Diabetologia (2022) 65:1278–1290
https://doi.org/10.1007/s00125-022-05710-9

ARTICLE

Insulin allergy: a diagnostic and therapeutic strategy based on a retrospective cohort and a case–control study

Agnès Sola-Gazagnes[1] · Catherine Pecquet[2] · Stefano Berré[3] · Peter Achenbach[4,5] · Laure-Anne Pierson[6] · Isabelle Virmoux-Buisson[1] · Jocelyne M'Bemba[1] · Fabienne Elgrably[1] · Philippe Moguelet[7] · Christian Boitard[1,3] · Sophie Caillat-Zucman[8,9] · Moussa Laanani[10] · Joel Coste[10] · Etienne Larger[1,3] · Roberto Mallone[1,3]

Received: 24 January 2022 / Accepted: 30 March 2022 / Published online: 4 May 2022

Abstract

Aims/hypothesis Insulin allergy is a rare but significant clinical challenge. We aimed to develop a management workflow by (1) validating clinical criteria to guide diagnosis, based on a retrospective cohort, and (2) assessing the diagnostic performance of confirmatory tests, based on a case–control study.

Methods In the retrospective cohort, patients with suspected insulin allergy were classified into three likelihood categories according to the presence of all (likely insulin allergy; 26/52, 50%), some (possible insulin allergy; 9/52, 17%) or none (unlikely insulin allergy; 17/52, 33%) of four clinical criteria: (1) recurrent local or systemic immediate or delayed hypersensitivity reactions; (2) reactions elicited by each injection; (3) reactions centred on the injection sites; and (4) reactions observed by the investigator (i.e. in response to an insulin challenge test). All underwent intradermal reaction (IDR) tests. A subsequent case–control study assessed the diagnostic performance of IDR, skin prick and serum anti-insulin IgE tests in ten clinically diagnosed insulin allergy patients, 24 insulin-treated non-allergic patients and 21 insulin-naive patients.

Results In the retrospective cohort, an IDR test validated the clinical diagnosis in 24/26 (92%), 3/9 (33%) and 0/14 (0%) likely, possible and unlikely insulin allergy patients, respectively. In the case–control study, an IDR test was 80% sensitive and 100% specific and identified the index insulin(s). The skin prick and IgE tests had a marginal diagnostic value. Patients with IDR-confirmed insulin allergy were treated using a stepwise strategy.

Conclusions/interpretation Subject to validation, clinical likelihood criteria can effectively guide diabetologists towards an insulin allergy diagnosis before undertaking allergology tests. An IDR test shows the best diagnostic performance. A progressive management strategy can subsequently be implemented. Continuous subcutaneous insulin infusion is ultimately required in most patients. ClinicalTrials.gov: NCT01407640.

Keywords Anaphylaxis · IgE · Immune tolerance · Intradermal reaction · Prick test · Skin test

✉ Agnès Sola-Gazagnes
agnes.sola@aphp.fr

1 Assistance Publique-Hôpitaux de Paris, Hôpitaux Universitaires de Paris Centre-Université Paris Cité, Cochin Hospital, Service de Diabétologie et Immunologie Clinique, Paris, France

2 Assistance Publique-Hôpitaux de Paris, Hôpital Tenon, Service d'Allergologie Dermatologie, Paris, France

3 Université Paris Cité, CNRS, Inserm, Institut Cochin, Paris, France

4 Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Diabetes Research, Munich-Neuherberg, Germany

5 Technical University of Munich, School of Medicine, Klinikum rechts der Isar, Forschergruppe Diabetes, Munich, Germany

6 Assistance Publique-Hôpitaux de Paris, Hôtel-Dieu, Service de Pharmacie, Pharmacologie, Toxicologie, Paris, France

7 Assistance Publique-Hôpitaux de Paris, Hôpital Tenon, Service d'Anatomo-Pathologie, Sorbonne Université, Faculté de Médecine, Paris, France

8 Assistance Publique-Hôpitaux de Paris, Hôpital Saint-Louis, Laboratoire d'Immunologie, Paris, France

9 Université Paris Cité, Inserm UMR976, Institut de Recherche Saint-Louis, Paris, France

10 Université Paris Cité, Assistance Publique-Hôpitaux de Paris, Cochin Hospital, Biostatistics and Epidemiology Unit, Paris, France

Research in context

What is already known about this subject?

- Although rare (estimated prevalence 0.1–3%), insulin allergy represents a significant complication in diabetes management
- There is currently no consensus on the diagnostic and therapeutic strategies that should be implemented in the case of insulin allergy

What is the key question?

- What is the most suitable diagnostic and therapeutic workflow for insulin allergy?

What are the new findings?

- Four simple clinical criteria can be used to grade the likelihood of insulin allergy as likely, possible or unlikely, and to guide decisions about the need for specialised allergology tests
- The test of choice to confirm insulin allergy and identify the allergen(s) is the intradermal reaction test, while skin prick and serum anti-insulin IgE tests display low sensitivity. Only patients classified as clinically likely and possible insulin allergy should undergo confirmatory skin tests
- A stepwise therapeutic strategy can subsequently be implemented, but continuous subcutaneous insulin infusion is eventually required in most patients

How might this impact on clinical practice in the foreseeable future?

- The proposed workflow, subject to validation, can be used for the clinical management of insulin allergy

Abbreviations

CSII	Continuous subcutaneous insulin infusion
GLP-1	Glucagon-like peptide 1
IDR	Intradermal reaction
OHA	Oral hypoglycaemic agent

Introduction

Insulin allergy can significantly complicate diabetes management. Although rare, with an estimated prevalence of 0.1–3% [1–3], the number of cases of insulin allergy may reach 800,000 out of approximately 90 million insulin-treated patients worldwide.

Clinical manifestations range from cutaneous reactions, which are either immediate (type I; pruritic urticarial papules) [4–6] or delayed (type IV; subcutaneous, inflammatory, non-pruritic and inconstantly painful nodules) [7–9], to less frequent systemic manifestations, including life-threatening anaphylaxis [10, 11]. Although insulin itself is the main allergen, excipients, the nickel used in needles and the latex used in vial caps and cartridge plungers can also be involved.

Allergen avoidance is challenging in insulin-requiring patients, calling for a rigorous diagnostic and treatment workflow. To this end, we analysed a retrospective cohort to validate clinical criteria that can guide diabetologists about the need for specialised allergology referral. We subsequently performed a case–control study to measure the diagnostic performance of allergology tests.

Methods

Retrospective cohort Fifty-two consecutive patients were referred from 2000 to 2010 for suspected insulin allergy to our diabetology clinic, which is the regional reference centre for insulin allergy. A non-opposition form signed at hospital admission allows anonymised data from these patients to be used for research purposes.

Clinical assessment in the diabetology clinic After verifying the use of proper subcutaneous injection techniques, standardised medical records were used to classify patients into three likelihood categories [12] based on four clinical criteria derived from our own experience [13] and general guidelines on evaluating suspected drug allergies [14]:

(1) local or systemic reactions suggestive of insulin allergy (i.e. immediate [<15 min] or delayed [>6 h] hypersensitivity reactions);
(2) reactions elicited by each injection of the index insulin(s);
(3) reactions centred on the injection sites;
(4) reactions observed by the physician (i.e. a positive insulin challenge test).

Clinically likely, possible and unlikely insulin allergy were defined by the presence of all, some or none of these four criteria, respectively.

