
Insulin Allergy

Leslie Grammer

Immunologic reactions to insulin¹⁻³ have been described since the early use of exogenous insulin for the treatment of diabetes. These immunologic reactions are of significant interest and, therefore, have received considerable attention in the medical literature over the years. The significant interest in immunologic reactions to insulin is the result of a multiplicity of factors. First, the prevalence of diabetes is such that many physicians care for diabetic patients on insulin. Second, the usual measure for dealing with a drug allergy, substitution of a noncrossreacting drug, is not possible in an insulin dependent diabetic patient. Finally, in contrast to most drugs that are low in molecular weight and function as haptens immunologically, insulin is a well characterized protein composed of 51 amino acids and, thus, can be used as a complete antigen in immunoassays *in vitro* or *in vivo*.

The majority of patients treated with exogenous insulin have some immunologic response such as development of low titers of insulin binding antibody.⁴ Fortunately only a minority, approximately 10%,^{4,5} experience local reactions requiring any intervention and only a tiny fraction, with reported incidences ranging 0.1%–2%,^{4,6,7} experience systemic allergic reactions. In spite of the availability of purified animal insulins and of human insulin obtained using recombinant DNA (rDNA) technology, immunologic reactions including local and systemic allergy continue to occur.^{8,9} This chapter will review the essential clinical and immunologic aspects of insulin allergy: the immunologic changes that may occur in insulin allergy; the clinical presentations and differential diagnoses; and the rationale for management approach.

Immunologic Classification

Both cellular and humoral immunologic reactions have been ascribed to exogenous insulin. All five antibody classes¹⁰ and altered T-cell activation and lymphokine production to insulin¹¹ have been reported. As with other immunologic reactions, the Gell and Coombs¹² classification is a convenient one for immunologic reactions to insulin. Such as classification is summarized in Table 1.

From the Section of Allergy-Immunology, Department of Medicine, Northwestern University Medical School, Chicago, IL.

Send correspondence and requests for reprints to Leslie Grammer, MD, 303 E. Chicago Avenue, Chicago, IL 60611.

Table 1. Gell and Coombs Classification of Immunologic Reactions to Insulin

Type I
Local reaction
Immediate
Biphasic
Generalized reaction and anaphylaxis
Type II
None reported
Type III
Local Arthus reaction
Serum sickness
Immunologic insulin resistance
Type IV
Local delayed hypersensitivity reaction

Type I

Type I reactions are IgE mediated and result in local or systemic reactions. In these reactions, the antigen or allergen crosslinks IgE on the surface of mast cells or basophils causing mediator release and formation. The mediators are responsible for the signs and symptoms of the local or systemic reaction. The majority of allergic reactions to insulin are type I, which may also be called immediate type or anaphylactic type.¹³

Type II

The second major type of hypersensitivity reaction is termed cytotoxic or cytolytic, and involves the combination of antibody with antigen on a cell, resulting in destruction of that cell. There is no evidence for implication of insulin as an antigen causing type II reactions.

Type III

The third major type of hypersensitivity is the toxic complex reaction in which antigen-antibody complexes result in complement fixation, leukocyte attraction, and inflammatory response. A local example of a type III reaction would be an Arthus reaction, a cutaneous reaction that occurs at the site of antigen injection 4–6 hours after injection. Such reactions have been ascribed to insulin.¹⁴ Serum sickness is the classic systemic example of a type III reaction. Mild forms of serum sickness, primarily consisting of adenopathy, have been reported with insulin as an antigen.¹⁵ The antibodies present in type III reactions are most commonly of the IgG class. Because these antibodies can bind insulin and make it unavailable at tissue sites, immunologic insulin resistance can be caused by such antibodies.¹⁵ As IgG can cross the placenta, these antibodies can also cause neonatal hypoglycemia.¹⁶

Type IV

The fourth major type of immunologic reaction is that of delayed hypersensitivity or cellular hypersensitivity. Such reactions are lymphocyte mediated

and have been described using in vitro stimulation of lymphocytes from insulin treated patients¹⁷ and by biopsy.¹⁴ Local reactions of this type due to zinc have been described.¹⁸

Insulin as an Antigen

The antigenicity of insulin can be derived from any of a number of components present in commercially available insulin preparations. Some of these components, such as the insulin molecule itself, are present in all preparations. Others, like zinc, are only contained in some longer acting preparations and still others, such as proinsulin, are absent from human (rDNA) insulin and present in animal insulins to a degree inversely proportional to purity. Table 2 lists examples of various components that have been implicated as antigens in insulin preparations.

