Recurrent Hypoglycemia in Pancreatic-Type Diabetes Mellitus and Grave Disease Patient

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INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic disorders, which is characterized by hyperglycemia. Based on etiology, there are some factors that may cause hyperglycemia i.e. lack of insulin secretion, reduced glucose-uptake, and increased glucose production. In 2001, an epidemiology study of 724 young-aged diabetes mellitus patients in India indicated that the prevalence of Fibrocalculous Pancreatic Diabetes (FCPD) was 11.04% of all diabetes mellitus patients who were less than 40 years old. FCPD is usually found in developing countries because it is related to malnutrition (protein energy deficiency). Genetic factors and cyanogenic glycosides of cassava may cause FCPD.

Ketoacidosis rarely appears in FCPD patients because they still have remaining functional β-pancreatic cells, low glucagons reserves, and decreasing body fat mass. Insulin is needed merely to control the blood glucose. The daily dose of insulin needed is approximately 40 ± 12 units. Most of FCPD patients are sensitive to insulin, therefore hypoglycemia usually occurs.

One of acute complications in diabetes mellitus is hypoglycemia. Glucose is the main energy supply for cerebral metabolism. The brain preserves glucose in the form of glucagons less than several minutes. Cerebral glucose supply depends on circulating blood glucose supply. Hypoglycemia may cause brain damage therefore it should be avoided.

Graves disease, which is found in 60-80% patients with thyrotoxicosis, usually occurs in 20-50 years of age. On physical examination, we discover hyperthyroid signs, ophthalmopathy, dermatopathy, and pre-tibial mix edema. In addition, we may also discover a diffuse and elastic enlargement of thyroid gland and may be a bruit, which indicates increased thyroid vascularization. On laboratory examination, we find high free T4 (fT4) level, low thyroid stimulatin hormone (TSH) level and positive antibody against TSH receptor.

There are three alternatives management in Graves disease, i.e.: anti-thyroid drugs, subtotal thyroidectomy, and radioactive iodium (RAI). For the young-aged Grave disease patients, the drug of choice is anti-thyroid drugs. If it is recurrent, we use surgery or RAI. While for old-aged patients, the drug of choice is RAI.

Anti-thyroid drug used in Graves disease is metimazole or propilthiouracyl. We prefer propilthiouracyl to metimazole for thyroid crisis because of rapid onset and its additional effect, i.e. inhibition of T4 to T3 conversion in peripheral tissues. Initially, a high-dose anti-thyroid drug is given until clinical or biochemical improvement is achieved. After that, the dose is reduced gradually to reach the maintenance dose and it is maintained for 12-18 months.

We discuss a diabetes mellitus patient who has been diagnosed since she was 22 years old. In addition, we also discover the signs and symptoms suggesting the presence of Graves disease. This case illustration describes two diseases which render the control of blood glucose level.

CASE ILUSTRATION

Mrs. S, 27 years old, Javanese, was admitted to emergency room (ER) of Cipto Mangunkusumo Hospital on 12 August 2004, with main symptom of unconsciousness since 2 hours before admission. Two weeks before admission, the patient felt weak; had palpitation, vomiting and high fever, therefore she did not receive the insulin. Because of higher fever, she was admitted to the ER of Cipto Mangunkusumo Hospital and was diagnosed as diabetic ketoacidosis and thyroid crisis. She was hospitalized for 2 weeks.
After that, she was getting better and she was sent home with regular insulin (Actrapid®) 3 x 15 U, intermediate-acting insulin zincum (Monotard®) 1 x 6 U at night, propilthiouracyl 3 x 200 mg, propanolol 2 x 10 mg. The patient was scheduled for control at metabolic endocrinology outpatient clinic in Cipto Mangunkusumo Hospital three days later, but she never came back.

Two days before admission, she was unconscious and had tonic-clonic seizure, fell down in the bathroom. She was conscious again and felt better after sweet-tea beverages. After that, she could eat a small portion and still continue an appropriate dose of insulin.

