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### Type 1 Diabetes Mellitus Comorbid with Malnutrition in Siblings

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#### ABSTRACT

**Background:** Diabetes mellitus is a disorder of the metabolic homeostasis controlled by insulin, resulting in abnormalities of carbohydrate and lipid metabolism. Type 1 diabetes mellitus is one of the most common chronic conditions in children. This study aims to describe two cases of type 1 diabetes mellitus accompanied by malnutrition in children at Dr. M. Djamil General Hospital Padang. **Case presentation:** The case series describes two cases of diabetes mellitus type one with comorbid undernutrition. Both patients had a family history of diabetes mellitus. And their sibling died because of diabetes type 1. Grandmother and grandfather from the father's side had diabetes. The management of this disease consists of the management of type 1 diabetes mellitus and its complications and accompanying malnutrition. **Conclusion:** The management of type 1 diabetes mellitus includes the administration of insulin according to the monitoring of blood sugar levels and the management of comorbid diseases that accompany it. Education about the use of insulin and diabetes diet patterns is very important for parents and children with type 1 diabetes mellitus.

#### 1. Introduction

Diabetes mellitus is a disorder of the metabolic homeostasis controlled by insulin, resulting in abnormalities of carbohydrate and lipid metabolism. Type 1 diabetes mellitus is one of the most common chronic conditions in children. The global incidence of type 1 diabetes is increasing worldwide, at an annual rate of 3-5%, particularly in children under the age of 5 years, and this trend leads to a significant health burden. Recent studies have shown that in European countries, childhood-onset T1D is associated with three to four-fold increased mortality when compared with the general population. Similar data emerged from a long-term study of a young cohort with T1D in the USA, where mortality was 7 times higher than in

the non-diabetic population.<sup>1,2</sup>

The etiology of diabetes involves complex genetic and environmental factors. A large number of epidemiological studies have indicated that a family history of diabetes, advanced age, obesity, physical inactivity, and abnormal lipid metabolism are independent risk factors for diabetes. Patients with a positive family history of diabetes experience a 3 to 4-fold higher risk of developing this disease than those with a negative family history of diabetes. The risk of diabetes increases with the number of affected relatives.<sup>3</sup> While the risk of type 1 diabetes in non-identical twins is similar to that of siblings. It exceeds 70% in identical twins with long-term follow-up.

Additional evidence for the contribution of genetic factors to the etiology of T1D is the occurrence of autoimmune diabetes in association with genetic mutations affecting key genes with immune function.<sup>4</sup>

Diabetic ketoacidosis (DKA) occurs in 10 to 70% of children with T1D, can occur with both types 1 and 2 diabetes mellitus, and has a significant risk of mortality, mostly due to cerebral edema.<sup>5,6</sup> Other potential complications of DKA include hypokalemia, hypophosphatemia, hypoglycemia, intracerebral and peripheral venous thrombosis, mucormycosis, rhabdomyolysis, acute pancreatitis, acute renal failure (ARF) and sepsis.<sup>7</sup> The development of ARF is a rare but potentially lethal disorder in children with DKA, with an estimated mortality of about 50%. The poor outcome of ARF associated with DKA underlines the importance of early recognition of ARF and early initiation of renal replacement therapy.<sup>8</sup> Unlike the adult population, pediatric mortality is mainly due to the development of cerebral edema. This study aims to describe two cases of type 1 diabetes mellitus in children at Dr. M. Djamil General Hospital Padang.

## 2. Case Presentation

This study reported two cases of type 1 diabetes mellitus in siblings of a family.

### Case 1

A 14 years old girl came to Dr. M. Djamil General Hospital as a referral patient from a regional hospital. Initial complaints of patients in the form of easy thirst, increased frequency of urination, and easy hunger since 1 month ago. Previous blood sugar checks at the public health center and regional hospitals showed an increase in blood sugar levels at any time. The patient's brother also had type 1 diabetes mellitus and had died of uncontrolled diabetes mellitus. The patient's grandparents also had diabetes mellitus and were not well controlled.

Physical examination showed that his general condition was moderate, blood pressure was 110/65 mmHg, heart rate was 88 beats/minute, and body temperature was 37.1°C. There was no pale, edema, jaundice, or cyanotic. Her weight was 24 kg, height

was 144 cm, and body mass index showed malnutrition. There were no abnormalities on regional physical examination of the chest and abdomen. Extremities were warm, and capillary refilling time was less than 2 seconds. Physiological reflexes were found to be normal, and the pubertal status was A1M3P1.

