

Type 2 Diabetes Mellitus with Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State and Metabolic Syndrome in a 16-Year-Old Boy: Lifestyle Modification as Management

Made LaksmiDewi Adnyana¹, I Made Arimbawa²

Udayana University, Medical Faculty, Department of Child Health, Sanglah Hospital, Denpasar, Indonesia

Abstract: ***Background:** Type 2 diabetes mellitus (T2DM) is characterized by hyperglycemia with insulin resistance and impaired insulin secretion. The severest form of T2DM present with hyperglycemia crisis such as diabetic ketoacidosis (DKA), hyperosmolar hyperglycemic state (HHS), or mixed syndrome (DKA and HHS). Management of children with T2DM is combination of pharmacology and lifestyle modification. Healthier lifestyle, proper nutrition, and routine exercise can be the key management of T2DM. **Objective:** The aim of this case report is to describe the combination of pharmacology and lifestyle modification as the management of T2DM in children. **Case:** A 16-year-old boy was presented with obesity. There was no classic sign of diabetes mellitus (DM) and vomiting. He was alert with no kussmaul breathe, high blood pressure, sign of mild dehydration, and acanthosis nigricans on his neck. Laboratory tests revealed high blood glucose, metabolic acidosis, high blood osmolality, with ketonuria and glucosuria. Low C-peptide with negative result of Insulin Autoantibody (IAA), confirmed of T2DM with a mixed syndrome and metabolic syndrome (MeTS). The patient was treated with rehydration, electrolyte correction, and intravenous insulin. One year of follow up with a lifestyle modification, the patient succeeded to decrease his body weight, his blood glucose was normal, and reached HbA1c level 5% without any medication. **Conclusion:** Lifestyle modification can be the management of children with T2DM presenting with MeTS.*

Keywords: Type 2 diabetes mellitus, children, obesity, lifestyle modification

1. Introduction

Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder of heterogeneous etiology with social, behavioral, and environmental risk factors. It has been proposed that hyperglycemia may worsen both insulin resistance and insulin secretory abnormalities, enhancing the transition from impaired glucose tolerance to diabetes mellitus [1]. Obese children are hyperinsulinemic and have approximately 40% lower insulin stimulated glucose metabolism compared with non obese children [2]. Most children with T2DM are obese or extremely obese at diagnosis and present with glucosuria without ketonuria, absent or mild polyuria and polydipsia, and little or no weight loss [1],[3].

The metabolic syndrome (MetS) is a group of cardiovascular risk factors that are associated with insulin resistance including central obesity (typically measured by high waist circumference or high BMI), hypertension, high fasting triglyceridees, low high density lipoprotein (HDL) cholesterol and high fasting glucose. Interventions that can reduce the proportion of children with MetS focused on altering dietary choices, increasing physical activity, and a combination of both [2].

Initial management of obese children and adolescents with type 2 diabetes mellitus should consist of behavior modification strategies for lifestyle change such as decreasing high-caloric high-fat food choice and sedentary behavior, while increasing physical activity. Weight control is essential for reaching the treatment goals and are effective to treat T2DM children [7].

There are three types of hyperglycemic crisis such as: diabetic ketoacidosis (DKA), hyperosmolar hyperglycemic state (HHS), mixed syndrome (both DKA and HHS as a mixed state of acidosis and hyperosmolality) [4],[5]. A few cases of mixed HHS and DKA have been reported, and most of these cases have been misdiagnosed as HHS. In children with mixed HHS and DKA, the treatment must take into account the potential complications such as electrolyte imbalance, cerebral edema and ischemic injury. The patient's circulatory status and fluid balance should be reassessed frequently because patients with mixed HHS and DKA have a higher risk of cerebral edema than those with HHS [6].

In this report, we presented a case of T2DM with the manifestation of mixed DKA and HHS, MetS, manage with the combination of pharmacology and lifestyle modification.

2. Case Report

A 16 year-old-boy came to emergency room and was referred from another general hospital. He complained of vomiting since one day before admission. Vomit contained the food he eat before, approximately half glass, no blood. He also complained prior nausea. Patients also complained of frequent urination since 3 days before admission, in which the patient can urinate ≥ 6 times at night. Urine colour was clear-yellow. No history dark yellow urine, pain during urination was denied. Patients also complained of frequent drink and always thirst since about 1 month ago, following with decrease of appetite, which did not improve with changes in the types of food. There was no significant decrease of his body weight. Symptoms of fatigue, prolonged wound healing, coughing, or flu symptoms were

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denied. His defecation pattern, both consistency and frequency, was normal.

