CASE REPORT

Insulin supersensitivity and normoinsulinaemic hypoglycaemia in uncontrolled type 2 diabetes mellitus: clinical usefulness of 3 h assessment in the 75 g oral glucose tolerance test

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Accepted 10 March 2014

SUMMARY

A 60-year-old man with uncontrolled type 2 diabetes mellitus (DM) (glycated haemoglobin 11%) had the unusual symptoms of palpitations and sweating after drinking an excessive amount of soft drinks. Three-hour data in the 75-g oral glucose tolerance test (75g-OGTT) repeatedly showed normoinsulinaemic hypoglycaemia. His diabetic disorder was based on a delayed insulin secretory response to hyperglycaemia and daily excessive intake of glucose from a high caloric diet and soft drinks. However, we paradoxically observed increased insulin sensitivity evaluated by a hyperinsulinaemic-euglycaemic clamp (glucose infusion rate: 64.83 µmol/kg/min). We considered that insulin supersensitivity might be involved in the pathogenic mechanisms of his clinical normoinsulinaemic hypoglycaemia. He was successfully treated by diet and exercise therapy without any hypoglycaemic medications or insulin. Assessment after the 75g-OGTT is useful for investigating the pathogenesis of DM. Insulin supersensitivity and normoinsulinaemic hypoglycaemia might play a role in clinical manifestation and pathogenesis of type 2 DM.

BACKGROUND

Hypoglycaemia is critically important in diabetes mellitus (DM). The mechanisms of hypoglycaemia should be carefully determined in each case.[1] Insulin resistance plays a crucial role in the pathogenesis of DM but increased insulin sensitivity (insulin supersensitivity) has not been documented in patients with type 2 DM.[2] The clinical role and significance of insulin supersensitivity are uncertain. The 75 g oral glucose tolerance test (75g-OGTT) is clinically useful for diagnosing DM. This test is also useful for evaluating pathogenic disorders in glucose metabolism, including hyperglycaemia and the secretory response of insulin to elevated glucose in a glucose load.[3 4]

CASE PRESENTATION

A 60-year-old man was diagnosed as having type 2 DM with hyperglycaemia by health screening 4 years ago. An oral antidiabetic drug was initially started. He was treated for 2 years and his glycated haemoglobin (HbA1c) dropped below 7.0%. He then decided that his diabetes condition was normal and discontinued medical treatments. After 2 years, during which he habitually drank soft drinks (Coca-Cola, soda pop) in large quantities (more than 2–3 L/day) every day, he noticed weight loss and thirst for 6 months. After drinking a large amount of soft drinks and passing out for 3–4 h, he usually felt palpitations, sweating and started to feel unwell. In this situation, he drank more soft drinks, and then his symptoms gradually disappeared. Recently, he experienced weight loss (−8 kg) in spite of hyperorexia. He was worried about his physical condition and consulted a primary doctor. The doctor diagnosed him with uncontrolled diabetes (HbA1c: 12.4%, postprandial (2 h) glucose level: 26.7 mmol/L) and prescribed an oral hypoglycaemic medicine. However, his uncontrolled diabetes did not improve. Finally, he visited our hospital to have his diabetes examined and treated. At our outpatient department, a 75g-OGTT indicated a high glucose level (14.5 mmol/L) and low insulin level (54.6 pmol/L) at 60 min, and a glucose level of 8.5 mmol/L and insulin level of 137.4 pmol/L at 120 min. This resulted in a pattern of impaired glucose tolerance with a decreased and delayed response of insulin secretion (homeostasis model assessment of insulin resistance: 0.48, homeostasis model assessment-β: 17.5, insulinogenic index: 0.013, Matsuda index: 16.1 and disposition index: 0.21).[4] Three hours after the 75g-OGTT, we observed palpitations and sweating, which he had previously noticed at home, leading to the onset of malaise. At the same time, his blood glucose level was 4 mmol/L (hypoglycaemia) with a low level of insulin (4.8 pmol/L). He was hospitalised in the Diabetes Care Center of Jinnouchi Hospital for close investigation of his pathophysiological condition and for treatment of his diabetes. He did not have diabetic neuropathy, retinopathy or nephropathy. He was not hypertensive. He was a smoker until the last 4 years, and had no cardiovascular disease, family history of DM, dyslipidaemia, liver disease or previous obesity. Other medical history included non-viral acute hepatitis (24 years old), a herniated disk (33 years old), varicose veins of the lower extremities (45 years old), and meniscus surgery for both knees (50 years old). On admission, his DM was poorly controlled with elevated HbA1c (11%) and hyperglycaemia at 2 h after his meal (13.5 mmol/L). A physical examination showed normal results (height: 174.7 cm, body weight: 63.7 kg, body mass index: 20.9) and data from a laboratory analysis were normal (data not shown).

