Insulin Autoimmune Syndrome in a Health Supplement User: The Effectiveness of Cornstarch Therapy for Treating Hypoglycemia

Arihika Deguchi, Yukiyoshi Okauchi, Setsuyo Suehara and Ikuo Mineo

Abstract

A 70-year-old woman with no history of diabetes was admitted to the hospital for the management of hypoglycemia. Her fasting plasma glucose level was 54 mg/dL with an extremely high serum immunoreactive insulin level (1,210 μU/mL). She had high titers of anti-insulin antibodies and exhibited the DRB1*0406 genotype for HLA-DR4, leading to a diagnosis of insulin autoimmune syndrome. She had been taking several health preparations for approximately 10 years; however, all were thiol group-free. Due to frequent episodes of nocturnal hypoglycemia, the health preparations were discontinued and the patient was treated with cornstarch. This protocol successfully ameliorated the hypoglycemic episodes and normalized the patient’s laboratory and serological test results.

Key words: insulin autoimmune syndrome, hypoglycemia, cornstarch therapy, HLA-DR4, methionine


Introduction

The first case of insulin autoimmune syndrome (IAS) was reported in 1970 by Hirata et al. (1). IAS is characterized clinically by episodes of spontaneous hypoglycemia and pathologically by the presence of large amounts of autoantibodies in the blood bound to insulin despite a lack of any history of use of insulin or oral glucose-lowering agents. However, since the antibodies have only weak affinity for insulin, the antibody-bound insulin readily separates, causing hypoglycemia.

IAS frequently develops in patients taking drugs containing thiol groups such as methimazole, penicillamine, and captopril. In addition, as today’s society becomes increasingly more health-conscious, more people are taking health supplements, with those taking α-lipoic acid-containing supplements increasingly developing IAS (2). α-lipoic acid includes a thiol group, strongly suggesting that this compound is the causative factor of IAS. We encountered an IAS patient who experienced frequent hypoglycemic episodes after long-term use of health supplements. Although the ingredients of these supplements did not contain any thiol groups, one of the metabolites did have a thiol group, suggesting that this metabolite provoked the IAS.

Cornstarch therapy has been reported to be useful in countering hypoglycemia in patients with glycogen storage disease type 1 and those with unstable control of type 1 diabetes (3, 4). We used cornstarch to treat IAS-related hypoglycemia in the present case. To our knowledge, there are no reports in the literature of this type of management. We herein report the first case of IAS in which hypoglycemic attacks were successfully suppressed using cornstarch therapy.

Case Report

The patient was a 70-year-old woman with a history of hypoglycemic attacks. Her family history was negative. Her medical history included acute hepatitis caused by non-B non-C hepatitis virus infection at the age of 55. She had been taking various health supplements (KENBI Family Co. Ltd., Tokyo, Japan) for approximately 10 years. Approximately two years before presentation, the patient started tak-
ing a supplement that contained methionine (70 mg/day); however, she denied taking any medications or health supplements known to contain thiol groups. On day 24 before admission to our hospital, she developed late-night palpitations and sweating. The same symptoms recurred typically at midnight or before dinner, and the patient relieved the symptoms by consuming carbohydrates. On day 21 before admission, she went to the local clinic for consultation, where she was found to have a low fasting plasma glucose (FPG) level of 32 mg/dL. Another test performed the following day showed an abnormally high serum level of immunoreactive insulin (IRI: 4,660 μIU/mL). She was referred and admitted to our hospital for further management of hypoglycemia and hyperinsulinemia. A clinical examination conducted on admission revealed a height of 150 cm, a body weight of 60 kg, a BMI of 26.6 kg/m², a temperature of 36.5 °C, a blood pressure of 144/80 mmHg and a pulse of 70 bpm. The findings of a physical examination were normal.

All health supplements were discontinued after admission to the hospital. On the second day, the patient exhibited fasting hypoglycemia with hyperinsulinemia (FPG: 54 mg/dL, IRI: 1,210 μIU/mL, Table 1). Her serum C-peptide level (CPR) was 5.3 ng/mL, indicating a divergence from the IRI level. High levels of anti-insulin antibodies were detected, with a binding rate of 88.8% and a concentration ≥5,000 nU/mL (5). A 24-hour urine analysis showed a CPR level of 115 μg/day, indicating increased pancreatic secretion of insulin. Serological tests showed the patient to be positive for antinuclear antibodies, anti-thyroglobulin antibodies, anti-TPO antibodies, and negative for anti-GAD antibodies and IA-2 antibodies. A 75 g oral glucose tolerance test indicated a diabetic pattern, with the blood glucose level reaching a peak of 246 mg/dL at two hours and the IRI and CPR levels reaching peaks at three hours. No reactive hypoglycemia was observed during the test over a 4-hour period (Table 2).

