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Case Report

Two Countries, One Metabolic Dilemma: Nutritional Management of Concurrent Maple Syrup Urine Disease and Type 1 Diabetes Mellitus

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What is already known on this topic?
Maple Syrup Urine Disease (MSUD) and Type 1 Diabetes Mellitus (T1DM) are distinct metabolic conditions that require individualized dietary management. The coexistence of MSUD and T1DM is extremely rare, and managing both simultaneously presents significant clinical and nutritional challenges. High levels of branched-chain amino acids (BCAAs), particularly leucine, may contribute to insulin resistance.

What this study adds?
This report presents two pediatric cases from different countries with coexisting MSUD and T1DM, highlighting the complexities of dietary and glycemic management in dual metabolic disorders. It demonstrates that tailoring dietary macronutrient distribution—by limiting carbohydrate intake and increasing leucine-free medical formula—can help maintain both metabolic and glycemic stability. The study underscores the potential role of BCAA metabolism in glucose regulation and the importance of interdisciplinary care in managing rare dual diagnoses.

Abstract
Maple Syrup Urine Disease (MSUD) and Type 1 Diabetes Mellitus (T1DM) are two distinct metabolic disorders with unique dietary management requirements. While MSUD necessitates strict restriction of branched-chain amino acids (BCAAs), T1DM requires precise carbohydrate counting to maintain optimal glycemic control. We report two cases of patients diagnosed with both MSUD and T1DM, highlighting the challenges and strategies in dietary management. Case 1, a 5-year-old girl, was diagnosed with T1DM after presenting with hyperglycemia and metabolic acidosis, despite previously stable MSUD management. The dietary regimen was modified to include a leucine-free amino acid formula and controlled carbohydrate intake to stabilize both leucine and glucose levels. Case 2, an 11-year-old boy with the diagnosis of MSUD, presented with hyperglycemia during a routine follow-up. Dietary management involved increasing the leucine-free formula while reducing carbohydrate intake to maintain metabolic control. Both cases emphasize the importance of individualized dietary plans, integrating BCAA restriction and carbohydrate regulation to prevent metabolic crises and achieve optimal glycemic control. These cases also underscore the need for a multidisciplinary approach involving pediatric endocrinologists, metabolic specialists, and dietitians to navigate the complexities of dual metabolic disorders effectively. Further studies are warranted to explore long-term outcomes and potential therapeutic targets in patients with concurrent MSUD and T1DM.
Keywords: Diabetes mellitus, dietary treatment, maple syrup urine disease

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Introduction

Maple syrup urine disease (MSUD) is a metabolic disorder resulting from a deficiency in the branched-chain alpha-ketoacid dehydrogenase (BCKAD) complex, leading to the accumulation of the branched-chain amino acids (BCAA): isoleucine, leucine, and valine. Elevated leucine levels are particularly neurotoxic, necessitating lifelong dietary BCAA restriction initiated immediately upon diagnosis (1,2).
Type 1 Diabetes Mellitus (T1DM), a chronic autoimmune disorder characterized by the destruction of pancreatic beta cells, necessitates lifelong insulin therapy. A fundamental aspect of T1DM management involves meticulous dietary planning, which includes prescribed daily caloric intake, specific recommendations for macronutrient distribution, and guidelines for meal and snack composition. Given that carbohydrates are the primary dietary factor influencing postprandial glucose levels, dietary strategies in T1DM focus on carbohydrate counting and regulation to maintain optimal glycemic control (3,4).
A previous case report highlighted a rare clinical presentation involving the coexistence of MSUD and T1DM, proposing that BCAA accumulation in T1DM may exacerbate insulin resistance (5,6).
In this report, we present two additional cases of patients diagnosed with both MSUD and T1DM from two distinct countries, aiming to emphasize the complexities and challenges associated with dietary management in the context of dual metabolic disorders.

Case 1

A 5-year-old female patient, diagnosed with classical MSUD in the neonatal period, presented to the pediatric emergency department with a two-day history of fever, poor feeding, and postprandial vomiting. The infant was delivered at term via cesarean section and was diagnosed with MSUD on the fifth postnatal day due to clinical findings of respiratory failure and metabolic acidosis. Genetic analysis revealed a homozygous c.702_703delT; p.Tyr235Thr(Fs) mutation in the *BCKDHA* gene. The pathogenicity of the variant was evaluated based on the American College of Medical Genetics and Genomics (ACMG) criteria and classified as 'likely pathogenic' using criteria PVS1, PM2, and PP3. The patient's management entailed a leucine-restricted diet, comprising the MSUD formula protein (MSUD 2 Prima®), which provided 1400 kcal/day with a macronutrient distribution of 8.5% protein, 56% carbohydrates, and 35.5% fat. Until the patient reached the age of five,

they exhibited clinical stability, with the exception of mild motor and cognitive delays, as well as sporadic instances of acute metabolic decompensation, precipitated by infections.