Case–control study Ten consecutive patients with a likely insulin allergy, 24 insulin-treated non-allergic patients and 21 insulin-naive patients were recruited over 3 years (2014–2016). Exclusion criteria were concomitant anticoagulant therapy (interfering with skin tests), severe renal failure (GFR <30 ml/min) and ongoing pregnancy. The study was completed by 10/10 participants with insulin allergy and 22/24 insulin-treated and 18/21 insulin-naive control participants. The main reason for dropping out of the study was an inability to attend the allergology appointment for skin tests; in one case the participant was undergoing concomitant anticoagulant therapy. All participants were examined by a single diabetologist and by an allergologist. The Ile-de-France II ethics committee approved the study (2009-A00954-53; ClinicalTrials.gov NCT01407640). Participants gave written informed consent.

IDR and skin prick tests Ten insulin formulations were selected for testing, based on the reported allergenic formulation(s) and their excipients (see electronic supplementary material [ESM] Table 1). As isolated excipients are not available, test panels included combinations to rule out allergies to excipients (e.g. insulin glulisine, which does not contain zinc, to exclude zinc allergy). All participants were examined by the same allergologist in the morning, after a breakfast preceded by their usual insulin injection(s). No participants were on antihistamine drugs or corticoids at the time of investigation.

To measure intradermal reactions (IDRs), insulins (100 U/ml) were injected intradermally in a volume of 20 μl at increasing tenfold concentrations in 0.9% saline (154 mmol/l NaCl), from 1/10,000 (2×10^{-4} U) to 1/10 (2×10^{-1} U) or until a local reaction was observed. Protamine (1000 U/ml; Sanofi, France) was tested in parallel at concentrations from 1/10,000 (2×10^{-4} U) to 1/10 (2×10^{-1} U), because of non-specific reactions at 2 U [15]. The whole procedure included up to 40 intradermal injections of ten formulations and lasted 90–120 min, with a cumulative insulin dose of <3 U under glucose monitoring. Index formulations (i.e. those reported to elicit reactions) were tested last. Skin prick tests were performed with undiluted preparations using the same insulin panel and latex (Stallergenes, France). IDR and skin prick test panels included glycerol saline (Stallergenes) and histamine (only for skin prick tests, 10 mg/ml; Stallergenes) as negative and positive controls, which were negative and positive, respectively, in all cases.

Reactions were measured after 20 min and after 24 and 48 h, when delayed reactions were reported. In the retrospective cohort, reactions were scored as positive if wheal-and-flare responses occurred, that is, both redness ≥10 mm and a papule ≥3 mm in diameter [16]. In the case–control study, reactions were scored as positive if the diameters of papules increased by >5 mm for IDRs and >3 mm for skin prick tests compared with the end of the injection, or if the diameter of the papules was >80% of that seen with the histamine positive control. Following IDR tests, punch skin biopsies were obtained for some insulin allergy participants and stained with haematoxylin–eosin–saffron.

In vitro anti-insulin antibody assays Serum anti-insulin IgE and IgG4 and anti-protamine IgE were measured using the Pharmacia CAP System FEIA (Phadia/ThermoFisher, Sweden). Anti-insulin IgE levels were further quantified using an in-house radio-binding assay [17] using Streptavidin Sepharose High Performance beads (GE Healthcare, Germany) coated with biotin-labelled mouse anti-human IgE (RRID:AB_396180). Briefly, sera (5 μl) were incubated with 1159 nU ^{125}I-labelled insulin (13.43 MBq/μg; Sanofi) in 25 μl 50 mmol/l Tris and 1% Tween-20 (pH 8; TBT) at 4°C for 72 h before adding 50 μl anti-IgE-coated bead suspension, incubating for 1 h at 4°C under agitation, washing in cold TBT and counting. Non-specific binding was determined using beads coated with biotin-labelled mouse anti-rat IgM (RRID:AB_395115). Results are expressed as nU bound insulin/ml, calculated as [(anti-IgE counts − control anti-IgM counts)/(total counts per tube)] × 1159 × 200. Anti-insulin antibodies were measured as described previously [18].

Statistical analysis Data were analysed using SAS software v9.4 (SAS Institute, USA) and two-tailed statistical tests, as detailed in the table legends.

Results

Patients with clinically likely insulin allergy have a shorter but variable duration of insulin treatment Table 1 summarises the clinical presentation of the 52 patients referred for suspected insulin allergy. Patients were first classified based on the presence or absence of the following clinical characteristics: (1) local or systemic reactions suggestive of insulin allergy, that is, immediate (<15 min) hypersensitivity (urticaria, i.e. erythematous, pruritic papules [Fig. 1a–c]; laryngeal angioedema) or delayed (>6 h) hypersensitivity (subcutaneous, inflammatory, non-pruritic and inconstantly painful nodules [Fig. 1d, e]); (2) reactions elicited by each injection of the index insulin(s); (3) reactions centred on the injection sites; and (4) reactions observed by the investigator in response to an insulin challenge test.

Reactions were categorised as clinically likely insulin allergy when all four criteria were present (26/52 patients, 50%). In this group, reactions were mostly local (19/26, 73%); reactions were systemic in 7/26 (27%) patients (i.e. generalised

Table 1 Clinical presentation and characteristics of the 52 patients referred for insulin allergy

Variable	Clinically positive		Clinically negative
	Likely IA (*N*=26)	Possible IA (*N*=9)	Unlikely IA (*N*=17)
Clinical criteria for IA likelihood			
Recurrent reactions suggestive of IA	26 (100)	0 (0)	0 (0)
Centred on injection sites	26 (100)	9 (100)[a]	0 (0)
Elicited by each injection	26 (100)	0 (0)	0 (0)
Observed by investigator	25 (96)[b]	0 (0)	0 (0)
Reported clinical reactions			
Local	19 (73)	9 (100)	5 (29)[c]
Systemic	7 (27)[d]	0 (0)	1 (6)[e]
Non-specific	0 (0)	0 (0)	11 (65)[f]
Immediate/delayed	20/6 (77/23)	7/2 (78/22)	3/14 (18/82)[g]
Age (years)	56 (17–75)	39 (25–81)	54 (24–82)
Sex (male/female)	14/12 (54/46)[h]	5/4 (56/44)	3/14 (18/82)[h]
BMI (kg/m^2)	29 (20–40)	23 (21–29)[i]	30 (23–38)
Type 1/type 2 diabetes	7/19 (27/73)	5/4 (56/44)	7/10 (41/59)
Diabetes duration (years)	11 (0–41)	11 (1–30)	19 (5–36)
HbA_{1c} (mmol/mol)	66 (42–130)	64 (33–74)	68 (34–127)
HbA_{1c} (%)	8.2 (6.0–14.0)	8.0 (5.2–8.9)	8.4 (5.3–13.8)
History of atopy	7 (27)	2 (22)	3 (18)
Duration of insulin treatment (months)	12 (0–492)[j]	120 (3–264)	78 (2–324)
Delay between first injection of index insulin and clinical reaction (months)	3 (0–24)	4 (0–72)	3 (0–72)
Index insulin			
Insulin detemir	8 (31)	3 (33)	4 (24)
Insulins containing protamine	17 (65)	4 (44)	7 (41)
Multiple insulins	12 (46)	3 (33)	4 (24)

Data are *n* (%) or median (range)

Percentages were compared using Fisher's exact test; numerical values were compared using the Mann–Whitney test

[a] Pruritus centred on the injection sites but no reactions suggestive of insulin allergy

[b] One patient with type 2 diabetes reported four episodes of laryngeal angioedema after insulin injections; no further clinical challenge was therefore attempted

[c] $p \leq 0.01$ vs the clinically likely and clinically possible groups

[d] Isolated systemic reactions: generalised urticaria/pruritus (*n*=5); laryngeal angioedema (*n*=2)

[e] Diffuse lipoatrophy not centred on the injection sites

[f] $p \leq 0.002$ vs the clinically likely and clinically possible groups. Non-specific reactions consisted of generalised pruritus (*n*=8), malaise or a generalised burning sensation (*n*=2) and diffuse papules (*n*=1)

[g] $p \leq 0.009$ vs the clinically likely and clinically possible groups

[h] $p=0.03$ vs the clinically likely and clinically unlikely groups

[i] $p \leq 0.03$ vs the clinically likely and clinically unlikely groups

[j] $p<0.05$ vs the clinically possible and clinically unlikely groups

IA, Insulin allergy

urticaria/pruritus [*n*=5] and laryngeal angioedema [*n*=2; graded as severe anaphylaxis] [19]). Immediate-type reactions were more common (77%) than delayed reactions (23%).