Three hours before admission, she felt weak again, lay down on bed and did not eat anything. Two hours before admission, her family found her unconscious, and directly bring her to Cipto Mangunkusumo Hospital. On the way to the Hospital, she had tonic clonic seizure again.

Her past medical history reveals that since 4 years before, she frequently felt hungry, thirsty, and frequently urinated. In addition, she also frequently felt pounded heart, unable to bear hot weather, sweating, good appetite but had weight loss.

At that time, she was hospitalized because of diabetic ketoacidosis, which was induced by urinary tract infection. She had regular control to metabolic endocrinology outpatient clinic in Cipto Mangunkusumo Hospital for only two years after the first hospitalization. There was free-insulin injection program for the poor diabetic patients at the clinic. After the program had been eliminated, she rarely came for control again.

According to confession of her father, she still had insulin injection before having meal in the period of 2000-2004, but the doses were inappropriate, she changed the dose by herself. Consequently, she was sent to the ER of Cipto Mangunkusumo Hospital for several times because of hypoglycemia. However, after being injected by 40% dextrose at the ER of Cipto Mangunkusumo Hospital, she always gets conscious again.

In the family history, no family member who had diabetes mellitus nor hyperthyroid. The patient is a housewife, has two children under five years old, and her husband works as cleaning service officer in an apartment. Half of the medical fund was supported by the government social insurance.

The physical examination at the ER of Cipto Mangunkusumo Hospital revealed: her general condition was soporous, severely ill, BP 90/50 mmHg, RR 26 x/minute, and pulse rate: 90 x/minute, temperature 37 °C, body height 147 cm, body weight 45 kg. No pallor in her conjunctiva, no jaundice on sclera, and there was exophthalmia. The jugular vein pressure was 5-2 cm H₂O and there was enlargement of thyroid gland by palpation, diffuse, elastic, smooth surface, no tenderness, and no bruit. Heart and lung examination revealed normal result. Abdominal examination revealed, no distention, no hepatomegaly or splenomegaly, and normal intestinal sound. The extremities were warm, no edema, and the pulsation of artery dorsalis pedis were: + normal / + normal. In pre-sacral area, we found an ulcer of 1 x 2 cm; the base was connective tissue, no pus or necrotic tissue.

The laboratory result indicated Hb 10.5 g/dL, leukocytes 8000/mm³, platelet 266,000/mm³, ureum 10 mg/dL, creatinine 0.6 mg/dL, Sodium ion 138 mmol/L, Potassium ion 3,7 mmol/L, blood glucose at that time 8 mg/dL, blood acetone (-). The blood gas analysis indicated a simple metabolic alkalosis. Infusion of NaCl 0.9% 1000 ml and 150 ml 40% dextrose were immediately administered.

One hour after administration of 150 ml 40% dextrose, the patient was still unconscious. The problem list was established as follows: unconsciousness due to hypoglycemia, type 1 diabetes mellitus, seizure observation, Graves disease, decubitus ulcer. After that, 50 ml of 40% dextrose was administered again, continued by infusion of 10% dextrose per 6 hours, a naso gastric tube (NGT) was inserted and oxygen was given at 3 lt/min, propanolol was stopped, propilthiouracyl 3 x 200 mg was continued. The neurology consultation, result was: general seizure and unconsciousness might be caused by metabolic disorder, and there was no focal neurology deficit at that time.

Then, the blood glucose level increased up to 519; therefore the infusion was substituted by regular insulin (Actrapid®) drip 1 U per hour in NaCl 0.9%. After that,
the blood glucose level decreased to 55 mg/dL, therefore we gave 100 ml of 40% dextrose and the infusion was changed to 10% dextrose per 6 hours. After the blood glucose was relatively stable above the level 200 mg/dL, the patient was sent to the ward. The therapy in the ward were: ceftriaxone 1 x 2 gram iv, ranitidine 2 x 1 ampol iv, propanolol 3 x 10 mg, propilthiouracyl 3 x 200 mg, sukralfat 4 x 1 table spoon.