Three days before admission, the patient complained of fever with a body temperature at 38°C. Fever is not accompanied by a cough, common cold or seizures. His parents take him to a hospital and find out that his blood sugar was high and being referred to our hospital.

Patient was the second child of three siblings. His older sister and younger sister are healthy. There was no history of diabetes mellitus in his family. His body weight was increased every month during the first year of life. Parents notice that patient's body weight was overweight since he was 6 years old. His current body weight was 122 kg, body height was 165 cm with nutritional status according to Waterlow was 234% (superobese).

His initial assessment revealed moderately ill and alert with E4V5M6 (15/15), pulse rate was 110 beats per minute, regular with good pulse quality, respiratory rate was 30 times per minute regular, no Kussmaul breathing, axillary temperature was 38°C. Blood pressure 150/70 mmHg, Oxygen saturation 98% in room air. There was acanthosis nigricans at the back of his neck, the mammae was prominent. (Figure 1,2) There was sunken eyes, no palpebral edema, no dry mucous membranes with normal findings on lung and heart auscultation. Abdominal examination was normal. Capillary refill time less than 3 second with warm extremities.



Figure 1: Acanthosis nigricans on the neck



Figure 2: The prominent mammae

Laboratory findings blood glucose 862 mg/dL, potassium 3.5 mmol/L, sodium 131 mmol/L, chloride 91.3 mmol/L, calcium 9.3 mg/dL. Blood gas analysis revealed pH 7.29, pO₂ 204.6 mmHg, pCO₂ 17 mmHg, HCO₃ 7.9 mmol/L (anion gap 31.8 mEq/L). Osmolarity 320 mOsm/kg. Urine

analysis result came with glucosuria (1000 mg/dL (4+)) and ketonuria (150 mg/dL (3+)). He was diagnosed with diabetic ketoacidosis with hyperosmolar hyperglycemic state, suspicion of type 1 differential diagnosis type 2 diabetic mellitus and super obese. Patient got rehydrated according to his dehydration grade (mild dehydration) with total 7400 ml per 48 hours. He also got insulin 0.1 IU/body weight/hour (5.2 IU/hour). Patient got monitored his blood glucose hourly, with reduction blood glucose target 75-100 mg/dl per hour. He planned to check HbA1c and C-peptide level. After 24 hours of rehydration, the patient still alert. Venous pH and bicarbonates improve gradually, pH 7.34, pCO₂ 26.2 mmHg, pO₂ 136.2 mmHg, HCO₃ 13.9 mmol/L, potassium 3.52 mmol/L, sodium 130 mmol/L (corrected sodium 133 mmol/L), chloride 94.2 mmol/L, calcium 9 mg/dL and insulin therapy was decreased gradually, patient also got calcium channel blocker as antihypertensive. Potassium maintenance 2 ml KCl + 4 ml NaCl 0.9% ~ 6 ml/hour. Another therapy was continued.

On the next day, the condition was getting better, patient alert with normal vital sign. Blood glucose were 163 mg/dL (morning), 177 mg/dL (noon), 255 mg/dL (afternoon), ureum 2.9 mg/dL, potassium 3.29 mmol/L, sodium 138 mmol/L (corrected sodium 140 mmol/L), chloride 100.2 mmol/L, calcium 8.9 mg/dL. Blood gas analysis: pH 7.4, pCO₂ 28.7 mmHg, pO₂ 161.2 mmHg, HCO₃ 17.3 mmol/L. Serum Osmolality: 293 mOsm/kg (normal)

On the fourth day, blood glucose was more controlled. Insulin was switched into Novorapid® 10-10-10 unit (SC), Levemir® 20 unit (night)(SC), Metformin 500 mg every 12 hours (oral). Another therapy was continued. Laboratory result revealed blood glucose 332 mg/dL, C-peptide 0.5 ng/mL (low). Liver function test: Albumin 4.6 g/dL, globulin 3 g/dL, total protein 7.6 g/dL, gamma GT 22 U/L. HbA1c 112 mmol/mol or 14.8%. Lipid profile: total cholesterol 164 mg/dL, LDL cholesterol 86 mg/dL, HDL cholesterol 28 mg/dL, triglyceride 523 mg/dL. The result of Insulin Autoantibody (IAA) and Islet Cell Autoantibodies (ICA) revealed IAA <0.4 U/ml and ICA was negative. Fasting Insulin was 16.4 uIU/ml (normal), with HOMA IR 5.44 showed condition of insulin resistency. Autoimmunity process can be ruled out. The diagnosis can be confirmed type II diabetes mellitus with metabolic syndrome.