Clinically possible insulin allergy was assigned when some but not all criteria were met (9/52 patients, 17%). All patients in this group reported pruritus centred on the injection sites, which was mostly immediate (78%) but inconsistent and without a skin reaction that could be verified by the physician.

Patients meeting none of the clinical criteria were classified as being clinically unlikely to have an insulin allergy (17/52 patients, 33%). Manifestations were variable and not consistently observed at each injection: either local reactions (5/17,

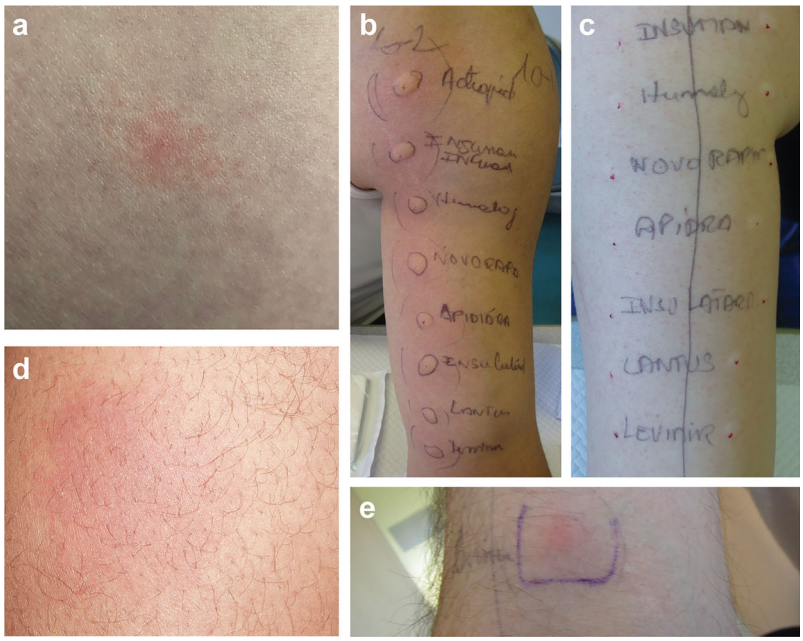

Fig. 1 Representative allergic skin reactions to insulin. (**a**) Immediate-type reaction to insulin lispro. (**b**) Positive IDRs, 20 min readout. (**c**) Negative IDRs, 20 min readout. (**d**) Delayed-type reaction to insulin detemir. (**e**) Positive IDR to insulin detemir, 24 h readout

29%; pruritus or pain in the area of the injection sites, but not centred on the injection sites) or, more frequently, non-specific systemic reactions without local manifestations (11/17, 65%). Non-specific and delayed reactions were more common in this group than in the clinically likely and clinically possible insulin allergy groups.

Table 2 IDR results and diagnostic performance of clinical likelihood criteria

Diagnostic accuracy	Clinically positive		Clinically negative
	Likely IA (*N*=26)	Possible IA (*N*=9)	Unlikely IA (*N*=17)
Positive IDR to index insulin	24/26[a]	3/9	0/14[b]
Sensitivity of clinical likelihood criteria	24/26	3/9	
	92% (75, 99)	33% (7, 70)	
	27/35		
	77% (60, 90)		
Specificity of clinical likelihood criteria			14/14
			100% (77, 100)
Positive predictive value	24/24	3/3	
	100% (100, 100)	100% (100, 100)	
	27/27		
	100% (100, 100)		
Negative predictive value	14/16	14/20	
	88% (65, 96)	70% (60, 79)	
	14/22		
	64% (49, 76)		

The sensitivity values (with 95% CIs) refer to the proportion of patients in the clinically likely insulin allergy and possible insulin allergy groups who were IDR positive. The specificity value (with 95% CI) refers to the proportion of patients in the unlikely insulin allergy group who were IDR negative

The histamine positive control and glycerol saline negative control results were positive and negative, respectively, in all cases (data not shown)

[a] $p \leq 0.001$ vs the possible and unlikely insulin allergy groups using Fisher's exact test

[b] Three patients in the clinically unlikely insulin allergy group presenting with chronic generalised pruritus without local reactions did not undergo IDR tests

IA, insulin allergy

Overall, patients in the clinically likely and clinically possible insulin allergy categories were considered clinically positive for insulin allergy; those assigned to the clinically unlikely insulin allergy group were considered clinically negative.

The clinical characteristics of the 52 patients are further summarised in Table 1 (additional details are provided in ESM Table 2). There was a higher percentage of women in the clinically unlikely group than in the clinically likely group. BMI was lowest in the clinically possible group. The distributions of age, type 1 and type 2 diabetes, disease duration, HbA_{1c} values and prior history of atopy were similar across the groups. The delay between the first injection of index insulin(s) and clinical manifestations was heterogeneous but was most commonly 3–4 months and was similar across the groups. However, patients with clinically likely insulin allergy had a shorter treatment duration.

Index formulations covered all major types of insulin but were more frequently insulin detemir, protamine-containing insulins and/or multiple insulins, irrespective of clinical likelihood of insulin allergy.

Collectively, the most relevant feature in the clinical history of patients with clinically likely insulin allergy was a shorter yet variable duration of insulin treatment.

Clinical likelihood criteria identify patients with an insulin allergy subsequently confirmed by an IDR test The IDR results are summarised in Table 2 (further details of the IDR tests are provided in ESM Table 3). Using the IDR test as the gold standard, the sensitivity of the clinical likelihood criteria was 92% (24/26 positive IDR tests) for likely insulin allergy patients, 33% (3/9) for possible insulin allergy patients and 77% (27/35) when considering both together, with a positive predictive value of 100%. The two IDR-negative patients with clinically likely insulin allergy reported delayed local reactions to insulin detemir. The specificity of the clinical likelihood criteria (i.e. IDR-negative patients identified as clinically negative [unlikely insulin allergy]) was 100% (14/14).

Besides confirming insulin allergy, an IDR test is useful for identifying allergenic formulations. Indeed, all positive IDR tests were positive for index insulin(s) and often also for other formulations. In all but one case (PIA08), the reported reaction type (immediate or delayed) was concordant with the IDR. Most delayed reactions (75%, 3/4) were associated with insulin detemir, as reported previously [9, 13]. Six patients testing positive to protamine also reacted to insulin formulations without protamine, indicating a concomitant allergy to protamine and insulin. No reaction to other excipients was observed. Reactions to the glycerol saline control were negative in all cases, thus ruling out an allergy to nickel used in needles.