At the ward, a liquid diet 4 x 250 ml was given, as well as NaCl 0.9% infusion per 6 hours and sliding scale insulin per 6 hours. Every time she had high blood glucose level 20 U regular insulin was administered, then her blood glucose level 6 hours later turned to a very low level. Therefore, we gave her infusion of D10% per 8 hours.

On the 4th day of hospitalization, the patient’s consciousness was changed from soporous to somnolent. The diet was still 4 x 250 ml milk through the NGT, she still had infusion of NaCl 0.9% per 8 hours and high sliding scale insulin per 6 hours. Because the patient still had hypoglycemia after regular sliding scale insulin, we gave her high sliding scale insulin. The regimen of this high sliding scale insulin was regular insulin 5 U for the blood glucose level of 250-300 mg/dL, 10 U for 300-350 mg/dL, and 15 U for >350 mg/dL. Nevertheless, the patient was still in hypoglycemia state. Six hours after administration of 15 unit regular insulin, the patient's blood glucose level decreased to 60 mg/dl.

On the 6th day of care, the patient’s consciousness was still somnolent. We gave her regular insulin drip 0.5 U/hours in NaCl 0.9%. In addition, we also gave her fixed-dose regular insulin 3 x 8 U sub-cutaneously and we suggest the examination of blood glucose level for every 6 hours, i.e. on 6.00 a.m, 12.00 p.m, 6.00 p.m and 12.00 a.m. However, the patient’s blood glucose level was still fluctuating.

On the 8th day of care, the patient’s consciousness changed to apathetic. She was confused, unable to remember what had happened, and slowly responded. Repeated neurologic consultations indicated that there was still no focal neurologic deficit. Liquid diet of 4 x 350 ml was still given. Propanolol was stopped because we assumed that the hypoglycemia might be induced by the administration of adrenergic β-blocker. Insulin drip was dyscontinued, and blood glucose examination was done for every 6 hour. If the blood glucose was more than 200 mg/dL, then an extra regular insulin of 8 U was given. Infusion of NaCl 0.9% and dextrose 5% were given by turns. By this way, only fixed-dosed short acting insulin of 4 x 5 U was administered.

On the 10th day of care, the patient was still apathetic and weak. Even when the propanolol has been stopped, there was no tachycardia. Therefore, we assumed that the hyperthyroid had been controlled in this patient, and the dose of propilthiouracyl was decreased to 3 x 100 mg.

On the 11th day of care, the patient was getting better. She became fully alert. Though she felt weak she was able to eat a little amount of porridge. The milk was still given 4 x 350 cc consistent with the administration timing for regular insulin 4 x 5 U.

On the 13th day of care, the patient could eat much more porridge. The milk was still given every 6 hour. The dose of regular insulin 4 x 5 U was still continued. We suspected pancreatic type diabetes mellitus, especially after we found a fibro calcification pancreas in abdominal USG in 2000, there was no history of diabetic ketoacidosis in the period of 2000-2004 though the patient did not inject insulin regularly. Therefore, we suggested the examination of ICA (Islet Cell Antibody) and fasting C-peptide level. In order to control the patient’s blood glucose level, we suggested glargin insulin (Lantus®) 1 x 10 U every morning (6.00 a.m) as well as regular insulin 4 x 5 U. That suggestion was implemented on the next day.

On the 14th day of care, fasting C-peptide examination was done. (ICA was not done because of financial problem). The patient’s condition was much better. She could eat porridge by herself, therefore the infusion was stopped. The diet was changed to soft diet 1700 calories, plus 2 x 25 grams milk. Combined therapy of regular and glargin insulin were started. The fasting blood glucose level was 156 mg/dL and 2 hours post-prandial blood glucose level was 124 mg/dL. This combination was assumed adequate enough to control the patient’s blood glucose level.