To cite: Sugiyama S, Jinnouchi H, Hieshima K, *et al*. *BMJ Case Rep* Published online: [*please include* Day Month Year] doi:10.1136/bcr-2013-201908

INVESTIGATIONS

Insulin sensitivity was evaluated by a hyperinsulinaemic-euglycaemic clamp examination using artificial pancreas (Nikkiso STG-22; Nikkiso, Tokyo, Japan) after admission.[5] Insulin was given as intravenous loading doses (started from 2.86 pmol/kg/min and gradually decreased to 1.00 pmol/kg/min; desired plasma insulin concentration was 600 pmol/L) over 10 min followed by a continuous infusion at 0.90 pmol/kg/min for 120 min. Plasma glucose concentrations were maintained at 5.6 mmol/L by a variable infusion of 10% glucose. Just after admission, his maximum stable value of glucose infusion rate during the hyperinsulinaemic-euglycaemic clamp was 64.83 μmol/kg/min (11.67 mg/kg/min), indicating extremely elevated insulin sensitivity. Immediately after admission, continuous glucose monitoring showed sustained hyperglycaemia (maximum: 13.7 mmol/L at 1 h) after supper, but there was no hypoglycaemia under the hospitalised diet with adequate calories. His antiglutamic acid decarboxylase antibody level was less than 1.5×10^3 U/L (negative) and his daily urinary C-peptide level as a measurement of insulin secretion was 17.2 nmol/day on the second day of admission and 23.9 nmol/day before discharge. Blood hormonal levels of the thyroid and adrenal glands were within normal limits. In a 75g-OGTT before discharge, his glucose metabolism condition improved to a normal glucose tolerance pattern (glucose was 9.9 mmol/L and insulin was 72.6 pmol/L at 60 min; glucose was 7 mmol/L, and insulin was 86.4 pmol/L at 120 min), but a hypoglycaemic attack with a normal blood level of insulin (glucose: 2.3 mmol/L, insulin: 16.8 pmol/L) was reproduced 3 h later in the 75g-OGTT (homeostasis model assessment of insulin resistance: 0.52, Matsuda index: 18.47). Therefore, this suggested that his state of insulin supersensitivity was still present. Before discharge, diurnal blood glucose changes were normalised by only diet and exercise therapy during the 3 weeks of hospitalisation (blood glucose profile: before breakfast, 5.4 mmol/L; post-2 h breakfast, 6.5 mmol/L; before lunch, 5.4 mmol/L; 2 h after lunch, 6.4 mmol/L; before supper, 6.6 mmol/L, 2 h after supper, 7.7 mmol/L).

DIFFERENTIAL DIAGNOSIS

Diabetes and reactive hypoglycaemia due to dumping syndrome are clinically well known after gastric surgery. However, our patient had no history of abdominal surgery, and endoscopic examinations demonstrated normal findings in his stomach and colon. The presence of insulinoma and malignant diseases can cause hypoglycaemia and weight loss, but his plasma insulin levels during hypoglycaemia were low. In addition, head, chest and abdominal CT did not show the presence of tumours.