Skin prick tests were performed in a subset of 24 patients (11 with likely insulin allergy, nine with possible insulin allergy and four with unlikely insulin allergy [ESM Table 3]). All positive reactions were in the likely insulin allergy group (5/11, 45%). Moreover, all skin prick-positive patients were also IDR positive. Anti-insulin IgE was measured in a subgroup of patients; 12/15 likely insulin allergy patients, 2/4 possible insulin allergy patients and 1/4 unlikely insulin allergy patients were positive. Similar to the skin prick test, all IgE-positive patients were also IDR positive (except for the clinically unlikely insulin allergy patient). Anti-protamine IgE measurements were negative in all patients (data not shown).

Collectively, positive clinical likelihood criteria identified patients with an insulin allergy that is subsequently confirmed by an IDR test with 77% sensitivity and 100% specificity. IDR tests identified immediate- and delayed-type reactions to index insulins and other allergenic insulin formulations, with no added value for skin prick and anti-insulin IgE tests.

Case–control study to define the diagnostic performance of skin prick and anti-insulin IgE tests The retrospective cohort results indicated that only patients with clinically likely or clinically possible insulin allergy should undergo skin tests to confirm or disprove diagnosis. To measure the diagnostic performance of allergology tests, we conducted a case–control study by recruiting patients with clinically likely insulin allergy in parallel with insulin-naive type 2 diabetic patients and non-allergic insulin-treated type 1 diabetic patients (Table 3). Although diabetes duration was shorter in the insulin allergy group, insulin treatment duration and doses were similar in insulin allergy and insulin-treated participants. In the insulin allergy group, type 2 diabetic participants were treated with slow-acting insulin and oral hypoglycaemic agents (OHAs), except for two participants who were weaned off insulin before study entry. History of atopy was not associated with insulin allergy. Considering that insulin-treated and insulin-naive control participants all had type 1 and type 2 diabetes, respectively, HLA haplotypes were compared between the insulin allergy group and the insulin-treated and insulin-naive groups combined, thus correcting for the potential bias of type 1 diabetes-associated haplotypes. HLA-A2 showed a slightly but significantly higher representation among insulin allergy participants than among the combined group (80% vs 42%, p=0.04).

Table 3 further summarises the timing of clinical reactions in insulin allergy participants (individual participants are described in ESM Table 4). Immediate-type reactions were most common (8/10, 80%). Participants were enrolled after a median time of 10 months (range 1–124 months) following their first reaction. Most (7/10) were still experiencing reactions at study entry (median time since last reaction 0 months, range 0–96 months); 2/10 were switched to OHAs and/or glucagon-like peptide 1 (GLP-1) analogues 2–3 weeks before

Table 3 Characteristics of case–control study participants and clinical reactions

Variable	A. Insulin allergy (*N*=10)	B. Insulin treated (*N*=24)	C. Insulin naive (*N*=21)	*p* value
Type 1 diabetes/type 2 diabetes/other, *n*	3/6/1[a]	24/0/0	0/21/0	0.70 (A vs B+C)
Age (years)	51.5 (22–73)	41.5 (19–71)	64.0 (45–80)	0.45 (A vs B+C)
Sex (male/female), %	40/60	50/50	57/43	0.68 (A vs B vs C)
BMI (kg/m^2)	25 (22–34)	25 (19–35)	29 (20–38)	0.12 (A vs B vs C)
HbA_{1c} (mmol/mol)	64 (55–78)	57 (37–77)	56 (41–79)	0.06 (A vs B vs C)
HbA_{1c} (%)	8.0 (7.2–9.3)	7.4 (5.5–9.2)	7.3 (5.9–9.4)	0.06 (A vs B vs C)
Insulin treatment, %	80[b]	100	0	0.08 (A vs B)
CSII, %	10	58	NA	0.06 (A vs B)
Diabetes duration (years)	11.2 (1.8–23.6)	19.3 (4.5–51.0)	13.4 (3.4–28.0)	0.04 (A vs B vs C)
Duration of insulin treatment (years)	1.1 (0.1–23.6)	10.4 (0.6–44.9)	NA	0.23 (A vs B)
Insulin dose (U/kg/day)	1.1 (0.2–1.9)	0.6 (0.3–1.4)	NA	0.08 (A vs B)
Use of other glucose-lowering treatment, %				
Metformin	60	4	90	NA
Sulfamides	40	0	71	NA
Gliptins	10	0	43	NA
GLP-1 analogues	10	0	14	NA
History of atopy, %	10	29	14	0.36 (A vs B vs C)
Use of corticoids or antihistamines, %	0	0	0	1.00 (A vs B vs C)
HLA, % (*n*)				
HLA-A2	80 (8)	46 (11)	38 (8)	0.04 (A vs B+C)
HLA-DRB1	10 (1)	33 (8)	14 (3)	0.43 (A vs B+C)
HLA-DRB2	0 (0)	0 (0)	19 (4)	1.00 (A vs B+C)
HLA-DRB3	30 (3)	63 (15)	24 (5)	0.49 (A vs B+C)
HLA-DRB4	60 (6)	46 (11)	33 (7)	0.30 (A vs B+C)
HLA-DRB7	30 (3)	17 (4)	24 (5)	0.67 (A vs B+C)
HLA-DRB13	50 (5)	8 (2)	33 (7)	0.10 (A vs B+C)
HLA-DQB1	20 (2)	42 (10)	10 (2)	1.00 (A vs B+C)
HLA-DQB2	70 (7)	71 (17)	52 (11)	0.73 (A vs B+C)
HLA-DQB3	60 (6)	33 (8)	62 (13)	0.50 (A vs B+C)
HLA-DQB6	30 (3)	4 (1)	38 (8)	0.67 (A vs B+C)
Characteristics of clinical reactions				
Immediate/delayed reactions, *n*	8/2	NA	NA	NA
Time since first reaction (months)	10 (1–124)	NA	NA	NA
Time since last reaction (months)	0 (0–96)	NA	NA	NA
Time since last insulin injection (months)	0 (0–0.75)	NA	NA	NA
Index insulin, % (*n*)				
NPH	30 (3)	NA	NA	NA
Detemir	30 (3)	NA	NA	NA
Glargine	30 (3)	NA	NA	NA
Short-acting insulin	10 (1)	NA	NA	NA
Aspart	20 (2)	NA	NA	NA
Multiple insulin formulations	20 (2)	NA	NA	NA

Continuous variables are expressed as median (range) and compared using the Kruskal–Wallis test. Two-way contingency analyses were performed using Fisher's exact test

[a] MODY3

[b] Insulin was discontinued before study entry in 2/10 participants (not considered for the calculation of daily mean insulin dose)

NA, not applicable

Table 4 Diagnostic performance of different assays in the case–control study

Diagnostic accuracy	IDR test	Skin prick test	Insulin IgE (Phadia)	Insulin IgE (in-house)
Positive, insulin allergy	8/10 (80.0)	1/10 (10.0)	5/9 (55.6)	5/10 (50.0)
Positive, insulin treated	0/22 (0)	0/22 (0)	3/22 (13.6)	0/22 (0)
Positive, insulin naive	0/18 (0)	0/18 (0)	2/20 (10.0)	0/18 (0)
Insulin allergy vs insulin treated				
Sensitivity	80 (44, 97)	10 (0, 45)	56 (21, 86)	50 (19, 81)
Specificity	100 (84, 100)	100 (85, 100)	86 (65, 97)	100 (85, 100)
Positive predictive value	100 (63, 100)	100 (3, 100)	63 (33, 85)	100 (100, 100)
Negative predictive value	92 (73, 99)	71 (52, 86)	83 (69, 91)	81 (70, 89)
Fisher's test	$p<0.0001$	$p=0.31$	$p=0.03$	$p=0.001$
Insulin allergy vs insulin naive				
Sensitivity	80 (44, 97)	10 (0, 45)	56 (21, 86)	50 (19, 81)
Specificity	100 (81, 100)	100 (81, 100)	90 (68, 99)	100 (81, 100)
Positive predictive value	100 (63, 100)	100 (3, 100)	71 (37, 91)	100 (100, 100)
Negative predictive value	90 (68, 99)	67 (46, 83)	82 (68, 90)	78 (66, 87)
Fisher's test	$p<0.0001$	$p=0.36$	$p=0.02$	$p=0.003$

Data are *n*/*N* (%) or, for diagnostic performance values, are % (95% CI)

For the in-house anti-insulin IgE assay, the positive cut-off value was >150 nU/ml (see ESM Fig. 1)

enrolment. One participant (46-PS) had been on continuous subcutaneous insulin infusion (CSII) for 9 years to treat insulin allergy but still experienced skin reactions 96 weeks before study entry.