Laboratory examination showed hemoglobin 12.6 g/dl, leukocytes 8310/mm<sup>3</sup>, platelets 414,000/mm<sup>3</sup>, hematocrit 37%, differential count 0/1/1/59/34/5, current blood sugar level 641 mg/dl, calcium 10.5 mg/dl, Sodium 135 mmol/L, potassium: 4.4 mmol/L, chloride: 101 mmol/L, urine ketones (+2), blood gas analysis showed metabolic acidosis. This patient was diagnosed with diabetic ketoacidosis et causa suspect diabetes mellitus type 1 accompanied by malnutrition (marasmus type V).

Management of the patient consisted of management of diabetic ketoacidosis and malnutrition. Management of diabetic ketoacidosis in the form of patients asked to fast and insulin drip 0.05 IU/kg BW/hour, ketone levels in urine were monitored every 2 hours, and blood glucose levels were evaluated every hour. Management of malnutrition in the form of high-calorie nutrition to reach the ideal weight according to age.

On the first day of treatment, the patient started fasting and closely monitored blood glucose and ketonuria. The results of the examination of blood glucose levels ranged from 400-645 mg/dL, and the patient was given an insulin drip of 0.05 IU/kg BW per hour.

On the second day of treatment, there was an improvement in the state of diabetic ketoacidosis, blood sugar levels began to stabilize in the range of 73-220 mg/dL, and urine ketone levels +1 in 2 examinations. Vital sign examination within normal limits. The patient was weaned from intravenous insulin and substituted with subcutaneous basal-bolus insulin. The patient got Insulin Levemir (morning 5 IU, afternoon 5 IU) and Novorapid (morning 3 IU, afternoon 3 IU, evening 3 IU). The total insulin dose was 1.58 IU/kg BW/day. The patient started to get diabetic meals of 1700 kcal, divided into breakfast

of 340 kcal (20 %), morning snack of 170 kcal (10%), lunch of 510 kcal (30%), an afternoon snack of 170 kcal (10%), dinner 340 kcal (20%) and evening snacks 170 kcal (10%).

During the third and fourth days of treatment, the patient's condition seemed good. Blood sugar levels when ranged from 268 - 472 mg/dL. Patients got Levemir (5 IU - 7 IU) and Novorapid (3 IU -3 IU-4 IU), and the total insulin dose on the third day was 0.9 IU/kg BW/day. On the fourth day, the patient received a total of 1.5 IU/kg BW/day insulin, consisting of Levemir (9 IU-10 IU) and Novorapid (6 IU - 6 IU - 6 IU).

On the fifth day of treatment, the C-peptide test result showed 0.3 ng/mL, and HbA1C result was 17.8%, blood sugar level was 181 - 255 mg/dL. Patients got Levemir (12 IU - 9 IU) and Novorapid (8 IU - 8 IU - 8 IU). The total insulin obtained was 1.87 IU/kg BW/day. Parents and patients were educated about diet management and insulin use.

On the seventh and eighth days of treatment, the patient's vital signs were within normal limits, with blood sugar levels ranging from 88-144 mg/dL. Patients got Levemir (11 IU – 12 IU) and Novorapid (8 IU-8 IU-9 IU). Total insulin on the seventh and eighth day of treatment was 2 IU/kg BW/day.

On the ninth and eleventh days of hospitalization, tolerance of intake was good and vital signs were within normal limits. Patients got Levemir (11 IU - 8 IU) and Novorapid (5 IU - 6 IU - 4 IU). Total insulin is 1.4 IU/kg BW/day. The patient planned to go home and outpatient.

## Case 2

A-12- years old boy came to Dr. M. Djamil General Hospital as a referral patient from a regional hospital. Initial complaints of patients in the form of easy thirst, increased frequency of urination, and easy hunger since 6 weeks ago. 2 weeks earlier, the patient had been examined at the nearest public health center. In checking blood glucose with a glucometer, blood sugar levels cannot be measured because they are very high. From his family history, his grandparents had a history of diabetes. This patient was little brother of

previous patients.

On physical examination, the general condition was found to be moderately ill. Blood pressure 90/60 mmHg, heart rate 92 times per minute, regular, respiratory rate 24 times per minute, and body temperature 36.3°C. The ratio of weight and height indicates undernutrition. Examination of the chest and abdomen region was within normal limits. Extremities were warm, and capillary refilling time was less than 2 seconds. Physiological reflexes were found to be normal, and the pubertal status was A1P1G1.