After treatment for 1 week, the patient was allowed to return home and control to endocrinology polyclinic every two weeks for blood sugar and patient compliance monitoring. The patient was recovered with no neurological sequelae. The patient also had a discussion with a nutritionist to help him gained ideal bodyweight.

Patient with the support of his parents tried to have a healthier lifestyle. He ate three times a day. He stopped drinking soda and having midnight snack. He joined a badminton club and spent 30-45 minutes a day for an exercise. One month of admission, blood glucose was controlled and insulin therapy was stopped. Metformin was continued.

One year of followup the patient was succeeded to decrease his body weight. He still doing badminton exercise every 3-5

times a day, with duration of 30-45 minutes for every exercise, with all that effort he did not need his insulin and metformin anymore. His blood pressure and lipid profile was normal without any medication. Now he is 17 years old with body weight of 90 kg, and height of 175 cm. His HbA1c was 5%. He is an university student now and still with his healthy lifestyle and routine exercise to maintain his body weight.

3. Discussion

Type 2 diabetes mellitus (T2DM) is a new clinical problem within pediatric practice. Recent reports indicate an increasing prevalence of T2DM in children and adolescents. The majority of young people who diagnosed with T2DM was found in specific ethnic subgroups such as African-American, Hispanic, Asian/Pacific Islanders and American Indians. Clinicians should be aware of the frequent mild or asymptomatic manifestation of T2DM in childhood. Screening for high risk groups such as children and adolescents with obesity, relatives with T2DM, and clinical features of insulin resistance (hypertension, dyslipidemia, polycystic ovarian syndrome, or acanthosis nigricans) is needed [1],[8].

Table 1: Clinical characteristics of type 1 and type 2 diabetes mellitus

	Type 1 diabetes mellitus	Type 2 diabetes mellitus
Age when diagnosis is established	Preschool-adolescents	>10 years old
Obesity	Uncommon	Common
Gender	Male = female	Female > male
Relatives	5% type 1 DM	75-100% type 2 DM
Population	Predominantly Caucasian	Predominantly Americans of Africans, Hispanic, Asian, and American Indian
B-cell autoantibodies	85%-98%	Uncommon
Insulin, C-peptide	Low	High
Ketoacidosis	Frequently	< 33%
Associated disorders	Autoimmune disorders (thyroid, adrenal, vitiligo), celiac disease	Acanthosis nigricans, PCOS, Metabolic syndrome

Obesity is the hallmark of T2DM. Most children with T2DM are obese or extremely obese at diagnosis and present with glucosuria without ketonuria, absent or mild polyuria and polydipsia, and little or no weight loss [1]. Currently, children with T2DM are usually diagnosed after 10 years old and in the middle to late puberty. In the T2DM mildest form, the diagnosis is made in an asymptomatic child during a routine medical check-up by detection of hyperglycemia or glycosuria. One third of patients are diagnosed by urinalysis during routine physical examination. In its severest form, the child presents with polyuria, polydipsia, and weight loss. Up to 33% in particular ethnic groups have ketonuria at diagnosis and 5%-25% ketoacidosis at presentation. Very rare, T2DM manifest with a hyperglycemic hyperosmolar coma [9].

Acanthosis nigricans and polycystic ovarian syndrome (PCOS), disorders associated with insulin resistance and

obesity, are common in youth with T2DM. (Table 1). Acanthosis is a cutaneous finding characterized by velvety hyperpigmented patches most prominent in intertriginous area. It is present in up to 50 up to 90% of children with T2DM. It is recognized more frequently in darker-skinned obese individuals. PCOS is characterised by hyperandrogenism and chronic anovulation. Lipid disorders and hypertension also occur more frequently in children with T2DM [2], [10].