Diagnostic performance of IDR and skin prick tests and histopathology The diagnostic performance of the IDR and skin prick tests was assessed by comparing clinically likely insulin allergy participants with either insulin-treated or insulin-naive control participants (Table 4). Both tests displayed 100% specificity and positive predictive values for both comparisons, but the sensitivity of the IDR test was far superior to that for the skin prick test (80% vs 10% for both comparisons). Negative predictive values were 67–71% for skin prick tests and 90–92% for IDR tests. As before, all positive IDRs were positive for index insulin formulation(s), alone or in combination with others (ESM Table 4). No reaction to excipients or latex was detected.

Punch skin biopsies performed at the IDR site in 4/10 insulin allergy participants showed superficial and deep urticarial perivascular lymphocytic infiltrates with some eosinophils (Fig. 2).

Collectively, IDR tests provide the best diagnostic performance (80% sensitivity, 100% specificity) and identify index insulin formulation(s), while prick tests are highly specific (100%) but poorly sensitive (10%).

Diagnostic performance of anti-insulin IgE assays A commercial anti-insulin IgE fluorimetric assay displayed 86% or 90% specificity, depending on the comparison, and 56% sensitivity (Table 4), with no correlation between anti-insulin IgE and

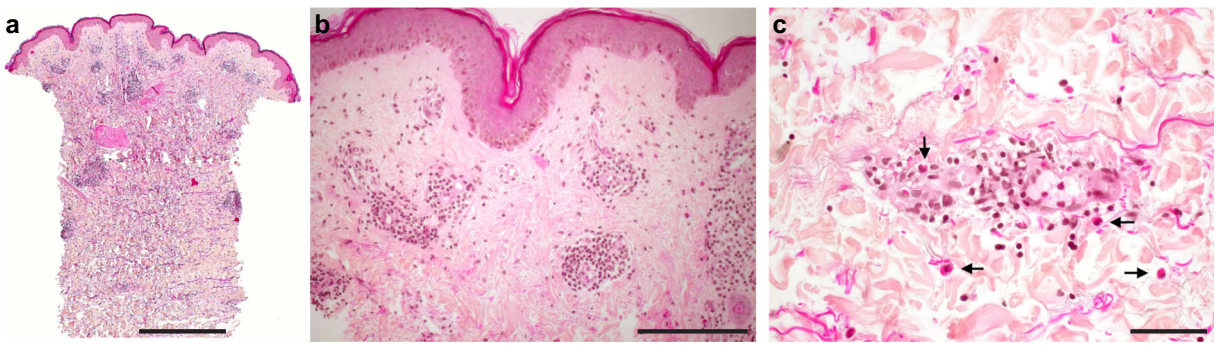

Fig. 2 Histopathology of a punch skin biopsy at the reaction site in an insulin allergy patient. Representative haematoxylin–eosin–saffron-stained section from participant 28-ET from the site of reaction following allergology tests showing superficial and deep dermal perivascular infiltrates composed of lymphocytes and a few eosinophils. (**a**) Original magnification ×40, scale bar 1 mm. (**b**) Original magnification ×100, scale bar 250 μm. (**c**) Original magnification ×400, scale bar 50 μm. Eosinophils are indicated by arrows

IgG4 levels (data not shown) and no added diagnostic value of IgG4 testing, as reported previously [20]. To improve specificity, we employed an in-house anti-insulin IgE radiobinding assay. With a positive cut-off value of >150 nU/ml, determined after carrying out a receiver operating characteristic analysis (AUC 0.819 [ESM Fig. 1a]), specificity reached 100% and sensitivity was 50% for the comparison between the insulin allergy group and either of the control groups (Table 4). The two anti-insulin IgE assays correlated well (Spearman r=0.818, p=0.011 [ESM Fig. 1b]). Anti-insulin antibodies were positive in all cases. Notably, anti-insulin IgE levels were inversely correlated with the index insulin concentration testing positive in the IDR tests, for both commercial assays (r=−0.839, p=0.033 [ESM Fig. 1c]) and in-house assays (r=−0.772, p=0.043 [ESM Fig. 1d]).

Collectively, the in-house anti-insulin IgE assay achieved 100% specificity and 50% sensitivity for detecting clinically likely insulin allergy participants.

Clinical correlates of IDR and anti-insulin IgE assays in individual participants IDR tests were negative in two insulin allergy participants (ESM Table 4). One (52-PC) reported immediate-type reactions to insulin detemir and was anti-insulin IgE positive in the in-house assay. The other (46-PS) was enrolled 96 months after her last skin reaction, although her IDR was positive for the index insulin and several others 9 years earlier, at the time of the first reactions and subsequent switch to CSII. Both anti-insulin IgE assays were negative, with high anti-insulin antibody levels. The two participants who were weaned off insulin shortly (2–3 weeks) before study entry (28-ET and 29-HD) still tested positive on the IDR test and both anti-insulin IgE assays.

The case of participant 38-RO is noteworthy. High anti-insulin IgE levels were detected with the commercial assay and, to a larger extent, with the in-house assay. This type 2 diabetic participant was first treated at diagnosis, 10 years before enrolment, with insulin detemir, which was discontinued 2 months later because of the presence of urticarial lesions. Insulin NPH was reintroduced 10 years later because of poor glycaemic control and was discontinued 3 days later on insulin allergy relapse with similar lesions. It was then resumed 6 months later because of persistent hyperglycaemia, followed by another immediate insulin allergy relapse and study entry 3 months later. The very high anti-insulin IgE levels observed likely reflect these three previous insulin challenges.

