Insulin antibodies in patients with type 2 diabetic receiving recombinant human insulin injection: A report of 12 cases

Anticorps anti-insuline chez les patients diabétiques de type 2 recevant des injections d’insuline humaine recombinante

Abstract

We report 12 cases of patients with type 2 diabetes receiving recombinant human insulin injection, who had uncontrolled hyperglycemia or frequent episodes of hypoglycemia, high levels of serum insulin and positive insulin antibodies. The clinical characteristics and insulin antibodies pharmacokinetics parameters were analyzed. After administration of glucocorticoids, changing insulin formulations or discontinuing the insulin and switching to oral antidiabetic agents, the level of insulin antibodies decreased and the plasma glucose restored. Thus, we recommend to identify the presence of high insulin antibodies in patients with type 2 diabetes who experience unexplained high plasma glucose or frequent reoccurrence of hypoglycemia.

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Résumé

Nous rapportons 12 cas de diabète de type 2 traités par injection d’insuline recombinante avec un déséquilibre glycémique et de fréquents épisodes d’hypoglycémies associés à des taux circulants élevés d’insuline et à la présence d’anticorps anti-insuline. Le profil clinique des patients et la cinétique des anticorps anti-insuline sont ici rapportés. Après l’administration de glucocorticoides et le changement de type d’insuline ou son arrêt au profit d’hypoglycémiants oraux, les taux circulants d’anticorps anti-insuline ont baissé avec restauration d’un meilleur équilibre glycémique. Nos résultats suggèrent que la présence d’anticorps anti-insuline doit être recherchée en cas de diabète de type 2 déséquilibré avec fréquent épisodes d’hypoglycémies.

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1. Introduction

Insulin antibodies are occasionally produced in diabetic patients treated with exogenous insulin [1]. Although the prevalence of insulin antibodies in exogenous insulin-treated patients have decreased since the wide use of purified and recombinant human insulin preparations [2], it has been reported by Fineberg et al. that insulin antibodies still appear in diabetic patients treated with recombinant human insulin [3], especially in the Oriental region [4,5]. Insulin antibodies may be associated with clinical events such as hypersensitivity reactions, pregnancy, glycemic variability, and metabolic control [3], and mainly with insulin resistance/hyperglycemia [4–8] or hypoglycemia [4,9,10].

Here we report 12 cases of patients with type 2 diabetic receiving long-term recombinant human insulin subcutaneous injection, who had either uncontrolled hyperglycemia or frequent episodes of hypoglycemia, higher levels of serum insulin and positive insulin antibodies. After administration of prednisone, changing insulin formulations or discontinuing the insulin and switching to oral antidiabetic agents, the level of insulin antibodies was decreased and the plasma glucose could be well controlled again.

2. Cases report

Of the 12 patients, 5 were man and 7 were women, with a mean age of 69.1 ± 7.7 years (range 62–80 years). The mean...
Serum Clinical k:

Table 1
Clinical data of the patients with insulin antibodies.

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Age (y)</th>
<th>Duration (y)</th>
<th>Hypoglycemia</th>
<th>HbA1c (%)</th>
<th>Induration and pruritus</th>
<th>Insulin Dosage (unit/d)</th>
<th>Insulin type</th>
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<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>76</td>
<td>11</td>
<td>Y</td>
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<td>Y</td>
<td>28</td>
<td>MPZRHI70/30</td>
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<tr>
<td>2</td>
<td>M</td>
<td>72</td>
<td>15</td>
<td>Y</td>
<td>9.0</td>
<td>Y</td>
<td>34</td>
<td>MPZRHI70/30</td>
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<tr>
<td>3</td>
<td>F</td>
<td>62</td>
<td>13</td>
<td>Y</td>
<td>10.5</td>
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</tr>
<tr>
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<td>M</td>
<td>70</td>
<td>19</td>
<td>Y</td>
<td>9.5</td>
<td>Y</td>
<td>34</td>
<td>IPBHI30R</td>
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<tr>
<td>5</td>
<td>M</td>
<td>67</td>
<td>13</td>
<td>N</td>
<td>9.1</td>
<td>Y</td>
<td>44</td>
<td>MPZRHI70/30</td>
</tr>
<tr>
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<td>F</td>
<td>75</td>
<td>15</td>
<td>N</td>
<td>10.2</td>
<td>Y</td>
<td>53</td>
<td>MPZRHI70/30</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>68</td>
<td>17</td>
<td>N</td>
<td>9.7</td>
<td>Y</td>
<td>70</td>
<td>MPZRHI70/30</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>80</td>
<td>9</td>
<td>N</td>
<td>10.1</td>
<td>N</td>
<td>43</td>
<td>IPBHI + BHII</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>78</td>
<td>27</td>
<td>N</td>
<td>12.2</td>
<td>N</td>
<td>68</td>
<td>IPBHI30R</td>
</tr>
<tr>
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<td>F</td>
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<td>19</td>
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<td>58</td>
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<td>N</td>
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<td>N</td>
<td>66</td>
<td>IPBHI + BHII</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>56</td>
<td>12</td>
<td>N</td>
<td>9.3</td>
<td>Y</td>
<td>52</td>
<td>IPBHI50R</td>
</tr>
</tbody>
</table>