TREATMENT

After hospitalisation, we prohibited the patient from drinking any soft drinks. We conducted dietary counselling, which provided sufficient calories for his diabetes treatment with 8374 kJ/day (126 kJ/kg; protein, 1.2 g/kg; NaCl, 7 g) and he was only provided with hospital food. We also prescribed exercise therapy, which was performed by using treadmills and bicycle ergometors at the exercise room in our hospital and walking around the hospital. Exercise trainers gave instructions regarding moderate-intensity physical exercise therapy in each 30 min session. Exercise intensity was determined by the Borg scale (Borg scale: 11 to 13). At least 30 min of exercise was recommended every day. After the results of continuous glucose monitoring, we recommended that the patient perform an additional session of exercise therapy after supper. After the additional session of evening exercise, his blood glucose levels 2 h after supper were decreased to 7.7 mmol/L. He was treated by diet therapy (8374 kJ/day) and exercise therapy twice a day without any oral hypoglycaemic medicines for 3 weeks in the hospital. We gave him instructions for self-monitoring of blood glucose. He was discharged with recommended diet and exercise therapy, and was followed-up monthly at the outpatient department of our hospital.

OUTCOME AND FOLLOW-UP

After discharge, the patient was well and his blood glucose levels were well maintained. He continued the diet and exercise therapy at home. He did not experience any hypoglycaemic attacks and symptoms. After outpatient treatment, we found a decrease in HbA1c by 2.6% and a recovery of body weight (61.7 kg to 64.2 kg) at the 1-month follow-up. His data of self-monitoring of blood glucose demonstrated well-controlled post-supper glucose levels at 5–9.7 mmol/L (mean: 7.5 mmol/L).

DISCUSSION

For the first time, we have clearly demonstrated the presence of insulin supersensitivity by the hyperinsulinaemic-euglycaemic clamp, with an extremely high glucose infusion rate in a patient with type 2 DM. In type 2 DM, the presence of insulin resistance and a decrease in insulin sensitivity are frequently found, and they have been extensively investigated.[2] Oral hypoglycaemic medication for improving insulin sensitivity, biguanide, has been proposed as the first-line treatment for type 2 DM.[6] However, there are no reports on the presence of insulin supersensitivity in type 2 DM, and the clinical significance of elevated insulin sensitivity has not been clarified. In our patient, when his homeostasis model assessment of insulin resistance was extremely low in the uncontrolled diabetic condition, he had a hypoglycaemic attack with a normal insulin blood level at 3 h in the 75g-OGTT. Even though his insulin sensitivity was not impaired and his insulin secretory capability was maintained, he developed type 2 DM. In Japan, many type 2 DM patients have an underlying pathogenic condition with a decreased or delayed insulin secretory response to hyperglycaemia after a meal, termed 'β-cell dysfunction.'[7] There might be a compensatory biological response enhancing insulin sensitivity to maintain glucose metabolism against blunted insulin secretion in the hyperglycaemic state.[8]

Insulin binding to insulin receptors evokes intracellular signalling cascades. Blood glucose is then incorporated into cells through glucose transporter-4, resulting in lower blood glucose levels. The insulin–insulin receptor signalling system is tightly regulated by various inhibitory regulatory factors.[9] The tumour suppressor phosphatase and tensin homologue (PTEN) has an inhibitory effect on insulin signalled by its phosphatase activity. A recent report showed a functional defect of PTEN by gene mutation of PTEN, which is involved in the clinical manifestation of enhanced insulin sensitivity and obesity.[10] However, our patient presented with only insulin supersensitivity, but not obesity, suggesting PTEN abnormality was unlikely. Pathophysiological actions exercise AMP-activated protein kinase activation, peroxisome proliferator activated receptor-γ activation and adiponectin can enhance insulin sensitivity.[11–14] However, the detailed molecular mechanism of insulin supersensitivity in the present case remains undetermined. In addition, details of the pathological and clinical conditions of insulin supersensitivity in type 2 DM are unknown. Further examinations are required for examining the frequency, mechanisms and pathological role of insulin supersensitivity in type 2 DM.