Therapeutic management Based on published literature [3, 10, 11, 21, 22], we undertook a stepwise therapeutic approach for patients with positive IDRs to index insulin: 31 patients with clinically likely insulin allergy (23 from the retrospective cohort [one was lost to follow-up] and eight from the case–control study) and three patients with possible insulin allergy, as detailed in ESM Tables 3 and 4 and summarised in Table 5. Mean follow-up duration was 4.7 years (range 0.5–12 years). First, spontaneous resolution was observed in 3/34 (9%) patients. Second, replacement of insulin detemir with OHA/GLP-1 or another insulin formulation resolved symptoms in 4/34 (12%) patients. Third, a re-evaluation of insulin dependency led to a switch to OHA/GLP-1 in 5/34 (15%) patients. Fourth, switch to another insulin formulation resolved insulin allergy in 3/34 (9%) patients. Fifth, antihistamine treatment (cetirizine, desloratadine) was attempted in those with immediate-type reactions and was sufficient in 4/34 (12%) patients in total. The remaining patients were switched to CSII with either aspart or lispro (15/34, 44%), often combined with squared boluses. At CSII initiation, a void subcutaneous catheter was left overnight to exclude reactions to the material. CSII was started at the usual dose, except for three patients with systemic manifestations, who started at a dose of 0.1 U/h, with 0.1 U/h increments every hour until normoglycaemia. In most patients, CSII prandial boluses up to 4 U were well

Table 5 Therapeutic management of patients with a positive IDR to index insulin

Therapeutic management	IDR+		IDR+	IDR+
	Likely IA		Possible IA	Total
	Retrospective	Case–control		
Spontaneous resolution	3/23	0/8	0/3	3/34 (8.8)
Detemir replacement	3/23	1/8	0/3	4/34 (11.8)
Switch to OHA/GLP-1	1/23	3/8	1/3	5/34 (14.7)
Switch to other insulin formulation	2/23	1/8	0/3	3/34 (8.8)
Antihistamine only	3/23	1/8	0/3	4/34 (11.8)
Switch to CSII ± squared bolus	11/23	2/8	2/3	15/34 (44.1)

Data are n/N (%)

One IDR+ patient in the likely insulin allergy group of the retrospective study was lost to follow-up and therapeutic management could not be evaluated

IA, insulin allergy

tolerated from the start; otherwise, they were omitted during the first few weeks.

Collectively, insulin allergy resolution can be achieved using a stepwise strategy that includes a switch to OHA/GLP-1 or other insulin formulations, antihistamine treatment and, eventually, CSII.

Discussion

We describe a large retrospective cohort of 52 consecutive patients referred for suspected insulin allergy, complemented by a case–control study of participants with and without insulin allergy. As described previously [5, 23], prior medical history was not associated with insulin allergy: insulin allergy was observed in both type 1 and type 2 diabetes, often in those without an atopic background, and with a variable delay after the introduction of index insulin(s), usually of a few months. While local reactions were more common, systemic reactions were observed in 27% of patients with clinically likely insulin allergy, including two cases of laryngeal angioedema. Non-specific and delayed reactions were more frequent in the clinically unlikely insulin allergy group.

Our first aim was to define whether clinical likelihood criteria can inform the need for further allergology workup at first referral to the diabetology clinic, where it is sometimes difficult or unsafe to perform challenge tests. The presence of all (clinically likely insulin allergy) or only some criteria (clinically possible insulin allergy) displayed 77% sensitivity and 100% specificity when considering an IDR test as the gold standard, suggesting that the criteria can guide decisions on whether to pursue further investigations.

Our second aim was to define the diagnostic performance of the confirmatory tests available on subsequent allergology referral. To this end, the presence of all four clinical likelihood criteria that define the likely insulin allergy group was taken as the most suitable reference, because such criteria include an insulin challenge test, which is the recommended diagnostic gold standard [14]. The IDR test displayed the best diagnostic performance (100% specificity, 80% sensitivity); the skin prick test had a low sensitivity of 10% (100% specificity) [10] and the anti-insulin IgE assays had an intermediate sensitivity of 50% and 56% (100% specificity using the in-house assay) [24]. These latter tests had no added diagnostic value, as all positive participants were also IDR positive. Moreover, IgE assays are relevant only for immediate-type (IgE-mediated) reactions. Indeed, insulin allergy participants with IDR-confirmed delayed reactions were either anti-insulin IgE negative or marginally positive.

IDR tests were also used to identify the main allergen [25], which was insulin in all cases. Multiple index insulins were often reported and tested positive in IDR tests. The single most frequently used formulations were detemir and protamine-containing insulins. Although allergies to protamine, insulin excipients or latex have been described previously [21, 22], our cohort confirms their rarity.

Despite the introduction of general guidelines for evaluating drug allergy [14], there is a lack of robust evidence on insulin allergy based on large series [25], and case–control studies are missing. Based on our results, we propose a systematic diagnostic workflow (Fig. 3, blue). First, patients referred for suspected insulin allergy should be classified based on the four clinical likelihood criteria. In their absence, insulin allergy is unlikely and further investigations are not warranted, as IDR tests to index insulin(s) are invariably negative in this scenario. IDR tests may still be useful in selected cases to avoid unjustified insulin withdrawal.

Conversely, the presence of these criteria meets the definition of positive clinical manifestations, with two different degrees of likelihood (likely or possible insulin allergy) depending on whether all or only some criteria are present. The single most important criterion is the observation of a positive reaction after an insulin challenge test, which should be performed whenever possible and, albeit not identifying the allergen(s), is considered diagnostic [14]. All patients with a positive test result should undergo further allergology assessment to establish the diagnosis (in the absence of a challenge test) and to identify allergenic and non-allergenic formulations. Nonetheless, switching to other insulin formulations or OHA/GLP-1 should not be delayed if possible and/or if needed, as both the IDR and IgE assays still yielded positive results 2–3 weeks after insulin withdrawal. Although poorly sensitive, skin prick tests are easier to perform and should be used for screening, because a positive result means that an IDR test is unnecessary, thus shortening the diagnostic workup and limiting the risks of systemic reactions. Anti-insulin IgE assays are not recommended for diagnosis [14, 25], but could be relevant to monitor insulin allergy desensitisation. Haastrup et al [26] screened 144 patients with suspected insulin allergy using the Phadia anti-insulin IgE assay, with only 34 (24%) testing positive, of whom 33 tested positive on a subsequent IDR test. Interestingly, 12/71 (17%) IgE-negative patients were also IDR positive. The 54% lower insulin allergy prevalence found in this study compared with our study (27/52 [52%] with IDR-confirmed insulin allergy) may reflect the sensitivity of the Phadia IgE assay (56%) and the fact that delayed (non-IgE-mediated) reactions are not detected by IgE assays. Moreover, our clinical likelihood criteria allow one third of patients to be excluded from further workup rather than testing for anti-insulin IgE in all patients.

Insulin detemir is associated with higher frequencies of cutaneous, mostly delayed, reactions [5, 9, 13]. Delayed reactions with other formulations have been described [27–29] but are rare, including with degludec (and liraglutide), despite it having a similar 16-carbon fatty di-acid chain. The crystallised structure of degludec (possibly masking some antigenic

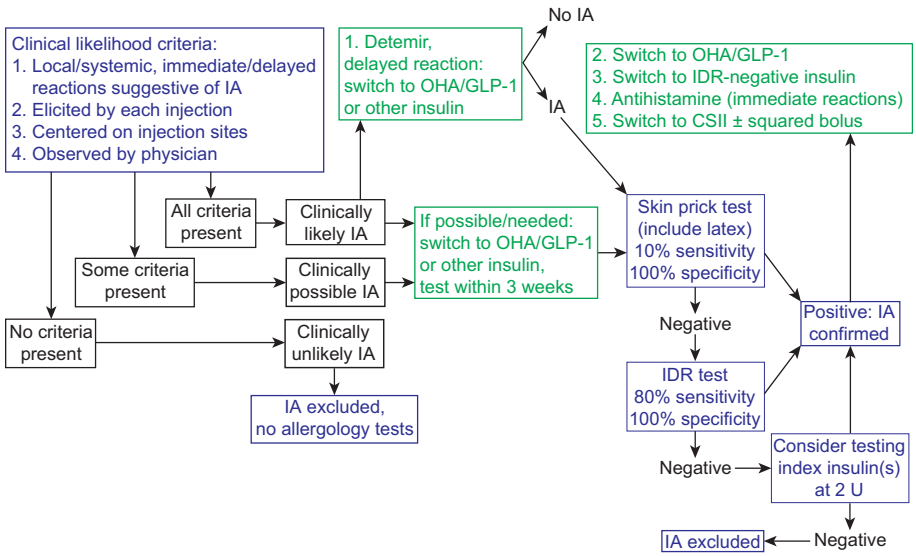

Fig. 3 Proposed diagnostic (blue) and treatment (green) workflow for insulin allergy. Switching to OHA/GLP-1 should be guided by C-peptide measurements. IA, insulin allergy

determinants) and slower release kinetics may explain its lower allergenicity [30]. Detemir reactions can be resolved by replacement with another insulin without the need for skin tests in the absence of relapse.