M: Male; F: Female; N: No; Y: Yes; BHII: biosynthetic human insulin injection; IPBHI: isophane protamine biosynthetic human insulin injection; IPBHI30R: isophane protamine biosynthetic human insulin injection (premixed 30R); IPBHI35R: isophane protamine biosynthetic human insulin injection (pre-mixed 50R); MPZRHII70/30: mixed protamine zinc recombinant human insulin injection (70/30).

Table 2
Serum insulin concentrations, levels and pharmacokinetics parameters of the insulin antibodies.

<table>
<thead>
<tr>
<th>No.</th>
<th>Insulin antibody (%)</th>
<th>Total serum insulin (mU/L)</th>
<th>Free serum insulin (mU/L)</th>
<th>Bound serum insulin (mU/L)</th>
<th>High-affinity antibody</th>
<th>Low-affinity antibody</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>k1 (10^-10 M)</td>
<td>b1 (pM)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>b2 (10^-8 M)</td>
</tr>
<tr>
<td>1</td>
<td>38.59</td>
<td>1125.3</td>
<td>199.0</td>
<td>926.3</td>
<td>2.86</td>
<td>58.60</td>
</tr>
<tr>
<td>2</td>
<td>60.80</td>
<td>1848.0</td>
<td>149.8</td>
<td>1708.7</td>
<td>0.85</td>
<td>407.30</td>
</tr>
<tr>
<td>3</td>
<td>60.21</td>
<td>1281.7</td>
<td>15.0</td>
<td>1266.7</td>
<td>3.03</td>
<td>1017.97</td>
</tr>
<tr>
<td>4</td>
<td>56.97</td>
<td>1118.6</td>
<td>52.5</td>
<td>1066.1</td>
<td>1.59</td>
<td>643.59</td>
</tr>
<tr>
<td>5</td>
<td>50.68</td>
<td>1050.7</td>
<td>32.1</td>
<td>1018.6</td>
<td>1.86</td>
<td>417.56</td>
</tr>
<tr>
<td>6</td>
<td>47.06</td>
<td>1085.3</td>
<td>98.9</td>
<td>986.4</td>
<td>4.29</td>
<td>539.87</td>
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<tr>
<td>7</td>
<td>51.74</td>
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<td>47.3</td>
<td>1008.4</td>
<td>1.56</td>
<td>218.41</td>
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<td>8</td>
<td>40.51</td>
<td>1012.3</td>
<td>46.4</td>
<td>965.9</td>
<td>5.08</td>
<td>449.80</td>
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<tr>
<td>9</td>
<td>49.69</td>
<td>1153.3</td>
<td>54.9</td>
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<td>3.70</td>
<td>303.48</td>
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<tr>
<td>10</td>
<td>47.27</td>
<td>1429.8</td>
<td>57.1</td>
<td>1372.7</td>
<td>2.44</td>
<td>352.80</td>
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<tr>
<td>11</td>
<td>31.16</td>
<td>1189.8</td>
<td>71.1</td>
<td>1118.7</td>
<td>1.72</td>
<td>84.66</td>
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<tr>
<td>12</td>
<td>29.48</td>
<td>1575.3</td>
<td>117.0</td>
<td>1458.3</td>
<td>4.84</td>
<td>91.04</td>
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</tbody>
</table>

k: affinity constant; b: binding capacity.