Animal Insulins

Insulin is a polypeptide composed of an A and B chain. The A chain contains 21 amino acids and the B chain contains 30 amino acids. The primary amino acid sequence of bovine insulin differs from human insulin by three amino acids, whereas porcine insulin differs by one amino acid. This greater difference between human and bovine insulins has been cited as a possible explanation for the greater antigenicity of bovine insulin, compared with porcine insulin that is generally observed with in vitro or in vivo assays.¹⁹⁻²¹ It is important to note that there are some patients who are more allergic to porcine than to bovine insulin. This is why it may be helpful to titer patients with systemic insulin allergy to available insulins and to choose the least allergenic insulin for desensitization. Although human (rDNA) is usually less allergenic than porcine, which is less allergenic than bovine, this is not always the case.⁸

Altered Tertiary Structure of Insulin

Homologous or even autologous proteins can be structurally altered by a number of procedures so that they may become antigenic. This was dem-

Table 2. Examples of Implicated Antigens in Insulin Preparations

Component	Example	Antigenic Characteristics
Heterologous insulin	Bovine insulin	Different primary amino acid sequence than human insulin Altered tertiary structure
Homologous insulin	Human insulin (rDNA)	Altered tertiary structure
Non-insulin protein contaminants	Porcine insulin	Different primary amino acid sequence than native human proteins
Non-protein additives	Zinc	Probably acts as hapten

onstrated in a patient allergic to animal insulins who also reacted to his own insulin after extraction by an acid–alcohol procedure.²² There are many case reports of patients with systemic allergic reactions to animal insulins who have immediate cutaneous reactivity or generalized anaphylaxis to human (rDNA) insulin.^{8,23–26} Sera from two patients allergic to animal and human (rDNA) insulin have been studied for antibody crossreactivity.^{8,27} In each serum, the binding of antibody to any insulin tested [bovine, porcine, human (rDNA)] could be completely inhibited by each insulin. Thus, in these two sera, the antigenic determinants recognized by antibody were similar in all three insulins. It is postulated that the antigenic determinants on human (rDNA) insulin occur as a result of processing and consequent alteration of tertiary structure and that similar alterations can occur in processing of animal insulins resulting in similar antigenic sites on bovine, porcine, and human (rDNA) insulin. The extent to which the immunologic responses in these two patients represent human responses in general requires further study.

Non-Insulin Protein Contaminants

Commercial insulin available in this country is resolved by gel chromatography to contain fewer than 50 ppm impurities. “Purified” insulin, as defined by the Food and Drug Administration, is insulin that is further refined to contain fewer than 10 ppm impurities.²⁸ It is interesting to note that before 1972, commercial insulin contained more than 1000 ppm impurities. Although non-insulin protein contaminants have been postulated as a cause of allergic reactions, there is very limited supporting evidence.

In a study of cutaneous reactivity to insulin in a group of insulin-dependent diabetics, it was shown that approximately 50% of the skin-reactive patients reacted to non-insulin porcine and bovine proteins. This suggested that patients receiving porcine and bovine insulin had been sensitized to non-insulin heterologous proteins.²⁰ In this same study, however, five patients with systemic allergen reactions to bovine and porcine insulin had no cutaneous reactivity to non-insulin heterologous proteins. All five had cutaneous reactivity to human, porcine, and bovine insulin. Thus, in these patients, the insulin molecule itself—not protein contaminants—appeared to be the allergen.

A common non-insulin protein contaminant is proinsulin, the larger precursor molecule. It consists of the 51 amino acid A and B chain of insulin and a connecting or C peptide. In a study of seven patients with systemic insulin allergy, intradermal reactivity to usual commercial insulin was similar to reactivity to “purified” insulin.²⁹ Moreover, in radioimmunoassay cross inhibition studies, the binding of proinsulin was completely blocked by insulin and was not inhibited at all by C peptide. This crossreaction of proinsulin with anti-insulin IgE and the absence of proinsulin specific IgE suggest that insulin, not proinsulin, is the causative allergen in these patients with systemic allergic reactions after insulin administration.