On the 16th day of care, the patient was able to sit and stand, finished her porridge, although she still felt rather weak. Because at that time the hyperthyroid signs were not clear and she had taken propilthiouracyl for 1 month, we expected a decrease value of fT4 level. Therefore, repeated fT4 examination was done.

On the 18th day of care, she was able to walk to the bathroom and able to finished her meal. The fT4 level was 0.370 ng/dL (the fT4 level a month before was 4.33 ng/dL), so that the propilthiouracyl dose was decreased to 3 x 50 mg. The fasting C peptide level at that time was < 0.5 ng/mL, lower than the C-peptide level when she was hospitalized at Cipto Mangunkusumo Hospital in the year of 2000, i.e. 1.2 ng/mL (normal : 0.5 – 2 ng/mL).
The patient was sent home on the 19th day of care in a good condition, with the following therapy:

- Diabetes mellitus diet 2100 calories
- Regular insulin (Actrapid®) 4 x 5 U sub cutaneously (6 a.m., 12 p.m., 6 p.m. and 12 a.m.)
- Glargin insulin (Lantus®) 1 x 10 U on 6 a.m.
- Propilthiouracyl 3 x 50 mg
- Education for the patient including: explanation about her disease, the importance of regular control to the metabolic endocrinology outpatient clinic, the signs of hypoglycemia and its management, diet, and motivation to enhance her compliance.

DISCUSSION

The diagnosis of diabetes mellitus in this patient is based on illness history including 3P symptoms (polyuria, polydipsi and polyphagia), loss of weight, and blood glucose level above 200 mg/dL of more than one examination. In this patient, we did not think about type 2 diabetes mellitus because the fasting C peptide level was very low. This indicated an absolute insulin deficiency as found in FCPD or type 1 diabetes mellitus.

Type 1 diabetes mellitus usually occur in adolescence, characterized by the tendency of diabetic ketoacidosis because of absolute insulin deficiency. Type 1 diabetes mellitus can be categorized into type 1 A and 1 B. Pathogenesis of type 1 A diabetes mellitus is related to autoimmune destruction of pancreas β-cell. While the etiology of insulin deficiency in type 1 B diabetes mellitus, which usually occurs in the Asians is uncertain. In type 1 diabetes mellitus patient, we could find another autoimmune disease such as Graves disease.

Type 1 diabetes mellitus can still be considered because she had diabetic ketoacidosis and there was co morbidity with Graves disease. We need ICA examination for confirmation. If ICA is found in this patient, then she has type 1 A diabetes mellitus. But if ICA is not found, there are two possibilities: this patient has type 1 B diabetes mellitus or other type of diabetes mellitus (non-type 1 diabetes mellitus). Because of financial problem, ICA examination was not done in this patient.

This patient had more than one hypoglycemia episodes. We could consider the possibilities of autonomic nerve neuropathy, slower adrenergic response against hypoglycemia due to severe hypoglycemia or propanolol. Seeing that the patient did not feel any typical sign or symptom of hypoglycemia, she did not realize the importance of drinking sweet tea. Consequently, the hypoglycemia became worse and she had tonic-clonic seizure.

Because the brain metabolism fully depends on circulating blood glucose supply, hypoglycemia may disturb cognition process. This has been proven in some studies. Decreased cognitive functions are apparent in diabetes mellitus patients who had recurrent hypoglycemia episodes.

In this patient, the recovery of consciousness was relatively slow. This might be due to the lack of oxygen in the patient’s brain during the seizure because of hypoglycemia and consequently hypoxic encephalopathy occured. After she was conscious, she had amnesia and slow cognition process. This patient likely had mild cognitive dysfunction due to recurrent hypoglycemia episode.

