Insulin hypersensitivity in type 1 diabetes: investigation and treatment with immunodepletion

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Abstract
A 12-year-old girl presented with type 1 diabetes which was well controlled for the first two years. Glycaemic control then markedly deteriorated with a very large increase in insulin requirement and the appearance of inflammatory nodules at injection sites. Immunoprecipitation studies showed this to be due to a type 3 hypersensitivity reaction with the generation of IgG autoantibodies binding to insulin itself. Trials of a wide range of different insulins and treatment with a hyposensitisation protocol provided no benefit. Following treatment with rituximab, antibody generation subsided. Since the clinical response was only partial she also received intravenous immunoglobulin. A reduced insulin requirement and better glycaemic control were achieved over time. These parameters have subsequently deteriorated again. Copyright © 2020 John Wiley & Sons. Practical Diabetes 2020; 37(2): 59–61

Key words
insulin hypersensitivity; rituximab

Introduction
Type 1 diabetes (T1DM) is an autoimmune disease commonly associated with other autoimmune conditions. The generation of antibodies to insulin can occur, but is rarely clinically significant. Generation of IgE anti-insulin antibodies can lead to Type 1 allergic reactions associated with urticaria, angioedema, bronchospasm and hypotension. In contrast, generation of IgG anti-insulin antibodies may cause deposition of antibody-insulin complexes with local cutaneous inflammatory reactions, or systemic symptoms of serum sickness. Where clinical features are severe and associated with insulin resistance, treatment with immunosuppressants, intravenous (IV) immunoglobulin, plasmapheresis or rituximab may be considered.

Presentation
In 2009, a 12-year-old girl presented with lethargy, polyuria, polydipsia and alopecia. Investigation confirmed a diagnosis of diabetes (DM). There was a strong family history of diabetes on the mother’s side. Although the patient’s mother did not have diabetes, an uncle had T1DM and both maternal grandparents had type 2 diabetes. All five of the grandmother’s siblings had diabetes as did her mother.

Because the patient had a weight of 99.7kg (BMI 35.9) and there was a family history of type 2 as well as T1DM she was initially started on metformin, but was rapidly switched to insulin when blood glucose measurements remained elevated and anti-GAD65 antibodies came back positive. Initially her blood glucose concentration was well controlled on insulin glargine 22U and insulin aspart 8U before meals. Despite missing some mealtime injections she recorded HbA1c results of 36 and 42mmol/mol. Over four months between August and December 2011, her HbA1c rose to 100mmol/mol with substantial increases in insulin requirements to >150U daily. At the same time she developed raised red painful and pruritic nodules at the site of insulin injection. These lasted approximately four days before resolving. Antihistamines produced only minimal improvement. Flares at distant injection sites sometimes occurred.

In the subsequent months (January to February 2012), she was admitted twice with ketoacidosis (DKA). On the second occasion she was suffering from troublesome local reactions with tender red subcutaneous (SC) nodules, as well as widespread lipoatrophy at older injection sites. Subcutaneous injection of different insulin products were tried including Actrapid, Humulin S, Porcine neutral, Bovine neutral,
Hypurin bovine lente and the analogues aspart, detemir, glargine, glulisine and lispro, but she reacted equally to them all. There was no reaction to SC injection of sterile water or needle insertion alone. Intravenous insulin was tolerated without any systemic clinical reaction and was used to manage her DKA. Intravenous insulin was continued for a period after she had recovered from the acute illness and this demonstrated a high insulin dose requirement: >130U per day.

Investigations, management and progress
Total IgE was 38.5kU/L (ref range <81, Sheffield Northern General Hospital Protein Reference Unit, Sheffield, UK). Specific serum anti-insulin IgE antibodies including human insulin IgE, bovine insulin IgE and porcine IgE were undetectable (analyses performed at King’s College Hospital). Anti-insulin IgG levels were present (15.7mgA/L). Anti-GAD65 antibodies were 1997U/ml (normal 1–5), and IA2 antibodies were also positive. C-peptide measured fasting with blood glucose of 20.1mmol/L, after omitting evening/overnight insulin, was 438pmol/L (normal fasting <500pmol/L). The serum concentration of insulin was high at >2100pmol/L. In case the insulin resistance reflected antibody to an excipient, we tested a range of insulins containing different excipients (Table 1) but with no discernible benefit. The high insulin concentration appeared due to the presence of insulin-IgG antibody complexes, as demonstrated by polyethylene glycol (PEG) precipitation and gel filtration. Insulin recovery after PEG precipitation was very low, with insulin protein G immunosubtraction studies giving an insulin recovery of 28%.

Hyposensitisation was attempted in December 2012 using continuous SC insulin infusion via insulin pump (CSII) alongside IV insulin to maintain glycaemic control. The protocol commenced with 1/1000 of the usual dose of insulin, with doubling of the infusion rate every 20–30 minutes. The gradual increase in CSII dose was initially well tolerated, but on the second day the patient developed cutaneous reactions each time bolus injections were given via the pump. A punch biopsy at the site of one of the skin reaction sites showed an eosinophilic infiltration.