Upon admission, the patient exhibited mild dehydration, mental retardation, and mild encephalopathy. Laboratory findings were significant for metabolic acidosis and ketosis, with WBC 12,100/mm³, Hb 14.1 g/dL, PLT 402,000/mm³, TNC 8,860/mm³, and CRP 112 mg/L. Liver and renal function tests were unremarkable, but the blood glucose level was markedly elevated at 339 mg/dL. Arterial blood gas analysis demonstrated as pH of 7.23, PCO_2 22.5 mmHg, HCO_3 9.3 mmol/L, lactate 1.6 mmol/L, and blood ketone level of 6.2 mmol/L. Plasma amino acid analysis revealed a leucine concentration of 1143 µmol/L (reference range: 55-164 µmol/L).

Initial management included fluid resuscitation with two boluses of 20 mL/kg saline, followed by maintenance fluid therapy consisting of 1/3 saline with 10% dextrose at 150 mL/kg/day (GIR: 7 mg/kg/min). Sodium bicarbonate was administered to correct metabolic acidosis. Due to persistent hyperglycemia (339-402-319 mg/dL), an insulin infusion was initiated at 0.05 U/kg/h. Empirical antibiotic therapy with ceftriaxone at 75 mg/kg/day was commenced following culture collection.

Due to the persistence of encephalopathy, hemodiafiltration was initiated. During dialysis, the patient was maintained on 150 mL/kg/day of fluid (GIR: 7 mg/kg/min) and 2 g/kg/day of lipid infusion. Blood glucose levels ranged between 375-406 mg/dL, with simultaneous ketone levels of 2.3 mmol/L. The insulin infusion rate was adjusted to maintain blood glucose levels within the target range of 150-250 mg/dL. Following stabilization, the dietary plan was modified to include 1.5 g/kg/day of leucine-free MSUD formula protein (Milupa MSUD2®), along with 300 mg/day of isoleucine and 300 mg/day of valine to prevent catabolism. After two days of dialysis, leucine levels decreased to 173 µmol/L. Once blood glucose levels stabilized, glucose infusion was discontinued, and oral formula intake was gradually increased (Table 1).

At discharge, the dietary regimen was adjusted to provide 1.5 g/kg/day MSUD formula protein and 4.5 g of natural protein derived from rice, fruits, and vegetables. Total caloric intake was targeted at 1600 kcal/day, consisting of 9.5% protein, 48% carbohydrates, and 42.5% fat. HbA1c was 8.8% (normal range: 4-6%), and C-peptide was low (0.470 ng/mL; normal range: 0.9-7.1 ng/mL). Autoantibody analysis revealed islet cell antibodies (weak positive), anti-insulin antibodies (18.5%; reference: 0-5.5%), and anti-GAD antibodies (139 U/mL; reference: 0-1 U/mL). Based on these findings, the diagnosis of T1DM was established.

Subsequent management included subcutaneous insulin therapy consisting of rapid-acting insulin with meals and basal insulin with glargine. Dietary management was further adjusted to provide 2.2 g/kg/day MSUD formula protein and 4.5 g/day of natural protein, with strict carbohydrate monitoring via carbohydrate counting. Carbohydrate intake was regulated, with three main meals containing 55 g of carbohydrates each and three snacks containing 9 g each. During the three-year follow-up period, the patient maintained metabolic stability, with only one episode of decompensation triggered by an intercurrent infection.

Case 2

An 11-year-old male patient with obesity (BMI: 18.6 kg/m²; 2.3 SDS) and a clinically and biochemically established diagnosis of MSUD—based on elevated BCAA levels and a favorable response to dietary treatment—was found to have hyperglycemia (444 mg/dL) during a routine outpatient visit. Despite adequate metabolic control of MSUD as indicated by a leucine level of 123 µmol/L, the patient reported a two-week history of polydipsia and polyuria. He was asymptomatic at presentation and was admitted for inpatient evaluation and management.

Initial laboratory assessment revealed a pH of 7.3, pO_2 28.9 mmHg, pCO_2 46 mmHg, HCO_3 26.6 mmol/L, and a blood ketone level of 2.4 mmol/L. HbA1c was markedly elevated at 11.8%, consistent with a new diagnosis of T1DM. Further autoimmune screening showed positive anti-IA-2 antibodies at 169.8 U/mL (>10) and anti-ZnT8 antibodies at 767.2 U/mL (>20), supporting the diagnosis of T1DM.