Pharmaceutical Formulation

Neutral regular insulin is insulin that has been crystallized in the presence of zinc. Patients receiving zinc insulin have been described to develop type

IV delayed hypersensitivity reactions. These reactions have then been alleviated by changing to an insulin that does not contain zinc.¹⁸ It should be noted that similar delayed hypersensitivity reactions have been described in which changing to zinc-free insulin did not alleviate the reaction.¹⁴

Protamine is contained in various longer acting insulin preparations: neutral protamine Hagedorne (NPH) insulin and protamine zinc insulin (PZI). There is a report of protamine as a cause of a generalized allergic reaction to NPH insulin.³⁰ There are also reports of patients on protamine insulins having severe allergic reactions to protamine used for heparin reversal.^{31,32} Positive skin tests to protamine have been reported in some but not all such patients.³³ In short, there are conflicting reports as to whether or not protamine causes immunologically mediated reactions.

Histocompatibility Antigens

In addition to the presence of an antigen, the other requisite for the development of insulin allergy is the genetic capability of a patient to immunologically respond to that antigen. There is experimental evidence to suggest that certain histocompatibility antigens, HLA-B7, DR2, and DR3, may predispose diabetic patients to insulin allergy.^{34,35} Thus, as with other allergic reactions,³⁶ it is probable that a patient not only needs to be exposed to an antigen but the patient must also be genetically capable of immunologically responding to that exposure.

Diagnosis and Treatment of Immunologic Reactions to Insulin

Local Reactions

Local reactions to insulin are common, especially in the early months of insulin administration. The incidence of such reactions has been reported to be 5%–15% in various series.^{4,5} The great majority of these reactions are immediate type IgE mediated reactions that occur at the site of subcutaneous insulin administration. These reactions, which consist of erythema and swelling, may be painful or pruritic. In general, these reactions occur only for a few weeks after initiation of insulin therapy. Subsequently, most subside and disappear with continued insulin therapy and are not a diagnostic or clinical management problem. Reassuring the patient that no significant problem exists and that the reactions will most probably subside is usually all that is necessary to manage these patients.³⁷

Sometimes, these local reactions are severe enough to cause significant discomfort to the patient. If this occurs, concomitant antihistamine administration may be helpful until the reactions spontaneously resolve. In cases in which this measure does not provide satisfactory relief, it may be necessary to divide the dose of insulin into two or more injection sites to reduce the local reaction size until there is spontaneous resolution of local reactions. There are reports that changing to a more purified, single species insulin can also reduce the size of local reactions.^{38,39}

Biphasic subcutaneous reactions may also occur at the site of insulin administration. These reactions consist of an immediate type reaction that resolves

to a variable extent, and which is then followed by a second, later onset reaction in 4–6 hours. The histopathology of these reactions has been studied and is identical to similar “late phase reactions” seen with ragweed injections.^{40,41} These biphasic reactions are transferable by Prausnitz–Küstner (PK) testing and, thus, are assumed to be IgE mediated. Management is the same as outlined above for immediate type local reactions. The biphasic reactions generally also subside with continued insulin administration.

At least one late local insulin reaction (4–6 hours) has been described that was “Arthus” in histologic type and was not transferable by PK testing.⁴² These reactions are rare and, thus, the natural history and management are not well described.

Late local reactions of the delayed hypersensitivity type have also been histologically described.¹⁴ These developed 8–12 hours after injection and were not transferable by PK testing. These reactions have been described in patients receiving insulins crystallized with zinc and these reactions have been alleviated by changing to insulin not containing zinc.¹⁸ However, there have been patients in whom such a change has not been useful in terms of patient management.

Lipodystrophy, either atrophy or hypertrophy, may occur locally at the site of insulin injection. Whether or not these abnormalities are immunologic is unknown. Purified insulin preparations are reported to ameliorate these problems significantly.^{43,44}

Systemic, Immediate Type Reactions

Immediate, generalized allergic reactions are of much greater concern than local reactions because of their potential seriousness. Fortunately they are much less common, with reported incidences from 0.1% to 2%.^{4,6,7} The clinical manifestation of these reactions are the same as those of any other anaphylactic reactions: urticaria, angioedema, bronchospasm, or hypotension. Any or all of these can occur and may be accompanied by other manifestations, such as pruritus, erythema, rhinorrhea, nausea, abdominal or uterine cramps. The most serious manifestations, laryngeal edema or shock, may be fatal; there are no recent case reports of fatality from insulin anaphylaxis. Drug therapy for these acute reactions is similar to management of any acute anaphylactic episode. Management depends on the particular symptoms that occur and on the severity of those symptoms. Treatment principles of anaphylaxis are outlined in several texts.^{45,46}