An abdominal contrast-enhanced CT scan, that included the pancreas, was negative for any intra-abdominal pathologies. Based on these findings, the patient was diagnosed with IAS. HLA-DR4 genotyping showed the patient to have the DRB1*0406 genotype, which added support to the established diagnosis. We measured the patient’s blood glucose levels every two hours throughout the night on days 4, 5, and 6 using a conventional self-monitoring glucose meter, the Glutest Every (Sanwa Kagaku Kenkyusho Co. Ltd., Nagoya, Japan). At 0AM on day 4, the patient exhibited a

### Table 1. Laboratory Findings

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Blood Count</td>
<td></td>
</tr>
<tr>
<td>WBC</td>
<td>6,300 μL</td>
</tr>
<tr>
<td>RBC</td>
<td>4.47×10³/μL</td>
</tr>
<tr>
<td>Hb</td>
<td>14.5 g/dL</td>
</tr>
<tr>
<td>Ht</td>
<td>43.3%</td>
</tr>
<tr>
<td>PLT</td>
<td>2.51×10³/μL</td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>54 mg/dL</td>
</tr>
<tr>
<td>HbA1c (NGSP)</td>
<td>6.3%</td>
</tr>
<tr>
<td>Glycoalbumin</td>
<td>18.6%</td>
</tr>
<tr>
<td>IRI</td>
<td>1,210 μIU/mL</td>
</tr>
<tr>
<td>Serum CPR</td>
<td>5.3 ng/mL</td>
</tr>
<tr>
<td>24-hr urinary CPR</td>
<td>115 μg/day</td>
</tr>
</tbody>
</table>

### Table 2. Results of the 75 g Oral Glucose Tolerance Test

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>0</th>
<th>30</th>
<th>60</th>
<th>120</th>
<th>180</th>
<th>240</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma glucose (mg/dL)</td>
<td>94</td>
<td>168</td>
<td>237</td>
<td>246</td>
<td>209</td>
<td>118</td>
</tr>
<tr>
<td>Immunoreactive insulin (IRI, μIU/mL)</td>
<td>149</td>
<td>341</td>
<td>499</td>
<td>720</td>
<td>900</td>
<td>633</td>
</tr>
<tr>
<td>Serum C-peptide (CPR, ng/mL)</td>
<td>2.8</td>
<td>6.9</td>
<td>10.2</td>
<td>11.7</td>
<td>13.9</td>
<td>9.5</td>
</tr>
<tr>
<td>IRI/CPR (molar ratio)</td>
<td>0.96</td>
<td>0.90</td>
<td>0.89</td>
<td>1.12</td>
<td>1.17</td>
<td>1.21</td>
</tr>
</tbody>
</table>

blood glucose level of 64 mg/dL without hypoglycemic symptoms, and thus was treated with 10 g of oral glucose. This resulted in a rise in the blood glucose level to 115 mg/dL after 30 minutes; however, the level decreased again to 63 mg/dL at 2AM, indicating temporary recovery from the hypoglycemia. On day 5, the patient started consuming a mixture of 50 g of cornstarch in water before going to bed. All blood glucose levels measured during the night on days 5 and 6 were over 81 mg/dL. The patient was discharged on day 9 with an outpatient treatment plan to continue taking cornstarch to prevent hypoglycemia. Follow-up visits showed a complete disappearance of the hypoglycemic episodes. Five months after discharge, the FPG level, the IRI level and the anti-insulin antibody binding rate were 117 mg/dL, 28.5 μIU/mL and 58.8%, respectively.