Grave disease is an autoimmune disease, characterized by positive antibody against TSH receptor. Most of the patients had typical characteristic such as the signs and symptoms of hyperthyroid, exophthalmia, and diffuse enlargement of thyroid gland. Diagnostic confirmation for Graves disease includes increased fT4 level and decreased TSH level. In
hesitant case, thyroid scan examination can be done to differ Graves disease with thyroiditis.8

The diagnosis of Graves disease in this patient is based on history, physical and laboratory examination on her first hospitalization. On history, we found hyperthyroid signs (trembling, sweating, unable to bear hot condition, heart pounding, increased appetite and loss of weight). While on physical examination we found exophthalmia, mild tremor, palpitation, damp skin and sweating, diffuse enlargement of thyroid gland. The laboratory result revealed increased fT4 level (13.4 ng/dL and 4.33 ng/dL) and decreased TSH (0.003 uIU/mL).

In Graves disease patients, there are increased thyroid hormone level and decreased TSH level. Increased thyroid hormone level may enhance glucose absorption in the intestine, increase glucose production in the liver and decrease insulin sensitivity in peripheral tissue. Hyperthyroid patients with diabetes mellitus, who were given insulin therapy needed high dose insulin, because the insulin degradation increased.13

Hypoglycemia in the patients with absolute insulin deficiency usually due to:14

• Excessive insulin dose, wrong timing, or wrong type of insulin
• Decreased exogenous glucose intake at night
• Excessive insulin utilization, such as on exercise
• Decreased endogenous glucose production, usually after alcohol intake
• Increased insulin sensitivity, such as in hypopituitary disorder or adrenocortical insufficiency
• Decreased insulin clearance, such as in renal failure

In this patient, we found recurrent hypoglycemia. There are some possible explanations about it, i.e.:

Inadequate Food Intake
After being discharged from hospital at the end of July 2004, the patient felt very weak (it may because her condition changed to hypothyroid due to propitbiouracyl) so that the patient always slept and skipped her meal.

Inadequate Dose, Type and Timing of Insulin Administration
When she went home from the last hospitalization, she got the following therapy: regular insulin (Actrapid®) 3 x 15 U and zincum middle-acting insulin (Monotard®), given at night before asleep.

As known, Monotard is a middle-acting insulin which has maximal effect in 4 – 12 hours.2 Because Monotard is injected before night sleep (10.00 p.m.), the possibilities of hypoglycemia before dawn is quite high, and the patient frequently forgets to drink milk before sleeping. Consequently, hypoglycemia occurs.

The Hyperthyroidism Effect
When she was hospitalized at the end of July 2004, the patient came in hyperthyroid state, which may cause increased blood glucose production. Consequently, she needed high-dose insulin.

When she went home, may be the hyperthyroidism has been controlled, but the dose of injected insulin was still high. Therefore hypoglycemia occurred.

The Propanolol Effect
At home, the patient had propanolol therapy in order to manage palpitation caused by hyperthyroidism. Propanolol is an adrenergic β-blocker drug. The body responds to hypoglycemia, and there is an activation of adrenergic hormone to increase the production of blood glucose. In the patient who had adrenergic β-blocker drug, this mechanism did not occur. Consequently, the patient was still in hypoglycemia state.

CONCLUSION
In order to prevent recurrent hypoglycemia, the following actions should be done: 1) Patient’s knowledge about the dangerous, signs and symptoms of hypoglycemia and appropriate diet. We suggest complete meal for the patient (rice + fish/meat = 2100 calorie) for 3 times daily, plus milk on 12.00 p.m. and 6 a.m., 2) Monotard is substituted by glargin insulin, which does not have peak effect and administered in the morning at 6 a.m., 3) Reevaluation of fT4 level in order to evaluate the patient’s thyroid status. Apparently, the fT4 level has been decreased and the dose of propitbiouracyl is decreased 3 x 50 mg, 4) Propanolol is stopped, 5) Instruction and motivation for the patient that it is necessary to have regular control to outpatient clinic of metabolic endocrinology at Cipto Mangunkusumo Hospital, and emphasizes the importance of good compliance.

REFERENCES