In almost all cases of systemic insulin allergy, there is interruption of insulin therapy.⁴⁷ That is, the patient was initially placed on insulin but then it was withdrawn. Subsequently, after a hiatus of months or years, it becomes clear that the patient will require insulin and it is resumed. In most cases of systemic insulin allergy, the patient then develops progressively larger local reactions that culminate in a systemic reaction.⁴⁵ The generalized reaction, which usually consists of urticaria or angioedema, is accompanied by a large immediate type reaction at the site of injection.⁴⁸

As the history accompanying systemic insulin allergy tends to be the one described above, the diagnosis is usually not difficult. However, in a patient

who is receiving several drugs, there may be some question as to whether the insulin or some other drug is causing the reaction. In these situations, the presence or absence of a large local reaction at the injection site should make the diagnosis clear. Two clinical entities that may also be confused with insulin allergy are idiopathic urticaria or idiopathic anaphylaxis.⁴⁸ If these entities occur coincidentally with the initiation of insulin therapy, insulin will be considered as a possible etiologic factor in the urticaria or anaphylaxis. The differential diagnosis is generally simple in this case as insulin allergy will be accompanied by a large local reaction at the injection site and idiopathic urticaria or idiopathic anaphylaxis will not.

In a case of suspected insulin allergy, the question of whether or not to perform in vitro tests for IgE antibody against insulin may be raised. Such tests are available and can be used as evidence that the reaction is IgE mediated. It should be recognized that many insulin treated patients without insulin allergy have measurable IgE to insulin in their serum.⁴⁹ It should also be recognized that such assays are of value for research purposes but are of little or no additional value in diagnosis over history, physical examination, and possibly skin testing. Moreover, in cases of systemic allergic reactions in patients requiring continued insulin therapy, there is not time to wait for the results of an in vitro assay. In short, in vitro tests are not necessary or helpful in clinical practice for diagnosis or management of patients with systemic insulin allergy.

Cutaneous testing may be helpful in excluding the diagnosis of insulin allergy provided that the testing is done correctly and the result is negative. If the result is positive it must be appreciated that this does not confirm insulin allergy. Studies of immediate cutaneous reactivity to insulin have demonstrated that positive skin tests are quite common in insulin treated patients. Lieberman et al²⁰ reported a positive skin test incidence of 40% in insulin treated diabetics and Arkins et al⁵⁰ reported a 50% incidence of positive skin tests in patients on insulin. Each of these studies was done in patients with no systemic or other clinical allergic reactions to insulin. Thus, the positive skin tests in these patients have no diagnostic relevance.

Cutaneous testing may be useful to compare the degree of sensitivity of a single patient to various insulins. For instance, a patient who has a systemic reaction to a mixture of bovine and porcine insulin can be tested with serial tenfold dilutions of separate human (rDNA), porcine, and bovine insulin. The insulin to which the patient is least reactive could be chosen for further therapy, if it is indicated.

Shortly after treatment of the anaphylactic symptoms of an insulin-allergic patient, the determination should be made as to whether or not further insulin therapy is essential for control of that patient's diabetes. Expert consultation should be obtained, if necessary. If insulin is required, it should be continued without interruption in therapy. Risks and benefits of such administration should be carefully explained to the patient and documented. The administration must be supervised by a physician knowledgeable about treatment of anaphylaxis. An allergist would probably be best qualified but such a subspecialist may not be available. For purposes of supervision and observation, hospitalization of these patients is recommended.

In patients who have had systemic reactions to insulin within 24 hours, the dose can simply be reduced to one-third, or for more caution, one-sixth of the dose that caused the reaction. It is very important that the insulin not be discontinued once it has been determined to be essential for diabetic control. Each day the insulin can be increased by 5 units until diabetic control is achieved. If a reaction occurs at some point, the dose is reduced to that previous dose that did not cause a reaction and another attempt should be made to slowly increase the dose. The principle for this approach is that a patient who has had anaphylaxis to a dose of allergen can receive a smaller dose of that allergen without a generalized reaction a short time later, but the risk increases the longer the interval becomes. Certainly, a delay of 1 week or so may result in a more sensitive subject and then desensitization is required as the safest approach.