Discussion

We made a diagnosis of IAS in this patient based on the following findings: 1) spontaneous hypoglycemia associated with high titers of insulin antibodies, 2) no history of treatment for diabetes, including insulin injection, 3) fasting hypoglycemia and the 4) absence of neoplastic lesions. Previous reports have indicated that HLA class II is involved in the development of IAS in the present case. We also hypothesized that the thiol groups in these agents reduce the disulfide bonds that link chain A and chain B in the insulin molecule and thus expose the self-peptide as an antigen (11), resulting in the production of antibodies against insulin. In the present case, the patient frequently took various types of health supplements, although based on the detailed interview, all supplements were thiol group- and α-lipoic acid-free. However, an examination of the sulfur-containing components of the supplements showed that one of the supplements contained a substantial amount of methionine. Methionine is a hydrophobic essential amino acid that contains a sulfur atom in its side chain. The metabolic pathway from methionine to cysteine is shown in Figure. The metabolite cysteine does have a thiol group, and methionine-derived cysteine may have played a pathogenic role in the development of IAS in the present case.

The clinical course of IAS includes spontaneous remission within three months of discontinuation of the causative drug in approximately 80% or more of patients (12), although some patients do show a refractory course after withdrawal, requiring steroid therapy or plasma exchange, while others can only be treated with a supplementary diet. However, appropriate treatment must be provided to prevent and correct the occurrence of hypoglycemic attacks, which can be serious and lead to accidents or even death. Although some reports have described the usefulness of supplementary diets in improving hypoglycemic symptoms in IAS patients, an improper diet containing monosaccharides may in fact promote hypersecretion of insulin and consequently lead to exacerbation of hypoglycemia. In the present case, despite taking glucose to correct nocturnal hypoglycemia, the patient experienced returns to hypoglycemia during the night.

The patient exhibited a diabetic response on a 75 g oral glucose tolerance test (Table 2). This finding suggests that insulin secreted in response to increased blood glucose levels following the glucose load became bound to antibodies, which consequently impaired its effects, even though an excessive amount of insulin was secreted. Our patient had a high 24-hr urinary CPR level (Table 1), thus suggesting that her pancreatic β-cells may also have been overstimulated following consumption of her daily diet. Frequent consumption of a carbohydrate-rich diet to treat hypoglycemia can also lead to obesity, as occurs in patients with insulinaemia. Therefore, care is needed when formulating the content of a supplementary diet.

Cornstarch is the general name for starch obtained from corn, and is a polysaccharide that is resistant to digestion. Uncooked cornstarch delays absorption and has been used to treat hypoglycemia in patients with glycogen storage disease type 1 (3) and those with type 1 diabetes with unstable glucose control (4). To our knowledge, however, the use of cornstarch to eliminate hypoglycemic attacks in IAS patients has not so far been reported. In the present case, cornstarch therapy was quite beneficial. The effect of cornstarch does not appear to be due to immune mechanisms, but simply to the provision of a sustainable supply of glucose throughout the night.
the night without causing sharp rises in the blood glucose levels (13). This explanation is consistent with the observation in this case that the hypoglycemic episodes resolved on the very night that cornstarch therapy was initiated. We do not deny that discontinuation of the health supplements or spontaneous remission prior to cornstarch therapy may have had a gradual effect on the improvement of hypoglycemia by reducing insulin autoantibodies.

Our study has several limitations. First, we were not able to measure continuous changes in the blood glucose levels throughout the night. Continuous glucose monitoring (CGM), devices developed recently in clinical practice, can detect hypoglycemia that is not noticed by patients. Since CGMs were not available in our hospital, we had to measure the blood glucose levels frequently using conventional methods. Second, we could not determine the presence of a causal relationship between the health supplements and the development of IAS in this patient. Methionine is usually provided in the diet at an approximate dose of 1,200-2,200 mg/day (14). On the other hand, the patient had been taking additional methionine at a dose of 70 mg/day in the form of free amino acids in health supplements. The conversion of methionine into cysteine may be more significantly activated by intake from health supplements than from diet, thus causing IAS via a possible immune mechanism involving thiol groups. However, the details are unclear and further studies are required. Third, we were unable to characterize the kinetic properties of the insulin autoantibodies present in this patient. According to earlier reports, Scatchard analyses have shown that the affinity constants are significantly lower and the binding capacities are significantly larger in antibodies obtained from IAS patients compared to those obtained from insulin-treated diabetics (15).

In conclusion, we presented a case of IAS most likely caused by methionine-containing supplementation, which has never previously been reported to induce the onset of IAS. Cornstarch therapy along with discontinuation of health supplements ameliorated the patient’s symptoms and corrected the laboratory findings, suggesting the potential usefulness of these treatments in the prevention of hypoglycemia in IAS patients.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

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References


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