Laboratory evaluation showed hemoglobin level 12.7 g/dl, leukocyte count 10.460/mm<sup>3</sup>, platelet 442.000/mm<sup>3</sup>, hematocrit 36%, differential count 0/13/0/49/34/4, current blood glucose level 447 mg/dl, calcium 9.2 mg/dl, sodium 133 mmol/L, potassium: 3.9 mmol/L, chloride: 100 mmol/L, blood gas analysis: 7.4/34/101/21.1/-3/98%.

This patient was treated as a suspect diabetes mellitus type 1 accompanied by undernutrition. Management for type 1 diabetes mellitus is in the form of administration of a total insulin dose of 0.8 IU/kg BW/day, which is divided into Novorapid (4 IU-4 IU-4 IU) and Levemir (5U-5U). Management of undernutrition in the form of diabetes diet 1700 kcal, divided into breakfast 340 kcal (20 %), morning snack 170 cal (10%), lunch 510 kcal (30%), afternoon snack 170 kcal (10%), dinner 340 kcal (20%) and evening snacks 170 kcal (10%).

On the first day of treatment, the patient's general condition was moderately ill, blood pressure 100/60 mmHg, pulse rate 88 times per minute, respiratory rate 22 times per minute, temperature 36.7°C. Blood glucose levels ranged from 260 - 399 mg/dL. Diabetes mellitus diet 1700 kcal, divided into breakfast 340 kcal (20 %), morning snack 170 kcal (10%), lunch 510 kcal (30%), afternoon snack 170 kcal (10%), dinner 340 kcal (20%) and evening snack 170 kcal (10%).

On the second day of treatment, evaluate blood glucose at about 73 - 397 mg/dl. The patient looked moderate ill, conscious, heart rate 110 times/minute, respiratory rate 22 times/minute, temperature 37°C, blood pressure 90/60 mmHg, the pupil was isochor,

diameter 2 mm, the light reflex was +/- normal, there was no nasal flare, chest, and stomach was normal, extremities were warm. Patients got Levemir 5 IU - 5 IU, Novorapid 4 IU - 4 IU - 4 IU (total insulin 0.8 IU/kg BW/day).

On the third and fourth days of treatment, vital sign measurements showed results within normal limits. Plasma glucose levels ranged from 114 - 372 mg/dL. Patients got Levemir 8 IU - 8 IU, Novorapid 6 IU - 5 IU - 6 IU (total insulin 0.8 IU/kg BW/day).

Follow-up on 5-6 days of treatment, vital sign measurements were within normal limits. Random plasma glucose levels ranged from 115 - 235 mg/dL. Patients got Levemir 12 IU - 9 IU, Novorapid 6 IU - 6 IU - 6 IU (total insulin 0.92 IU/kg BW/day). The doctor and nutritionist provide diet instructions using a food model to the patient and her family. The patient was given education on how to use insulin properly and count for calorie intake independently. The C-Peptide test result was 0.4 ng/mL, and the HbA1C result was 21.4%.

On the seventh and eighth days of treatment, the patient complained of coughing, still complaining of coughing. Blood pressure 100/70 mmHg, pulse 88x / minute, respiratory rate 20x / minute, temperature 36.9°C. Plasma glucose levels ranged from 44 - 241 mg/dl. Patients got Levemir 13 IU - 12 IU, Novorapid 6 IU - 8 IU - 9 IU (total insulin 1.3IU/kg BW/day).

On the ninth and eleventh of hospitalization, the vital sign is stable, and the patient is no longer complaining of coughing. Plasma glucose levels ranged from 142 to 214 mg/dL. Laboratory results revealed C-peptide 1 ng/ml. Patients got Levemir 12 IU - 13 IU, Novorapid 12 IU - 8 IU - 9 IU (Total insulin 1.35 IU/kg BW/day), vit B6 1 x 10 mg. The team of doctors decided to send the patient home and undergo outpatient treatment.