Once the necessity of insulin has been established, the risks and benefits of desensitization should be explained to the patient. The desensitization procedure should be performed in the hospital, and equipment and personnel must be immediately available to treat anaphylaxis. The principle of desensitization is that there is a very minute dose of insulin that the patient will tolerate without allergic reaction. That dose is given and then subsequent increasing doses are given until a large local, mild systemic, or therapeutic dose of insulin is obtained. If large local or mild systemic reactions occur, the dose is reduced to the previous dosage that did not cause a reaction and again slowly increased. Using this sort of desensitization regimen, we have successfully desensitized all 30 patients in which insulin was required for diabetic control. A number of desensitization schedules have been proposed.^{37,48,50,51} A representative insulin desensitization schedule is shown in Table 3.

During insulin desensitization the serum IgE against insulin may increase initially and then decrease or may simply decrease with no initial rise.¹⁰ Those results suggest that during insulin desensitization, the IgE against insulin is neutralized by the insulin administration. It has also been suggested that after desensitization IgG against insulin, acting as blocking antibody, may be the protective mechanism that allows for insulin therapy in the previously allergic patient. One reason for this suggestion is that IgG mediated immunologic

Table 3. Desensitization Schedule

Day	Time	(min)	Route	Dose (U)
1	AM	0 min	Scratch	10^{-4}
		10 min	SQ	10^{-5}
		20 min	SQ	10^{-4}
2	AM		SQ	10^{-3}
	PM		SQ	10^{-2}
3	AM		SQ	1
	PM		SQ	5
4	AM		SQ	10
	PM		SQ	20
5	AM		SQ	30
6	AM		SQ	30

insulin resistance may follow insulin desensitization.^{10,52-54} Although it is possible that IgG against insulin may contribute to protection of the desensitized patient, the most likely explanation for successful desensitization is decrease in IgE against insulin.

Immunologic Insulin Resistance

Systemic anaphylactic reactions are rare and immunologic insulin resistance is even more rare. IgG against insulin has been demonstrated to be responsible for immunologic insulin resistance.^{10,52} In the majority of patients, with a high insulin requirements (>200 U/day) in whom the question of immunologic insulin resistance was considered, another reason was found for high insulin requirement. The diagnosis is made by excluding other causes of insulin resistance, such as infection, by demonstration of elevated IgG to insulin and by response to corticosteroids. The patients we reported³⁷ have responded to low to moderate dose prednisone therapy. In cases in which immunologic insulin resistance may be present, a trial of 30 mg prednisone daily is recommended. If immunologic insulin resistance is present, a precipitous decrease in insulin requirement will occur. Subsequently, lower dose alternate day prednisone will suffice and may be discontinued. When prednisone is started it is important to realize that the insulin requirement may decline very rapidly and that hypoglycemia may occur unless the managing physician is alert to this possibility. Blood glucose must be checked frequently and insulin dose adjusted in response to declining glucose values.

Serum Sickness

One patient with insulin resistance has been reported who also had generalized adenopathy and was considered to have serum sickness.¹⁰ This patient had very elevated levels of IgG against insulin and insulin-IgG anti-insulin complexes in the serum. With prednisone, lymphadenopathy disappeared and insulin requirement decreased. In general, the literature reports of patients with insulin resistance would suggest that serum sickness is very unusual.^{10,52-54}

Summary

While immunologic responses to insulin such as cutaneous reactivity and antibody against insulin are common significant clinical problems related to those immunologic reactions are uncommon. Immunologic responses that have been described included Gell and Coombs type I, II, and IV. The antigen may be the result of any of several factors: insulin as a heterologous protein, altered tertiary structure of insulin, presence of non-insulin protein contaminants, or pharmaceutical formulation additives.

IgE mediated local reactions are the most common and almost always subside spontaneously. IgE mediated anaphylaxis is the most important immunologic problem; it can be managed safely and successfully by temporary

reduction in dose or by insulin desensitization. Other systemic immunologic reactions, insulin resistance and serum sickness, are extremely rare and respond to corticosteroid therapy.

Supported by USPHS Grant AI 11403 and the Ernest S. Bazley Grant.