We repeatedly found the onset of hypoglycaemia with normal to low insulin levels at 3 h after the 75g-OGTT in our case. Hypoglycaemia found in the present case could be pathogenically classified as postglucose load reactive hypoglycaemia. A role for an exaggerated insulin secretory response is usually the major cause of reactive hypoglycaemia,[15] but we did not observe any higher levels of insulin in this case. The detailed mechanisms of normoinsulinaemic hypoglycaemia are still uncertain. Our patient had no liver disease or renal disease, and it is possible that unexpected glucose-lowering effects due to insulin supersensitivity could be involved in this phenomenon. We did not measure blood catecholamine levels, plasma glucagon levels, incretin levels or the response of glucagon secretion during the OGTT. The patient's clinical manifestation of a hypoglycaemic attack associated with palpitations and sweating after excessive intake of soft drinks could be based on his insulin supersensitivity with the presence of a sympathetic counter-regulatory response. In the practical situation, hypoglycaemia with insulin supersensitivity might increase activation of sympathetic nerves and enhance the coagulation cascade, potentially leading to vascular dysfunction and an adverse cardiovascular outcome in patients with type 2 DM. Postprandial hyperglycaemia identified by transient hyperglycaemia in the 75g-OGTT causes a higher mortality. However, it is possible that insulin supersensitivity-related reactive hypoglycaemia after transient hyperglycaemia, such as in our case, could contribute to increased mortality and cardiovascular events.

There are many patients with poorly controlled type 2 DM attributable to soft drink polyposia and excessive caloric intake with a high caloric diet.[16] We demonstrated that good glucose control was effectively achievable by taking a diet with an appropriate amount of calories and exercise therapy during 3 weeks hospitalisation in our case. Performing adequate dietary therapy for outpatients at home is difficult, even if sufficient instructions are given for a diet in the outpatient department. In our case, good glucose control was finally achievable without any oral hypoglycaemic medications or insulin use. This is because we correctly determined the patient's diabetic pathogenesis, and provided sufficient explanation of his disease pathogenesis, education and treatment in hospital by exercise therapy and a diet with reasonable calories, while prohibiting soft drink intake during hospitalisation. Because of the presence of insulin supersensitivity in our case, we did not treat him with biguanide. By thorough management under a hospitalised environment and education, diet and exercise therapy were shown to be effective, and these effects continued in the outpatient's follow-up.

Hypoglycaemia can occur in uncontrolled type 2 DM patients who have insulin supersensitivity. There is the unusual possibility that a patient can present with hypoglycaemia caused by hyperglycaemia and a delayed insulin secretory response with insulin supersensitivity. We experienced a type 2 DM patient with insulin supersensitivity and normoinsulinaemic hypoglycaemia. This pathogenesis needs to be recognised and understood, and clinical attention is necessary for achieving optimal therapy for type 2 DM.

Learning points

- We experienced an unusual type 2 diabetes mellitus (DM) case with increased insulin sensitivity.
- Three-hour assessment during the 75 g oral glucose tolerance test is clinically useful for evaluating the possible occurrence of reactive hypoglycaemia and to examine the pathogenesis of DM.
- Insulin supersensitivity can paradoxically be present in type 2 DM, and it might cause reactive hypoglycaemia with normal or low plasma insulin levels.
- Normoinsulinaemic hypoglycaemia and insulin supersensitivity might play a role in the clinical manifestation and pathogenesis of type 2 DM.

Acknowledgements The authors thank Dr Keizo Kajiwara and Dr Fumio Miyamoto for their helpful discussion. The authors thank Takashi Umabayashi for his skilful technical assistance.

Contributors SS and HJ equally contributed to this report.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed

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Findings that shed new light on the possible pathogenesis of a disease or an adverse effect