### 3. Discussion

The case series describes two cases of diabetes mellitus type one with comorbid undernutrition. Both of the patients had a family history of diabetes mellitus. Their sibling died because of diabetes type 1,

and their grandmother and grandfather from the father's side had diabetes. A previous study found individuals with a positive family history of diabetes experience 3- to 4-fold higher risks for this disease than those with a negative family history of diabetes, and the risk of developing diabetes is related to the type and number of affected relatives. In the nationwide cross-sectional study, results showed that the proportion of first-degree relatives with a positive family history of diabetes was up to 15.5% in the Chinese population. Of these, the proportion of at least two generations of first-degree relatives with a positive family history of diabetes was 1.6%. The age of diagnosis of diabetes in those with a positive family history of diabetes was earlier than in those with a negative family history of this disease and 12.2% of the children had at least one affected first-degree relative. Familial clustering of T1D is likely caused by both genetic and environmental risk factors. The risk-associated HLA genotypes have been observed more often in familial T1D, although not all studies have found significant differences. It has been proposed that familial T1D is mainly attributed to HLA class II genes and not genes outside the HLA region. Support comes from GWA studies where the effect sizes for non-HLA loci were smaller in families with affected siblings than in sporadic cases.<sup>9</sup>

Diabetes mellitus (DM) is a group of chronic metabolic diseases characterized by elevated levels of blood glucose as the result of defects in insulin secretion, insulin action, or both.<sup>10</sup> New-onset T1DM presents in the majority of pediatric patients with the classic symptoms of polyuria and polydipsia (69%) and somewhat less frequently with polyphagia and weight loss (33%). Both patients showed classic symptoms of diabetes such as polyphagia, polyuria, and polydipsia. Diabetes mellitus diagnosis can be enforced if there is a symptom of classical diabetes supported by a random plasma glucose test higher than 200 mg/dl or fasting blood glucose above 126 mg/dl.

HbA1 in patient SW was 17.8%, and SD was 21.4 % (normal range is 3,8-6,4%), indicating that they have recently experienced diabetes mellitus type 1.

Hemoglobin is the oxygen-carrying pigment that gives blood its red color and is also the predominant protein in red blood cells. About 90% of hemoglobin is hemoglobin A. Although one chemical component accounts for 92% of hemoglobin A, approximately 8% of hemoglobin A is made up of minor components that are chemically slightly different. These minor components include hemoglobin A1c, A1b, A1a1, and A1a2. Hemoglobin A1c (HbA1c) is a minor component of hemoglobin to which glucose is bound. HbA1c also is sometimes referred to as glycated, glycosylated hemoglobin, or glycohemoglobin.

Both patients have examined C-peptide with a result of C-peptide 0,3 ng/ml for the girl and 0,4 ng/ml for the boy, showing low C peptide levels so that patients can be grouped in diabetes mellitus type 1. C-peptide levels are elevated in individuals with type 2 diabetes mellitus in contrast to patients with type 1 diabetes mellitus or MODY diabetes. C-peptide is a small 31-amino acid peptide, and it is cleaved from proinsulin in the synthesis of insulin. Proinsulin consists of A and B chains and connecting peptides in the middle, called C-peptides. Type 1 diabetes mellitus (T1DM), also known as juvenile diabetes or insulin-dependent diabetes, is the most common type of diabetes mellitus in children and adolescents, it is a chronic condition in which the pancreas produces little or no insulin by itself, and despite of being named juvenile diabetes, this disease may develop at any age.<sup>9</sup>

Case 1 was diagnosed as mild diabetes ketoacidosis based on symptoms of polyuria, polydipsia, polyphagia, and hyperglycemia (blood glucose: 641 mg/dl), pH:7.26, bicarbonate concentration: 9 mmol/L, and ketonuria: (+2), but the patient didn't have a sign of dehydration. The patient was temporarily fasting, was given fluid maintenance, and treated with an insulin drip of 0,05 IU/kg/hour. Urine ketone was checked every 2 hours, and random blood glucose was checked every hour. DKA defined as a venous pH <7.3 or serum bicarbonate concentration <15 mmol/L, serum glucose concentration >200 mg/dL (11 mmol/L) together with ketonemia, glucosuria, and ketonuria. DKA degree is mild if

venous pH >7.2 and <7.3, bicarbonate <15 mmol/L. In this patient, with pH more than 7,2 and bicarbonate less than 15, the degree of DKA is mild.