References

1. Wilder RM, Boothby WM, Barborka CJ, Kitchen HD, Adams SF: Clinical observation on insulin. *J Metab Res* 2:701-728, 1922
2. Williams JR: A clinical study of the effects of insulin in severe diabetes. *J Metab Res* 2:729-751, 1922
3. Lawrence RD: Local insulin reactions. *Lancet* i:1125-1126, 1925
4. Ross JM: Allergy to insulin. *Pediatric Clinics of North America* 31:675-687, 1984
5. Paley RG, Turnbridge RE: Dermal reactions to insulin therapy. *Diabetes* 1:22-27, 1952
6. Hanauer L, Batson JM: Anaphylactic shock following insulin injection. *Diabetes* 10:105-109, 1961
7. Shipp JC, Cunningham RW, Russell RO, Marble A: Insulin resistance: Clinical features, natural course and effects of adrenal steroid treatment. *Medicine* 44:165-186, 1965
8. Grammer LC, Metzger BE, Patterson R: Cutaneous allergy to human (rDNA) insulin. *JAMA* 251:1459-1460, 1984
9. Goldman RA, Lewis AF, Rose LI: Anaphylactoid reactions to single component pork insulin. *JAMA* 236:1148-1149, 1976
10. Patterson R, Mellies CJ, Roberts M: Immunologic reactions against insulin: IgE anti-insulin, insulin allergy and combined IgE and IgG immunologic insulin resistance. *J Immunol* 110:1135-1145, 1973
11. Rosenwasser LJ: Immunologic reactivity to insulin: animal models and clinical syndromes. *Clin Immunol Rev* 1:311-335, 1981-82
12. Gell PGH, Coombs RRA (eds): *Clinical Aspects of Immunology*, 3rd Ed. Philadelphia, FA Davis, 1975, p 764
13. Pruzansky JJ: Cellular aspects of immediate hypersensitivity, in Patterson R (ed): *Allergic Diseases*. Second edition. Philadelphia, J.B. Lippincott, 1980, pp 59-75
14. deShazo RD, Boehm TM, Kumar D, Galloway JA, Dvorak HF: Dermal hypersensitivity reactions to insulin: Correlations of three patterns to their histopathology. *J Allergy Clin Immunol* 69:229-237, 1982
15. Patterson R, O'Rourke J, Roberts M, Suszko IM: Immunologic reactions against insulin: IgG anti insulin and insulin reactions. *J Immunol* 110:1126-1134, 1973
16. Home PD, Alberti KG: The new insulins. Their characteristics and clinical indications. *Drugs* 24:401-413, 1982
17. White WB, DeMartino SA, Yoshida T: Severe delayed inflammatory reactions from injected insulin. Association with cell-mediated immunity. *Am J Med* 79:909-914, 1983
18. Feinglos MN, Jegasothy BV: Insulin allergy due to zinc. *Lancet* i:122-124, 1979
19. Fireman P, Fineberg SE, Galloway JA: Development of IgE antibodies to human (recombinant DNA), porcine, and bovine insulins in diabetic subjects. *Diabetes Care* 5(suppl 2):119-125, 1982
20. Lieberman P, Patterson R, Metz R, Lucena A: Allergic reactions to insulin. *JAMA* 215:1106-1112, 1971
21. Kumar D: Insulin allergy: differences in the binding of porcine, bovine and human insulins with anti-insulin IgE. *Diabetes Care* 4:104-107, 1981
22. Patterson R, Lucena G, Metz R, Roberts M: Reaginic antibody against insulin: Demonstration of antigenic distinction between native and extracted insulin. *J Immunol* 103:1061-1071, 1969
23. Small P, Lerman S: Human insulin allergy. *Ann Allergy* 53:39-41, 1984