In this case, he is a dark skinned non-caucasians boy. He at his late puberty at the age of 16 years old when diagnosed as T2DM. The nutritional state was obesity. He came to emergency ward with the symptom of mixed type of KAD and HHS. Acanthosis nigricans was found at his neck.

Distinguishing children with type 1 diabetes mellitus (T1DM) from those with T2DM may be difficult. There is overlap in presentation; children with T2DM may present with glucose toxicity, even ketoacidosis, requiring insulin. The distinction between T1DM and T2DM may not be apparent until insulin requirements have declined significantly. Increasing obesity in the general population further blurs the distinction between T1DM and T2DM in children. C-peptide is a useful and widely used method of assessing pancreatic beta cell function [11].

Type 2 diabetes mellitus (T2DM) results from the combination of severe insulin resistance and loss of functional β -cell mass. C-peptide levels are considered the best surrogate marker of β -cell function and may be useful for differentiating type 1 diabetes (T1D) from T2D in newly diagnosed children with diabetes. C-peptide reflects insulin secretion from pancreatic β cells, and the amount of secreted insulin reflects the metabolic needs of the body. Its levels reflect the residual insulin secretion function of β cells in the following manner: 1 molecule of proinsulin decomposes into 1 molecule of insulin and 1 molecule of C-peptide. As a result, measuring the C-peptide level is meaningful in diagnosing T1DM. The main cause of T1DM is disruption of β cells by autoimmunity, which leads to decreased insulin secretion function, on the other hand T2DM have a higher C-peptide level. In some cases, C-peptide levels are lower in children with a longer duration of T2D and that waning of residual β -cell function is associated with elevated HbA1c levels and more frequent use of insulin. Measuring C-peptide once the glucotoxicity is corrected is better initially. C-peptide levels can be low due to glucotoxicity [12],[13].

In this case, patient came from a family without any history of diabetes mellitus. Patient came with obesity, clinical manifestation of mixed KAD and HHS, high blood pressure, laboratory result of HbA1c was higher than 6.9% (14.8%), C-peptide 0.5 ng/mL (low), the result of Insulin Autoantibody (IAA) revealed IAA <0.4 U/ml (normal) and Islet Cell Autoantibodies (ICA) was negative. Fasting insulin was 16.4 uIU/ml (normal), with HOMA IR 5.44 showed condition of insulin resistency. Lipid profile: total cholesterol 164 mg/dL, LDL cholesterol 86 mg/dL, HDL cholesterol 28 mg/dL, triglyceride 523 mg/dL, confirmed that patient have Type 2 Diabetes Mellitus with a metabolic syndrome. Low C-peptide might happen because of the long

duration of T2DM manifest from obesity and also from patient high level of HbA1C.

Diabetic ketoacidosis (DKA) is a serious complication of adolescent diabetes mellitus (DM). When it comes down to diagnosis of T2DM in children, the rate of showing a presentation of DKA is relatively low, but it has often been reported in recent case studies. On the other hand, diabetes with extreme hyperglycemia and hyperosmolality without ketosis is comprehended as hyperglycemic hyperosmolar state (HHS). HHS has a high mortality and morbidity rate in elderly patients with T2DM, however, has not been significantly recognized in young patients [2].

A few cases of mixed HHS and DKA have been reported, and most of these cases have been misdiagnosed as HHS. With increasing rates of childhood obesity and pediatric T2DM, cases of mixed HHS and DKA are expected to occur more frequently than before. In children with mixed HHS and DKA, treatment must be considering the potential complications, such as electrolyte imbalance, cerebral edema, and ischemic injury. The patient's circulatory status and fluid balance should be reassessed frequently because patients with mixed HHS and DKA have a higher risk of cerebral edema than those with HHS [14],[15], [16].