Case 2 was diagnosed with diabetes mellitus type 1 based on symptoms of polyuria, polydipsia, polyphagia, and hyperglycemia. Diabetes mellitus is a metabolic disease characterized by elevated levels of blood glucose as the result of defects in insulin secretion, insulin action, or both.<sup>11,12</sup> Patient was treated by given basal insulin bolus and given diabetic meals 1700 kcal, divided into breakfast 340 kcal (20%), morning snack 170 kcal (10%), lunch 510 kcal (30%), afternoon snack 170 kcal (10%), dinner 340 kcal (20%) and evening snack 170 kcal (10%). Insulin therapy in T1DM utilizes subcutaneous delivery of rapid or short-acting insulin with meals and snacks. The overall guiding principle for medical nutrition in T1DM is that the same healthy diet that would be ideal for an individual without diabetes would be ideal for an individual with T1DM. Thus, an appropriate diet seeks to obtain approximately 50% of calories from carbohydrates, 30% from protein, and 20% from fat while limiting saturated fat and cholesterol intake.<sup>13,14</sup>

The prognosis of both patients is Bonam for ad Vitam because blood glucose is controlled, dubia ad Bonam for ad functionam because there are no complications of diabetes ketoacidosis and diabetes mellitus in this patient.

Type 1 diabetes is caused by an absolute insulin deficiency, the result of a loss of the insulin-producing beta cells of the pancreas. Type 1 diabetes mellitus may account for 5 percent to 10 percent of all diagnosed cases of diabetes. Risk factors are less well-defined for type 1 diabetes than for type 2 diabetes, but autoimmune, genetic, and environmental factors are involved in the development of this type of diabetes. Type 2 diabetes mellitus, previously called non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes, is characterized by two underlying defects. The earliest abnormality in an individual who develops type 2 diabetes mellitus is insulin resistance, which initially is compensated for with an increase in insulin secretion.<sup>15,16</sup>

Approximately 10-12% of children diagnosed with T1D have a first-degree relative with T1D at diagnosis, and if follow-up is continued for decades, this number increases to over 20%. Compared to the general population, first-degree relatives of T1D patients are at an 8-15-fold increased risk for T1D. The proportion of children with T1D who have second-degree relatives with T1D has been reported to be 5-16%. Compared to the general population, the risk of T1D for second-degree relatives is approximately two-fold. The cumulative incidence of T1D for siblings of T1D patients is 3-6% by the age of 20 years and the lifetime risk for parents is 2-6%.

T1DM was strongly associated with poverty and markers of undernutrition, most marked in the rural cases. Affected patients reported a history of childhood malnutrition and the loss of the patient's mother during early childhood; this was coupled with evidence of disproportionate skeletal growth, especially in men, and other evidence of poverty and overcrowding. Reductions in total food intake during pregnancy or early postnatal life lead to decreased glucose tolerance and diabetes in the offspring.<sup>17</sup>

Undernutrition at particular times in pregnancy affects the methylation and alters the activity of many genes that control hepatic and pancreatic function. These epigenetic changes alter genes that control growth and transcription factors important for pancreatic development and  $\beta$ -cell differentiation, such as IGF2, PDX1, and HNF4- $\alpha$ , resulting in a permanently reduced  $\beta$ -cell mass and reduced insulin secretion. Altered HNF4- $\alpha$  function (gene mutations or deletions) in humans has also been associated with maturity-onset diabetes of the young, a non-obese form of diabetes that can be mistaken for T1DM. Deficiencies in the postnatal diet can also affect IGF2 imprinting in mice and lead to reduced IGF2 levels. Changes in micronutrient levels alone in the peri-conceptual period can alter the methylation of many genes, even when the caloric intake is maintained. In sheep, altered levels of micronutrients that contribute to the methylation process, such as vitamin B<sub>12</sub>, folic acid, and methionine, have been shown to change the

methylation status of many genes in the liver and pancreas; it is of interest that more than 50% of the affected loci are specific to males. Most studies have linked early undernutrition with insulin resistance and type 2 diabetes (T2DM). However, it is clear that T1DM can also occur and that the effects of early undernutrition are manifest as T1DM or T2DM according to the degree, timing, and macro or micronutrient specificity of the nutritional deficit. In the case of people living in urban areas of developing countries, a change to a western-type diet and the development of obesity would increase the risk of developing insulin-resistant T2DM. MRDM was previously known as 'tropical diabetes', and patients present at a young age, resistant to ketosis in undernourished individuals with high subsequent insulin requirements.<sup>16,17</sup>

#### 4. Conclusion

Management of type 1 diabetes mellitus includes administration of insulin according to monitoring blood sugar levels and management of comorbid diseases that accompany it. Education about insulin use and diabetes diet patterns is very important for parents and children with type 1 diabetes mellitus.

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