In April 2013, rituximab was given as four doses (375mg/m²) at weekly intervals in order to try and remove anti-insulin producing B-lymphocytes. Specific approval was required since rituximab is not licensed for use in children. A typical skin lesion prior to immunodepletion therapy is shown in Figure 1.

### Table 1. Additives within common insulin preparations

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<tr>
<th></th>
<th>Zinc</th>
<th>Cresol</th>
<th>Glycerol</th>
<th>Phenol</th>
<th>Protamine</th>
<th>Trometamol</th>
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</tr>
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<tr>
<td>Hypurin bovine lente</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Methyl parahydroxybenzoate</td>
</tr>
</tbody>
</table>

Figure 1. Cutaneous reaction to insulin injection caused by antibody to insulin itself, prior to immunodepletion therapy.
Figure 1. Despite complete elimination of circulating CD19 and CD20 B-lymphocytes, her diabetic control remained poor (biphasic insulin aspart [Novomix 30 120U twice daily]; HbA1c 142mmol/mol, and she was admitted in April 2014 with DKA. Anti-GAD65 antibodies remained high at 144U/mL. By January/February 2015, her anti-insulin IgG antibodies had declined to within the normal range at 3mgA/L (reference range 0–5), plasma insulin was significantly lower at 359pmol/L, and insulin recovery after PEG precipitation had improved to 76%. She still reacted to SC insulin injections with redness at injection sites but no discomfort or nodule formation. A punch biopsy of skin now showed normal histological appearances. Because of these continuing (but lesser) skin reactions, high insulin requirement and high HbA1c, she was in September 2015 given IV immunoglobulin to boost the immunodepletion. Over the next two years (to June 2017), she shed 36kg (weight 63.9kg, BMI 25), her dose of insulin decreased to 77U daily (Toujeo [weight 63.9kg, BMI 25], her dose of insulin decreased to 77U daily (Toujeo 35U am and 32U pm); her HbA1c improved (87mmol/mol) and she no longer developed inflammatory reactions on SC injection. Subsequently, her glycaemic control has deteriorated with increasing insulin dose and admissions with DKA.

Discussion
Following the diagnosis of T1DM, this patient’s diabetes was initially well controlled, but deteriorated two years later at which time she developed inflammatory reactions to the SC insulin injections and evidence of severe insulin resistance. Anti-insulin IgG antibodies were confirmed by PEG precipitation studies and gel filtration. Patients can develop antibodies to the excipients (especially metacresol) in insulin preparations. We excluded such reactions by testing a range of insulins containing differing excipients (Table 1). Hypurin bovine lente does not include metacresol but the patient also reacted to this preparation. Such testing is important because occasionally an insulin preparation can be identified that does not cause a reaction.1,2

Type 1 allergic reactions mediated by IgE anti-insulin antibodies are the more common form of insulin allergy. Desensitisation may be successful.3 Insulin given IV is less likely to provoke localised reactions due to immune complex deposition4 and can be used to maintain glycaemia. An alternative strategy has been management with insulin pumps (CSII). The slow infusion of smaller volumes of insulin seems beneficial, in both type 15 and type 2 diabetes.6,7 High-affinity IgG antibodies will cause insulin resistance. With low-affinity antibodies, insulin may separate from the antibody complex causing troublesome delayed hypoglycaemia.8 Our patient exhibited the clinical characteristics of the former, predominantly. Polyclonal antibody generation may occur.8 Glucocorticoids may be used to reduce the inflammatory response in the skin but will worsen glycaemic control.9,10 Rituximab is a monoclonal antibody that depletes B cells in bone marrow and other sites, and has been used to reduce auto-antibodies in a number of diseases. Experience in insulin antibody syndromes is very limited although it has been previously used.8 In our patient, depletion of CD19 B-lymphocytes was followed by reductions in insulin antibodies six to 12 months later. The clinical effect of rituximab is often delayed as seen in this case and in other diseases, such as in the treatment of lupus nephritis. Following further immunodepletion with IV immunoglobulin therapy, the anti-insulin IgG level remained low. By 2017, skin reactions had ceased and there were significant insulin dose reductions. It is difficult to be sure what additional effect the IV immunoglobulin had. It was associated with symptomatic improvement, but the IgG insulin antibody level had declined before this. The effects of IV immunoglobulin are usually more short-lived than those of rituximab. Plasmapheresis and mycophenolate mofetil are other treatments which have been used.11,12

Conclusions
Insulin hypersensitivity should be suspected if there is a marked increase in insulin requirement accompanied by evidence of inflammatory cutaneous reactions. Antibodies to insulin rather than to excipients should be sought. Hyposensitisation may be effective for IgE-mediated type 1 reactions. B-cell and antibody depletion should be considered for type 3 hypersensitivity mediated by IgG antibodies according to antibody titres and symptoms. Depending on the antibody affinity for insulin, hypoglycaemia can be problematic but was not a major issue here. The clinical course of insulin antibody mediated disease is variable and spontaneous resolution may occur.

Acknowledgements
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Declaration of interests
There are no conflicts of interest declared.

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References are available online at www.practicaldiabetes.com.
Insulin allergy in type 1 diabetes

References