duration of the diabetes was 15.3 ± 4.8 years. All of the patients had not taken any thiol-containing drugs, and their past medical histories were unremarkable. Physical examination upon admission found that the patients were conscious with stable vital signs, and none of them had a history of other agents used or heart, lung, abdominal or other abnormalities, which might affect glycemic control or induce insulin autoimmune syndrome (IAS). Abdominal computerized tomography (CT) or ultrasonography revealed no pancreatic abnormalities. The insulin preparations of the patients used before admission were recombinant human insulin including biosynthetic human insulin injection, isophane protamine biosynthetic human insulin injection, isophane protamine biosynthetic human insulin injection (premixed 30R, premixed 50R) and mixed protamine zinc recombinant human insulin injection (70/30). Four patients (patients No. 1–4) exhibited frequent episodes of hypoglycemia and unstable blood glucose levels, the average dosage of their insulin preparation was 32.0 ± 2.8 U/day; the rest eight patients (patients No. 5–12) had no recurrent hypoglycemia but unexpected

Fig. 1. Representative images of Scatchard plots of insulin antibodies (Case 2). Bound: bound insulin, Free: free insulin.
hyperglycemia, and the average dosage of their insulin preparation was 57.5 ± 10.8 U/day. It was worth noting that 9 of 12 patients showed induration and pruritus at the injection sites. The detail data of patients were shown in Table 1. All the serum samples were insulin antibody positive (47.0 ± 10.4%), because the binding values exceeded 5.0%. The results from radioimmunoassay analysis showed that there were high concentrations of total insulin (1243.8 ± 252.8 mU/L), while free insulin were very low (70.0 ± 49.0 mU/L), suggesting that most of the exogenous insulin was bound to insulin antibodies (1173.8 ± 257.9 mU/L). The accuracy of insulin antibody and serum insulin concentrations was presented in Table 2. To investigate the detailed pharmacokinetics parameters of the insulin antibodies, equilibrium-binding assay was performed and analyzed by Scatchard plots (Table 2). As shown in Fig. 1, the insulin antibodies binding data showed bimodal distributions, suggesting two classes of antibodies characterized by the high-affinity/low-capacity and low-affinity/high-capacity sites. All the patients discontinued recombinant human insulin treatment after admission. As shown in Table 3, three patients were managed by changing to human insulin analogs, three patients were switched to oral antidiabetic agents, five patients were managed by human insulin analogs with oral antidiabetic agents, only one patient were treated by prednisone, and tapered to 5 mg/for 2 months. All the patients were re-evaluated about 8 months later to assess changes in the levels of insulin antibodies. Both the levels of insulin antibodies (15.2 ± 5.6%) and HbA1c (7.0 ± 0.4%) were decreased in all patients.

3. Discussion

Although the wide use of recombinant human insulin has reduced the production of insulin antibodies [1], it was reported that insulin antibodies still appear in about 40% of diabetic patients treated with human insulin [2,11]. In this study, we have described a series of cases and performed further research, which is different from previous individual case report. Exogenous insulin may induce human body to produce insulin antibodies, it may change the insulin pharmacokinetics, leading to glycemic variability, insulin resistance or hypoglycemia and other clinical manifestations [3,12].

Two situations have been involved in insulin antibodies production, one is autoimmune insulin antibodies in patients without previous insulin exposure, which is called IAS, and the other is insulin-induced antibodies in insulin-treated diabetic patients. Unlike our previous reported case of IAS [13], in the present report, these patients produced insulin antibodies without any evidence of autoimmune disease. The mechanisms underlying insulin antibodies production with recombinant human insulin injection are unknown. Factors that can lead patients with type 2 diabetic to produce insulin antibodies include the recipient’s immune response genes, age, the purity, molecular structure, storage condition, formulation of insulin and the sites of insulin delivery [3]. Furthermore, it should be noted that most of our patients did not replace the needles of injection pen as the instruction recommended, and physical examination showed induration and pruritus at the injection sites, so we speculated that insulin antibodies might be associated with repeated use of the same needle. When the needle was reused, it might be contaminated, which became a risk factor causing immune response. Therefore, the method of insulin injection is another factor that may affect insulin antibodies production.