24. Garcia-Ortega P, Knobel H, Mirada A: Sensitization to human insulin. *Br Med J* 288:1271, 1984
25. Altman JJ, Pehuet M, Slama G, Tchobroutsky C: Three cases of allergic reactions to human insulin. *Lancet* ii:524, 1983
26. Wiles PG, Guy R, Watkins SM, Reeves WG: Allergy to purified bovine, porcine, and human insulins. *Br Med J* 287:531, 1983
27. Grammer LC, Roberts M, Patterson R: IgE and IgG antibody against human (rDNA) insulin in patients with systemic insulin allergy. *J Lab Clin Med* 105:108–113, 1985
28. Skyler JS: A plethora of insulins. *Diabetes Care* 3:638–639, 1980
29. Kumar D, Rosenquist RJ, Parameswaran V: Insulin allergy: Reaginic antibodies to insulin and proinsulin. *J Clin Endocrinol Metab* 49:252–254, 1979
30. Sanchez MB, Paolillo M, Chacon RS, Camejo M: Protamine as a cause of generalized allergic reactions to NPH insulin. *Lancet* i:1243, 1982
31. Cobb CA, Fung DL: Shock due to protamine hypersensitivity. *Surg Neurol* 17:245–246, 1982
32. Stewart WJ, McSweeney SM, Kellett MA, Faxon DP, Ryan TJ: Increased risk of severe protamine reactions in NPH insulin dependent diabetics undergoing cardiac catheterization. *Circulation* 70:788–792, 1984
33. Weiler JM, Freiman P, Shareth MD, Metzger WJ, Smith JM, Richerson HB, Ballas SK, Halverson PC, Shulan DJ, Matsuo S, Wilson RL: Serious adverse reactions to protamine sulfate: Are alternatives needed? *J Allergy Clin Immunol* 75:297–303, 1985
34. Schernthaner G, Ludwig H, Jarisch R, Bruneder H: Immediate type allergy against insulin itself: clinical and immunologic studies on a diabetic patient with insulin intolerance. *Diabetes Care* 4:196–201, 1981
35. Bertrams J, Gruneklee D: Association between HLA-B7 and allergic reactions to insulin in insulin-dependent diabetes mellitus. *Tissue Antigens* 10:273–277, 1977
36. Marsh DG, Meyers DA, Bias WB: The epidemiology and genetics of atopic allergy. *NEJM* 305:1551–1558, 1981
37. Patterson R, Grammer LC, Chen PY: Insulin hypersensitivity: pathogenesis, diagnosis and management in Gupta S (ed): *Immunology of Clinical and Experimental Diabetes*. NY, Plenum, 1984, pp 401–414
38. Davidson JA, Galloway JA, Petersen BH, Wentworth SM, Crabtree RE: The use of purified insulins in insulin allergy. *Diabetes* 23(suppl 1): 352, 1974 (abstract)
39. Pietri A, Raskin P: Cutaneous complications of chronic continuous subcutaneous insulin infusion therapy. *Diabetes Care* 4:624–626, 1981
40. deShazo RD, Levinson AI, Dvorak HF, Davis RW: The late phase skin reaction: Evidence for activation of the coagulation system in an IgE-dependent reaction in man. *J Immunol* 122:692–698, 1979
41. Solley GO, Gleich GJ, Jordan RE, Schroeter AL: The late phase of the immediate wheal and flare skin reaction: Its dependence upon IgE antibodies. *J Clin Invest* 58:408–420, 1976
42. deShazo RD, Levinson AI, Boehm T, Evans R III, Ward G: Severe persistent biphasic local (immediate and late) skin reactions to insulin. *J Allergy Clin Immunol* 59:161–164, 1977
43. Ferland L, Ehrlich RM: Single peak insulin in the treatment of insulin-induced fat atrophy. *J Pediatr* 86:741–743, 1975
44. Hulst SH: Treatment of insulin induced lipoatrophy. *Diabetes* 25:1052–1054, 1976
45. Weiszer I: Allergic Emergencies in Patterson R (ed): *Allergic Diseases*. Second edition, Philadelphia, J.B. Lippincott, 1980, pp 374–391
46. Orange RP, Donsky GJ: Anaphylaxis in Middleton E, Reed CE, Ellis EF (eds): *Allergy: Principles and Practice*, St. Louis, C.V. Mosby, 1978, pp 563–573
47. Mattson JR, Patterson R, Roberts M: Insulin therapy in patients with systemic insulin allergy. *Arch Intern Med* 135:818–821, 1975
48. Grammer LC, Chen PY, Patterson R: Evaluation and management of insulin allergy. *J Allergy Clin Immunol* 71:250–254, 1983
49. Kumar D: Anti-insulin IgE in diabetes. *J Clin Endocrinol Metab* 45:1159–1164, 1977
50. Arkins JA, Engbring NH, Lennon EJ: The incidence of skin reactivity to insulin in diabetic patients. *J Allergy* 33:69–72, 1962

51. Galloway JA, Bressler R: Insulin treatment in diabetes. *Medical Clinics of North America* 62:663–680, 1978
52. Witters LA, Ohman JL, Weir GC, Raymond LW, Lowell FC: Insulin antibodies in the pathogenesis of insulin allergy and resistance. *Am J Med* 63:703–709, 1977
53. Lowell FC: Immunologic studies in insulin resistance. *J Clin Invest* 23:225–231, 1944
54. Dolovich J, Schnatz JD, Reisman RE, Yagi Y, Arbesman CE: Insulin allergy and insulin resistance. *J Allergy* 46:127–137, 1970