [62] reported a 7-year-old boy who developed insulin allergy and extensive lipoatrophy although his insulin treatment switched to CSII after first signs of insulin allergy had appeared. Durand-Gonzalez et al. [63] reported that insulin allergy reappeared 7 weeks after the initiation of CSII in a patient with gestational diabetes who had first developed insulin allergy while using insulin injections.

Other treatment options

Systemic steroids and/or immunosuppressive agents such as azathioprine and methotrexate can be used in the treatment of generalized insulin allergy; however this type of treatment is usually not associated with permanent recovery, and side effects are common [5, 64]. Tacrolimus aiming for serum trough levels between 5 and 10 ng/ml was given to a patient with generalized insulin allergy; however no improvement of his symptomatology was observed [65]. In a very recent paper, Yong et al. [66] reported a patient with severe generalized insulin allergy who was treated successfully by the sequential use of two targeted biologic agents, rituximab and omalizumab, in a two-step therapeutic approach which also consisted of the use of prednisolone and mycophenolate mofetil. On the other hand, steroids or immunosuppressive agents are usually required to treat immunological insulin resistance. Systemic steroids can be used as initial management at high doses followed by maintenance at relatively low doses [67]. Several immunosuppressive agents including cyclophosphamide, ciclosporin, azathioprine, mycophenolate mofetil, and rituximab have been used in the treatment of insulin resistance due to anti-insulin receptor autoantibodies [68–72]. The use of insulin-like growth factor 1 may be another alternative to insulin in patients with insulin antibodies as it has been reported to be effective as a blood-glucose lowering agent in those patients [73].

Circulating immune complexes, immunoglobulins, complement, auto-antibodies, cytokines, and soluble adhesion molecules can be removed from the intravascular space with plasmapheresis. Plasmapheresis has been used in several diseases characterized by the presence of autoantibodies. The effect of plasmapheresis is temporary, as de novo synthesis of antibodies is ongoing since cellular components of the immune system are not directly affected by plasmapheresis [74]. Plasmapheresis has been used in treatment of type B insulin resistance, which is caused by polyclonal immunoglobulin G antibodies directed against the insulin receptor [67]. The presence of large amount of insulin antibodies may abolish the effect of steroid or immunosuppressive treatment on hyperglycemia. Plasmapheresis may also be helpful to remove antibodies and immune complexes from circulation before commencing steroids [75]. The first case regarding the use of plasmapheresis in the treatment of type III insulin allergy and serum sickness like reactions has been described by our group [76].

Pancreas transplantation is an alternative treatment of generalized insulin allergy. Until now, two patients, who underwent pancreas transplantation for generalized allergy to insulin, have been reported. In 1998, Oh et al. [77] reported the first case of generalized insulin allergy requiring pancreas transplantation. The patient was a woman with type 1 diabetes, and her generalized allergy to insulin had not been improved by switching of her insulin to another preparation, desensitization treatment, steroids, and cyclophosphamide. The other case was reported by Malaise et al. [78] in 2005, a 29-year-old type 1 diabetic man with life-threatening generalized insulin allergy treated successfully with implantation of a vascularized solitary cadaver pancreas.

Conclusions

Insulin allergy is still a major problem in the management of diabetes, although its incidence has dramatically decreased since the introduction of human insulin preparations. While immediate type IgE-mediated reactions (type I) are the most common presentation of insulin allergy, immune complex type reactions presenting with localized Arthus reaction or generalized serum sickness (type III), and delayed-type hypersensitivity reactions (type IV) can occur in diabetic patients who develop allergic reactions to human insulin. Furthermore, immunological reactions to insulin may lead to insulin resistance. The evaluation of human insulin allergy consists of differential diagnosis of allergic reactions to human insulin from any other lesions due to incorrect injection technique, local agents such as alcohol wipes and allergic reactions to pharmaceutical additives in insulin preparations, determination of the type of allergic reaction, and the sort of human insulin which is the most likely cause of these symptoms. If the allergic reaction is due to any additive agent, it can be managed by switching insulin preparation to another insulin preparation which is free of suspected additive agent. Allergic reactions may resolve

with the use of alternative insulin preparations even in the case of allergy directly against human insulin. Desensitization by specific immunotherapy is an effective way to treat insulin allergy. Other treatment options include the use of antihistamines, local and systemic steroid therapies, immunosuppressive agents, and targeted biologic agents. The use of CSII seems to be a good option to treat human insulin allergy as small doses of insulin being continuously delivered and incrementally increasing doses of insulin to obtain low constant blood levels may lead to desensitization. Rapid-acting insulin analogues may have a positive effect on improving allergic reactions; however, controversial data are present in literature. Two reports reveal that there may be a tolerance to i.v. insulin, suggesting that insulin molecule aggregation in subcutaneous tissue may somehow mediate the immunological reaction. Although the underlying mechanism is unclear, potential immunological tolerance to i.v. use of insulin should be kept in mind especially for patients with type 1 diabetes. Plasmapheresis constitutes a choice of treatment for the treatment of type III insulin allergy and serum sickness like reactions, and hypoglycemia and hyperglycemia due to insulin antibodies. Pancreas transplantation may be a considerable option for life-threatening generalized insulin allergy.

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