In the present study, the average insulin dosage was high, especially in the patients with hyperglycemia. The possible reason is that most of the exogenous insulin is bound to insulin antibodies and existence of insulin resistance. The relationship between insulin dose requirements and insulin antibodies levels need further study. Insulin antibodies can be divided into two populations: high-affinity/low-capacity and low-affinity/high-capacity [3]. In the present study, the binding affinity and capacity of the insulin antibodies were analyzed by Scatchard plots using the radioligand binding assay, which indicated that both of them were involved. This result is similar to previous research [9,10]. Because of massive volumes of insulin binding to the insulin antibodies, a marked increase in insulin resistance is induced, insulin antibodies could reduce insulin action, thus triggering hyperglycemia (“tampon-like effect”). On the other hand, insulin antibodies could also enhance and prolong the pharmacodynamic action of insulin by serving as a carrier, when massive volumes of insulin become dissociated, free insulin increases all at once, thus leading to hypoglycemia (“reservoir-like effect”) [5,12,13].

It has been reported that metformin combined with α-glucosidase inhibitor can significantly lower plasma insulin antibodies concentrations [4]. In another report, it was noted that insulin lispro reduces insulin antibodies in a patient with type 2 diabetes with immunological insulin resistance [14]. Results from a multinational randomized parallel group clinical trial showed that treatment with glargine in patients previously treated with insulin for at least 1 year did not result in increased insulin antibodies levels [15], which suggested that treatment with glargine was also feasible. In addition, Koyama et al. [9] successfully treated two patients with hypoglycemia and hyperglycemia due to insulin antibodies against therapeutic human insulin using plasmapheresis and prednisolone. Consistent with these previous reports, our treatment indicate that changing insulin formulations, discontinuing the insulin and switching
to oral antidiabetic agents or administration of prednisone can decrease the level of insulin antibodies and restore plasma glucose (Table 3). The exact mechanism of action was unclear, there are several possible explanations:

- oral antidiabetic agents may strengthen the free insulin action, and promote the dissociation of insulin immune complexes;
- insulin analogs are less immunogenic than human insulin;
- glucocorticoids may inhibit insulin antibodies production or promote insulin antibody immune complex dissociation.

However, the results of a recent study by Hattori et al. [16] found that insulin glargine and aspart were more antigenic than other insulin analogs. The reasons for these discordant results are not clear but may be attributed to the different study protocols and the sensitivity of methods for detecting insulin antibodies. The clinical significance of insulin antibodies remains controversial. We were unable to estimate the relationship between insulin antibodies and clinical data in our patients because of the small sample size. Further studies are required to expand the sample size and analyse statistically.

Taken together, although high level of insulin antibodies caused by exogenous human insulin was rare, it affected glycemic control seriously. Thus, when we encounter type 2 diabetic patients receiving long-term recombinant human insulin treatment with unexplained high plasma glucose or frequent reoccurrence of hypoglycemia, we should pay attention to whether they have the presence of high insulin antibodies.

Disclosure of interest

The authors declare that they have no competing interest.


Xiaolei Hu a,b,1
Xiaowen Ma b,1
Xin Wang b
Xiuli Zhao b
Xuling Xu b
Hui Gong a
Fengling Chen b,a
Junjie Sun c

a Department of Endocrinology, The first affiliated hospital of Bengbu medical college, Bengbu, Anhui, China
b Department of Endocrinology, Shanghai 3rd People’s Hospital, School of medicine, Shanghai Jiao Tong University, Shanghai, China
c Department of Nuclear Medicine, Bengbu Medical College, Bengbu, Anhui, China

* Corresponding author.
E-mail address: cfl1993@126.com (F. Chen)

1 These two authors contributed equally to this study.

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Upper gastrointestinal haemorrhage due to a small extra-papillary duodenal neuroendocrine tumour expressing somatostatin

Hémorragie digestive haute compliquant une tumeur neuroendocrine duodénale extra-papillaire de petite taille exprimant la somatostatine

Neuroendocrine tumours (NETs) are rare tumours [1]. Duodenal NETs represent 1 to 3% of gastrointestinal NETs with an increasing incidence from 1.09/100,000 in 1973 to 5.25/100,000 in 2004 [2,3]. Among those, the tumours expressing somatostatin are the second more frequent beside those expressing