Prior to admission, the patient's MSUD diet consisted of a leucine-free amino acid mixture providing 1 g/kg/day of protein, with valine and isoleucine supplementation adjusted based on plasma levels. The diet also included 3 g of natural protein sourced from eggs, yogurt, legumes, and rice, while fruits, vegetables, tubers, fats, and low-protein products were unrestricted. The macronutrient distribution was 55% carbohydrates, 32% fats, and 13% proteins, totaling 2,238 kcal/day and 1.31 g total protein/kg/day (Table 1).

Management of the hyperglycemia and ketosis included intravenous regular insulin and fluid resuscitation. Following stabilization, the patient was initiated on a multiple daily insulin injection regimen, consisting of rapid-acting insulin with meals and a daily basal insulin.

To prevent potential metabolic decompensation, dietary management was adjusted to provide 1.5 g/kg/day of leucine-free amino acid mixture while suspending natural protein intake temporarily. Only fruits, vegetables, olive oil, and specialized low-protein foods were permitted to mitigate the risk of leucine elevation. Carbohydrate intake was regulated, with three main meals containing 60 g of carbohydrates each and two snacks containing 20 g each. Education regarding carbohydrate counting was provided to the patient and family, aligning with protocols for pediatric diabetic patients.

Upon achieving metabolic stabilization and normalization of leucine levels, the dietary plan was adjusted to its pre-admission macronutrient composition, with continued emphasis on carbohydrate control. The revised dietary regimen provided 52% carbohydrates, 30% fats, and 18% proteins, totaling 1,690 kcal/day and 1.33 g total protein/kg/day.

During the subsequent two-month follow-up period, the patient remained metabolically stable without any episodes of metabolic decompensation related to either MSUD or T1DM. The comprehensive dietary management strategy effectively maintained glycemic control and metabolic stability in the context of these dual metabolic disorders.

Discussion

The coexistence of MSUD and T1DM poses a significant clinical challenge, primarily due to the distinct and potentially conflicting dietary management requirements of these conditions. In MSUD, lifelong restriction of branched-chain amino acids (BCAAs) is necessary to prevent metabolic crises and neurotoxicity. In contrast, the dietary management of T1DM does not involve carbohydrate restriction per se, but rather focuses on individualized meal planning tailored to the patient's age, gender, and pubertal stage, with insulin regimens adjusted accordingly. Carbohydrate counting is a cornerstone of T1DM management, enabling flexible insulin dosing to maintain optimal glycemic control. The two cases presented in this report illustrate the complex interplay between BCAA metabolism and glucose regulation, underscoring the importance of a coordinated and individualized dietary approach to prevent metabolic decompensation and ensure effective management in patients with dual diagnoses (5-8).

In both Case 1 and Case 2, dietary management involved reducing the proportion of daily caloric intake from carbohydrates to 45–50%, while increasing calories derived from fat and protein through the use of leucine-free medical formulas. This approach allowed for adequate energy intake without worsening hyperglycemia or elevating leucine levels. Natural protein intake was carefully adjusted according to blood leucine concentrations to prevent metabolic decompensation and ensure glycemic control. In Case 1, the patient required an insulin infusion starting at 0.05 U/kg/h during acute decompensation, which was subsequently transitioned to a basal-bolus regimen upon stabilization. In Case 2, multiple daily insulin injections were initiated following diagnosis, and insulin doses were titrated based on carbohydrate intake and clinical status, with temporary increases noted during periods of intercurrent infections. These observations suggest a potential link between MSUD decompensation and increased insulin requirements, possibly reflecting transient insulin resistance. It is important to note that current T1DM management does not support carbohydrate restriction; instead, it emphasizes individualized meal planning and flexible insulin dosing based on carbohydrate counting. Furthermore, excessive intake of fat and protein (>25 g fat or >40 g protein per meal) necessitates additional insulin administration to maintain postprandial glycemic targets. Although detailed macronutrient breakdowns are provided, neither patient consistently exceeded the fat or protein thresholds that would have necessitated complex insulin dosing strategies. These cases highlight the importance of a nuanced dietary and insulin strategy in managing coexisting MSUD and T1DM.