Table 2. Difference in laboratory values in patients presenting with HHS, DKA, or a mixed type

	HHS	DKA	Mixed
Glucose (mg/dL)	>600	<600	>600
Bicarbonate (mEq/L)	>15	<15	<15
Osmolarity (mOsm/L)	>320	<320	>320
pH	>7.3	<7.3	<7.3
Urine ketones	0 to trace	>3+	Mixed

In this case, level of consciousness was alert, while based on the laboratory examination with plasma glucose level 862.4 mg/dL (>600 mg/dL), arterial pH 7.29 (<7.3), serum bicarbonate level 7.9 mEq/L (<15 mEq/L), anion gap 31.8 mmol/L (>12 mmol/L), serum osmolality 320 mOsm/kg, urine keton 150 mg/dL (+3). According to these marks, patient categorized with mixed type, diabetic ketoacidosis with hyperglycemic hyperosmolar state at the onset of type 2 diabetes mellitus. (Table 2).

The goals of therapy in patients with hyperglycemic crises include: 1) improvement of circulatory volume and tissue perfusion, 2) gradual reduction of serum glucose and plasma osmolality, 3) correction of electrolyte imbalance, and 4) identification and prompt treatment of co-morbid precipitating causes [18]. Because therapy for either DKA or HHS consists of fluid administration, intravenous insulin infusion, and electrolyte replacement, mixed cases are managed using the same approach. The therapeutic regimen was done according to the prominent clinical features present. In younger patients with mixed features, rapid correction of metabolic abnormalities and, consequently, of hyperosmolality by administration of hypotonic fluids and insulin should be avoided to decrease the risk for precipitating cerebral edema [17]. In this case, patient got rehydration with isotonic saline solution (NaCl 0.9%) for almost 48 hours, insulin administration 0.1 unit/kg/hour, and potassium maintenance.

The metabolic syndrome (MetS) is a group of cardiovascular risk factors that are associated with insulin resistance and are driven by underlying factors, including visceral obesity, systemic inflammation, and cellular dysfunction. These risks increasingly begin in childhood and adolescence and are associated with a high likelihood of future chronic disease in adulthood. Efforts should be made at both recognition of this metabolic risk, screening for potential associated T2DM, and targeting affected individuals for appropriate treatment with an emphasis on lifestyle modification. Effective interventions have been associated with reductions in MetS - and in adults, reductions in the severity of MetS have been associated with reduced diabetes and cardiovascular disease [19].

Table 3: Pediatric and adolescent metabolic syndrome (MetS) criteria adapted from the National Cholesterol

Central Obesity (WC)	High BP (mmHg)	High Triglycerides (mg/dL)	Low HDL (mg/dL)	High Fasting Glucose
WC ≥90th percentile	Systolic or diastolic DBP ≥90% for age, sex, height	TG ≥ 110 mg/dL (≥1.24 mmol/L)	HDL ≤40 mg/dL (<1.03 mmol/L)	≥100 mg/dL (5.6mmol/L) or known T2DM

In this case, patient's body weight was 122 kg, body height was 165 cm, abdominal circumference was 115 cm, and nutritional status according to Waterlow was 234% (superobese). At first admission and routine follow up at the hospital, blood pressure remain high 150-160/70-80 mmHg (>P99). Total cholesterol 164 mg/dL, LDL cholesterol 86 mg/dL, HDL cholesterol 28 mg/dL, triglyceride 523 mg/dL. This condition confirmed patient with metabolic syndrome (MetS). (Table 3).

The strong connection between MetS and obesity, most interventions for MetS have paralleled those for pediatric obesity in general, namely interventions aimed at altering unhealthylifestyle factors that likely contributed to the metabolic problems in the first place. This includes diets that are high in saturated fat and carbohydrates (and ultimately an excess of overall calories) and physical activity levels that less than the recommendations. Interventions that have been assessed for reducing the proportion of children with MetS have thus focused on altering dietary choices, increasing physical activity, and a combination of both. The goal is to decrease the ratio of energy ingested and energy expended, primarily to reduce the degree of central obesity that drives the metabolic abnormalities [19],[22].

The main approach for dietary changes for children and adolescents as recommended by the American Academy of Pediatrics, the American Heart Association, and the World Health Organization has been an increase in vegetable and fruit consumption and a reduced intake of saturated fat replaced by unsaturated fat (e.g., olive oil and other vegetable oil), as well as a reduction in sugar intake. Patients with MetS should be reducing consumption of sugar-sweetened beverages, saturated fat, and calorie-dense food (e.g., fast food) and toward increasing consumption of oil and vegetables likely through negotiating individual changes with adolescents and their families [23].