Guidelines can also be proposed for the subsequent management of IDR-confirmed insulin allergy cases (Fig. 3, green). First, replacement of insulin with OHA/GLP-1 should be evaluated in C-peptide-positive type 2 diabetic patients. Second, replacement with another insulin formulation should be attempted. As insulin itself was the allergen in our study and multiple index insulin formulations were often identified, replacement with another, preferably IDR-negative, insulin [25, 26] was seldom possible. Antihistamine agents (or topical sodium cromoglicate) should therefore be considered as third-line treatment for immediate-type reactions. Although its efficacy has been described previously [31], we did not consider local corticoid treatment [25] because its vasoconstrictive effects [32] can reduce systemic insulin bioavailability. As reported previously [26], most patients (44%) ultimately required CSII, which should be the first-line treatment for anaphylactic reactions. CSII benefit is twofold [3, 10]. First, diluted insulin exposure limits allergenicity, especially with prolonged (30–60 min) prandial boluses. Second, although other protocols have been described [10, 22, 25], CSII favours insulin desensitisation [13] by providing an escalating, continuous low-dose antigen exposure [33]. Although intravenous insulin infusion [34] or other exceptional procedures [35, 36] were not required in our study, CSII did not resolve insulin allergy in one patient. Another three patients were not able to tolerate boluses higher than 4 U and required additional measures (e.g. low carbohydrate/glycaemic index diets, alpha-glucosidase or sodium–glucose cotransporter 2 inhibitors, bolus fractionation).

Our study has some limitations. First, the highest insulin concentration used for the IDR tests was 0.2 U, as recommended previously [25] to limit hypoglycaemia risk, which might explain the negative results in 4/36 (11%) patients with clinically likely insulin allergy (with two displaying delayed reactions to detemir). Of note, these clinically likely insulin allergy patients may have been correctly classified because they underwent a challenge test, typically with a higher dose of insulin of 1–2 U. Nonetheless, another IDR test with a higher, undiluted 2 U dose of insulin taken with carbohydrates should be carried out in cases of negative IDR tests. Second, the IDR sensitivity of 80% was probably underestimated by the omission of this further testing and by inclusion of one patient already under CSII who experienced her last clinical reaction 96 months before enrolment. Another IDR-negative patient (52-PC) reported immediate-type reactions to insulin detemir. Although reactions to detemir are more frequently delayed, the allergic nature of detemir reactions has been questioned [37], which justifies the proposed first-line replacement trial without allergology referral. Third, although allergies to excipients (e.g. zinc, metacresol) were excluded with the proposed test panel, latex allergy may have been associated with insulin allergy but was not tested in all patients. The diagnostic workup should therefore include a latex skin prick test. Fourth, the number of patients analysed is small because of the rarity of insulin allergy, and the proposed workflow requires validation in larger studies.

The short time frame available to treat insulin allergy patients without compromising glycaemic control and the frequent ultimate resort to CSII for patients not otherwise requiring it underline the need for novel therapeutics (e.g. omalizumab) [35]. Testing of such strategies would be facilitated by the short follow-up needed to assess clinical outcomes. It may be beneficial to consider insulin allergy as a proof-of-concept setting for strategies to restore immune tolerance to insulin for preventing type 1 diabetes [38]. Of note, allergy desensitisation protocols are being considered to this end [39,

40]. While prevention trials require large screening efforts to stratify disease risk and years of follow-up to assess outcomes, trialling the same therapeutics in insulin allergy patients would require only a few months of follow-up. On the one hand, this could provide treatment options for an otherwise rare condition that is not attractive for dedicated drug development. On the other hand, these trials could allow effective agents to be repurposed for type 1 diabetes prevention.

In conclusion, clinical likelihood criteria can be used by diabetologists to guide insulin allergy diagnosis and decisions about the need for specialised skin tests. A stepwise management strategy has been proposed. CSII is eventually required in most patients, underlining the need to develop alternative desensitisation strategies.

Supplementary Information The online version contains peer-reviewed but unedited supplementary material available at https://doi.org/10.1007/s00125-022-05710-9.

Acknowledgements The authors would like to thank M. C. Gagnerault (Université Paris Cité, CNRS, Inserm, Institut Cochin, Paris, France) for biobanking of patient samples.

Data availability Data are available from the authors on request.

Funding This study was funded by a Programme Hospitalier de Recherche Clinique of the Assistance Publique–Hôpitaux de Paris (to ASG) and by the Fondation Francophone pour la Recherche sur le Diabète (to RM). The funders had no role in the study.

Authors' relationships and activities The authors declare that there are no relationships or activities that might bias, or be perceived to bias, their work.