The relationship between branched-chain amino acid (BCAA) accumulation and insulin resistance has garnered increasing attention in recent years, particularly in the context of coexisting metabolic disorders such as maple syrup urine disease (MSUD) and type 1 diabetes mellitus (T1DM). Elevated levels of branched-chain amino acids (BCAAs) have been associated with impaired insulin sensitivity and disrupted glucose utilization, especially in patients with type 1 diabetes mellitus (T1DM), as demonstrated in Case 1. In this patient, a precipitous and substantial increase in blood glucose levels occurred despite previously stable metabolic control of MSUD under specialist supervision. This clinical observation is consistent with emerging evidence suggesting that the BCAAs themselves are not the primary contributors to mitochondrial dysfunction, cellular stress signaling, and beta-cell apoptosis. Rather, it is the toxic metabolic byproducts of the BCAAs that are responsible for these adverse effects, which ultimately worsen insulin resistance (5-9).

One proposed mechanism involves the regulatory role of adiponectin (APN), a hormone known to modulate mitochondrial phosphatase 2C (PP2Cm), which plays a critical role in BCAA catabolism. Disruption of this regulatory axis has the potential to exacerbate BCAA accumulation and contribute to insulin resistance in affected individuals (6,9). Conversely, insulin resistance has been shown to promote aminoacidemia by increasing protein catabolism, a process typically inhibited by insulin, or by impairing branched-chain amino acid (BCAA) oxidation in peripheral tissues (10). Of particular significance is the observation that the concurrence of MSUD and T1DM can markedly elevate the risk of diabetic ketoacidosis (DKA). This heightened risk is attributable to the fact that both conditions are associated with ketotic metabolic states, and their combined effect may be synergistic in amplifying insulin resistance (10).

The clinical outcomes observed in these cases provide substantial evidence that the concurrent administration of dietary and pharmacological interventions can effectively stabilize metabolic and glycemic parameters. During the subsequent follow-up period, both patients exhibited stable leucine levels and attained glycemic control without substantial metabolic crises, despite the presence of dual diagnoses. This finding aligns with the conclusions of previous studies, which indicated that effective management of MSUD can prevent metabolic decompensation, even in the presence of T1DM (5,6). Moreover, the implementation of structured carbohydrate counting and targeted insulin therapy in T1DM patients with MSUD proved instrumental in preventing severe hyperglycemia and ketosis episodes.

In both cases presented, the diagnosis of T1DM was supported by positive autoantibodies, including anti-GAD, anti-IA-2, and anti-ZnT8, indicating a classic autoimmune etiology rather than a secondary metabolic consequence of MSUD. This underscores the importance of monitoring glucose metabolism and autoantibody profiles in MSUD patients, especially when nonspecific symptoms such as polydipsia or weight loss emerge. Notably, despite long-term follow-up of many MSUD patients in clinical practice, the co-occurrence of T1DM is rarely reported in the literature. This may suggest either a coincidental association or under-recognition due to overlapping or misattributed symptoms during decompensation episodes. Further investigation into the true incidence and mechanisms of this co-occurrence is warranted. In this context, a deeper understanding of the pathophysiological mechanisms underlying the coexistence of MSUD and T1DM is needed, particularly the potential role of BCAA in modulating insulin sensitivity. Additionally, exploration of the impact of adiponectin (APN) and other metabolic regulators on BCAA metabolism may provide valuable insights into novel therapeutic targets aimed at mitigating insulin resistance in patients with dual diagnoses.

Ethics

Informed Consent: Consent form was filled out by all participants.

Conflict of interest: None declared.

Authorship Contributions

Concept: Engin Köse, Marta Suárez González, Isolina Riaño Galán, Fatma Tuba Eminoğlu, Design: Engin Köse, Pınar Kılıçdağı Çanakcı, Furkan Yolcu, Data Collection or Processing: Engin Köse, Marta Suárez González, Isolina Riaño Galán, Pınar Kılıçdağı Çanakcı, Furkan Yolcu, Ayşegül Ceran Analysis or Interpretation: Engin Köse, Pınar Kılıçdağı Çanakcı Literature Search: Engin Köse, Marta Suárez González, Pınar Kılıçdağı Çanakcı, Writing: Engin Köse, Pınar Kılıçdağı Çanakcı, Marta Suárez González, Fatma Tuba Eminoğlu.

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Table 1: Dietary composition and caloric distribution in MSUD patients before and after T1DM diagnosis.

Parameter	Case 1		Case 2	
	MSUD	**MSUD + T1DM**	**MSUD**	**MSUD + T1DM**
Total Calories (kcal/d)	1400	1600	2238	1690
Protein (% of kcal)	8.5%	9.5%	13%	18%
Carbohydrates (% of kcal)	56%	48%	55%	52%
Fat (% of kcal)	35.5%	42.5%	32%	30%

MSUD: Maple Syrup Urine Disease, T1DM: Type 1 Diabetes Mellitus.