Increases in physical activity serve to maintain or increase total energy expenditure. The US Center for Disease Control and Prevention and the World Health Organization recommend at least 60 minutes of moderate to vigorous physical activity among school-age children and adolescents though adolescents do particularly poorly in meeting these goals, with <30% engaging in this much activity. Physical activity is particularly good at increasing insulin sensitivity. Increased walks with family, friends or pets can be a way to ensure continued activity. Finally, participation in sports, either through schools, clubs or regular meetings with friends, can further sustain physical activity and maintain higher energy expenditure. There is a tendency toward declining physical activity with age, so encouragement at continuing activity starting at younger ages may be more successful [19].

The most effective interventions are likely to include a combined approach incorporating reducing calorie intake while increasing energy expenditure. This is because isolated increased physical activity may lead to a compensatory increase in food intake, while isolated caloric restriction results in a lowering of basal metabolic rate while a combination of these approaches aims to prevent these counterproductive reactions. Combined interventions to reduce MetS have focused on nutritional counselling with specific goals for physical activity usually consisting of at least three weekly exercise sessions. This kind of approach can produce dramatic reductions in MetS over time, with one group reporting a decrease from 27% at baseline to 8.3% after one year of combined nutrition and activity interventions [20],[21].

In this case, patient with central obesity with diagnose of T2DM. Patient was hospitalized with the manifestation of mixed type of KAD and HHS. After giving insulin therapy the blood glucose was lower than before. Proper nutrition and routine physical activity decreased the blood glucose and decreased patient's body weight. He also stopped consuming soda and sugar-sweetened beverages. This condition made the patient didn't need insulin or metformin anymore, and the patient could maintain the normal blood glucose level and blood pressure.

Management of T2DM should be focused on a multidisciplinary and family-centered. Metformin and insulin are the only medications for T2DM that are approved by the U.S. Food and Drug Administration for use in children and adolescents[18]. Metformin in combination with diet and exercise is first-line therapy in children 10 years old and older. Metformin should be initiated at a dosage of 500 mg per day, regardless of the patient's weight, then titrated in 500 mg intervals over four weeks to the maximum dosage of 2,000 mg per day. Although newly diagnosed T2DM may respond to metformin and lifestyle changes, insulin therapy must be initiated if the patient has signs of ketosis or ketoacidosis[2]. Insulin is also recommended for patients without signs of ketosis or ketoacidosis who have random plasma glucose levels of 250 mg/dL (13.9 mmol/L) or greater, or whose HbA1c level is greater than 9%. Insulin may be beneficial for these patients on a short-term basis

and can be discontinued after initiating metformin therapy and lifestyle changes [7],[8].

Non pharmacological therapy in T2DM and their families should be provided with developmentally and culturally appropriate comprehensive lifestyle programs that are integrated with diabetes management aiming to achieve 7-10% decrease in excess weight. Given the necessity of long-term weight control and lifestyle management for children and adolescents with T2DM, lifestyle intervention should be based on a chronic care model and offered in the context of diabetes care [9]. Youth with diabetes, like all children, should be encouraged to participate in at least 30–60 minutes of moderate to vigorous physical activity at least 5 days per week (and strength training on at least 3 days per week) and should be encouraged to decrease sedentary behavior. Nutrition for youth with T2DM, like all children, should focus on healthy eating patterns that emphasize consumption of nutrient-dense, high-quality foods and decrease consumption of calorie-dense, nutrient-poor foods, particularly sugar-added beverages [7],[9].

In this case, at first patient got intravenous insulin because the condition of mixed type HHS and KAD, HbA1c of 14.8%. After few days blood glucose maintain normal and switched to basal bolus Novorapid® 10-10-10 unit (SC) and Levemir® 20 unit (SC). Metformin 500 mg every 12 hours (orally). He also joined a badminton club, exercised more than 5 times a week for about 45 minutes. He also had a healthier diet that appropriate for T2DM.

4. Conclusion

Type 2 diabetes mellitus (T2DM) in children was increasing because the incidence of obesity in children was higher which is strongly correlated with metabolic syndrome. Manifestation of the disease was different from T1DM because there are factor of insulin resistance in T2DM. In T2DM it can be symptomatic or asymptomatic. Management of T2DM which is lifestyle modification such as proper nutrition and routine physical activity can maintain normal blood glucose and HbA1c.

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