Contribution statement ASG, CP, CB and EL designed the study. ASG, CP, IVB, JM and FE examined the patients and compiled the clinical data and results of the skin prick tests. ASG, CP, LAP, EL and RM analysed the data. SB, PA and SCZ performed the in vitro assays and analysed the data. PM performed the histopathological analyses. ML and JC performed the statistical analyses and supervised the study methodology. ASG, EL and RM wrote the manuscript. All authors approved the final version of the manuscript. ASG and RM are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Lindholm A, Jensen LB, Home PD, Raskin P, Boehm BO, Rastam J (2002) Immune responses to insulin aspart and biphasic insulin aspart in people with type 1 and type 2 diabetes. Diabetes Care 25(5):876–882. https://doi.org/10.2337/diacare.25.5.876
2. Fineberg SE, Huang J, Brunelle R, Gulliya KS, Anderson JH Jr (2003) Effect of long-term exposure to insulin lispro on the induction of antibody response in patients with type 1 or type 2 diabetes. Diabetes Care 26(1):89–96. https://doi.org/10.2337/diacare.26.1.89
3. Radermecker RP, Scheen AJ (2007) Allergy reactions to insulin: effects of continuous subcutaneous insulin infusion and insulin analogues. Diabetes Metab Res Rev 23(5):348–355. https://doi.org/10.1002/dmrr.714
4. Ghazavi MK, Johnston GA (2011) Insulin allergy. Clin Dermatol 29(3):300–305
5. Fineberg SE, Kawabata TT, Finco-Kent D, Fountaine RJ, Finch GL, Krasner AS (2007) Immunological responses to exogenous insulin. Endocr Rev 28(6):625–652. https://doi.org/10.1210/er.2007-0002
6. Sola-Gazagnes A, Pecquet C (2004) [Allergy to insulin in 2003]. Journ Annu Diabetol Hotel-Dieu 161–179
7. Darmon P, Castera V, Koeppel M-C, Petitjean C, Dutour A (2005) Type III allergy to insulin Detemir. Diabetes Care 28(12):2980. https://doi.org/10.2337/diacare.28.12.2980
8. Blumer IR (2006) Severe injection site reaction to insulin detemir. Diabetes Care 29(4):946. https://doi.org/10.2337/diacare.29.04.06.dc05-2503
9. Sola-Gazagnes A, Pecquet C, M'Bemba J, Larger E, Slama G (2007) Type I and type IV allergy to the insulin analogue detemir. Lancet 369(9562):637–638. https://doi.org/10.1016/S0140-6736(07)60301-8
10. Akinci B, Yener S, Bayraktar F, Yesil S (2010) Allergic reactions to human insulin: a review of current knowledge and treatment options. Endocrine 37(1):33–39. https://doi.org/10.1007/s12020-009-9256-1
11. Jacquier J, Chik CL, Senior PA (2013) A practical, clinical approach to the assessment and management of suspected insulin allergy. Diabet Med 30(8):977–985. https://doi.org/10.1111/dme.12194
12. Meyboom RH, Hekster YA, Egberts AC, Gribnau FW, Edwards IR (1997) Causal or casual? The role of causality assessment in pharmacovigilance. Drug Saf 17(6):374–389. https://doi.org/10.2165/00002018-199717060-00004
13. Sola-Gazagnes A, Pecquet C, Radermecker R et al (2003) Successful treatment of insulin allergy in a type 1 diabetic patient by means of constant subcutaneous pump infusion of insulin. Diabetes Care 26(10):2961–2962. https://doi.org/10.2337/diacare.26.10.2961
14. Broyles AD, Banerji A, Castells M (2020) Practical guidance for the evaluation and Management of Drug Hypersensitivity: general concepts. J Allergy Clin Immunol Pract 8(9S):S3–S15. https://doi.org/10.1016/j.jaip.2020.08.002
15. Lee AY, Chey WY, Choi J, Jeon JS (2002) Insulin-induced drug eruptions and reliability of skin tests. Acta Derm Venereol 82(2):114–117. https://doi.org/10.1080/00015550252948149
16. Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P (2002) General considerations for skin test procedures in the diagnosis of drug hypersensitivity. Allergy 57(1):45–51
17. Bonifacio E, Scirpoli M, Kredel K, Fuchtenbusch M, Ziegler AG (1999) Early autoantibody responses in prediabetes are IgG1 dominated and suggest antigen-specific regulation. J Immunol 163(1):525–532
18. Naserke HE, Bonifacio E, Ziegler AG (1999) Immunoglobulin G insulin autoantibodies in BABYDIAB offspring appear postnatally: sensitive early detection using a protein a/G-based radiobinding assay. J Clin Endocrinol Metab 84(4):1239–1243. https://doi.org/10.1210/jcem.84.4.5597
19. Brown SG (2004) Clinical features and severity grading of anaphylaxis. J Allergy Clin Immunol 114(2):371–376. https://doi.org/10.1016/j.jaci.2004.04.029
20. Datema MR, Eller E, Zwinderman AH et al (2019) Ratios of specific IgG4 over IgE antibodies do not improve prediction of peanut allergy nor of its severity compared to specific IgE alone. Clin Exp Allergy 49(2):216–226. https://doi.org/10.1111/cea.13286
21. Bodtger U, Wittrup M (2005) A rational clinical approach to suspected insulin allergy: status after five years and 22 cases. Diabet Med 22(1):102–106. https://doi.org/10.1111/j.1464-5491.2004.01352.x

22. Heinzerling L, Raile K, Rochlitz H, Zuberbier T, Worm M (2008) Insulin allergy: clinical manifestations and management strategies. Allergy 63(2):148–155. https://doi.org/10.1111/j.1398-9995.2007.01567.x
23. Schernthaner G (1993) Immunogenicity and allergenic potential of animal and human insulins. Diabetes Care 16(S3):155–165. https://doi.org/10.2337/diacare.16.3.155
24. Velcovsky HG, Federlin KF (1982) Insulin-specific IgG and IgE antibody response in type I diabetic subjects exclusively treated with human insulin (recombinant DNA). Diabetes Care 5(S2):126–128. https://doi.org/10.2337/diacare.5.2.s126
25. Broyles AD, Banerji A, Barmettler S et al (2020) Practical guidance for the evaluation and Management of Drug Hypersensitivity: specific drugs. J Allergy Clin Immunol Pract 8(9S):S16–S116. https://doi.org/10.1016/j.jaip.2020.08.006
26. Haastrup MB, Henriksen JE, Mortz CG, Bindslev-Jensen C (2018) Insulin allergy can be successfully managed by a systematic approach. Clin Transl Allergy 8:35. https://doi.org/10.1186/s13601-018-0223-x
27. Grammer LC, Chen PY, Patterson R (1983) Evaluation and management of insulin allergy. J Allergy Clin Immunol 71(2):250–254. https://doi.org/10.1016/0091-6749(83)90107-0
28. deShazo RD (1978) Insulin allergy and insulin resistance: two immunologic reactions. Postgrad Med 63(1):85–92. https://doi.org/10.1080/00325481.1978.11714725
29. Paley R, Tunbridge R (1952) Dermal reactions to insulin therapy. Diabetes 1(1):22–27. https://doi.org/10.2337/diab.1.1.22
30. Fujishiro M, Izumida Y, Takemiya S et al (2016) A case of insulin allergy successfully managed using multihexamer-forming insulin degludec combined with liraglutide. Diabet Med 33(11):e26–e29. https://doi.org/10.1111/dme.12998
31. Loeb JA, Herold KC, Barton KP, Robinson LE, Jaspan JB (1989) Systematic approach to diagnosis and management of biphasic insulin allergy with local anti-inflammatory agents. Diabetes Care 12(6):421–423. https://doi.org/10.2337/diacare.12.6.421
32. Borelli C, Gassmueller J, Fluhr JW, Nietsch KH, Schinzel S, Korting HC (2008) Activity of different desoximetasone preparations compared to other topical corticosteroids in the vasoconstriction assay. Skin Pharmacol Physiol 21(3):181–187. https://doi.org/10.1159/000131082
33. Krishna MT, Huissoon AP (2011) Clinical immunology review series: an approach to desensitization. Clin Exp Immunol 163(2):131–146. https://doi.org/10.1111/j.1365-2249.2010.04296.x
34. Asai M, Yoshida M, Miura Y (2006) Immunologic tolerance to intravenously injected insulin. N Engl J Med 354(3):307–309. https://doi.org/10.1056/NEJMc052463
35. Yong PF, Malik R, Arif S et al (2009) Rituximab and omalizumab in severe, refractory insulin allergy. N Engl J Med 360(10):1045–1047. https://doi.org/10.1056/NEJMc0808282
36. Malaise J, Leonet J, Goffin E et al (2005) Pancreas transplantation for treatment of generalized allergy to human insulin in type 1 diabetes. Transplant Proc 37(6):2839. https://doi.org/10.1016/j.transproceed.2005.05.020
37. O'Goshi K, Serup J, Blaaholm B, Thomsen HK, Rossing P, Tarnow L (2011) Experimental testing of skin reactions to insulin detemir in diabetes patients naïve to insulin detemir. Skin Res Technol 17(4):411–419. https://doi.org/10.1111/j.1600-0846.2011.00551.x
38. Serra P, Santamaria P (2019) Antigen-specific therapeutic approaches for autoimmunity. Nat Biotechnol 37(3):238–251. https://doi.org/10.1038/s41587-019-0015-4
39. Larche M, Wraith DC (2005) Peptide-based therapeutic vaccines for allergic and autoimmune diseases. Nat Med 11(S4):S69–S76. https://doi.org/10.1038/nm1226
40. Alhadj Ali M, Liu YF, Arif S et al (2017) Metabolic and immune effects of immunotherapy with proinsulin peptide in human new-onset type 1 diabetes. Sci Transl Med 9(402):eaaf7779. https://doi.org/10.1126/scitranslmed.aaf7779