

Severe growth retardation during carbohydrate restriction in type 1 diabetes mellitus: A case report

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Highlights

- Carbohydrate restriction in a child with T1DM severely impaired height growth velocity.
- Growth charts are useful to detect inappropriate dietary restriction.

Abstract. Carbohydrate restriction is not typically recommended for children with type 1 diabetes mellitus (T1DM) because of concerns regarding growth retardation, ketoacidosis, severe hypoglycemia, and dyslipidemia. There is no consensus regarding the effects of carbohydrate restriction on the growth of children with T1DM. However, some previously reported cases of T1DM exhibited growth retardation during carbohydrate restriction, whereas others showed no obvious impairment. A female child with T1DM exhibited severe height growth velocity impairment during carbohydrate restriction in early childhood. Her height standard deviation score (SDS) was 1.12 at the initial T1DM diagnosis (2 yr and 11 mo of age) and -1.33 at 4 yr and 8 mo of age. Her height velocity was only 1.7 cm/yr (SDS -7.02). Discontinuing carbohydrate restriction substantially improved her height growth velocity. Implementing a carbohydrate-restricted diet in children with T1DM can negatively affect height growth velocity.

Key words: carbohydrate restriction, low carbohydrate diet, type 1 diabetes mellitus, growth retardation

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Introduction

Carbohydrate restriction is typically not recommended in children with type 1 diabetes mellitus (T1DM) because of the risk of growth retardation, hypoglycemia, ketosis, and dyslipidemia (1, 2). According to the International Society for Pediatric and Adolescent Diabetes guidelines 2022, the recommended macronutrient intake for children and adolescents is 40–50% energy from carbohydrates, 30–40% energy from fat, and 15–25% energy from protein (2). However, some patients with T1DM are placed under carbohydrate restriction to achieve better control of the blood glucose level, reduce insulin doses, or lose weight (3). Recently, a single-center study developed a protocol for safe carbohydrate restriction in children with T1DM (4), although 39% of children with T1DM who had experienced a low-carbohydrate diet started restriction without consulting a diabetologist (3). The available evidence regarding the impact of carbohydrate restriction on the growth of children with T1DM remains insufficient. Minor decreases in height standard deviation scores (SDS) were reported in 34 children with T1DM who underwent carbohydrate restriction (5). Their height SDS decreased from 0.41 at diagnosis to 0.2 at data collection (5). Some children with T1DM who were carbohydrate-restricted had no obvious growth retardation (6, 7), whereas others had severely retarded growth (8, 9). Herein, we report the case of a female child with T1DM who developed severe growth retardation, particularly in height, during carbohydrate restriction in early childhood.

Case Report

A female aged 2 yr and 11 mo presented with diabetic ketosis. Her fasting C-peptide level was extremely low (0.09 ng/mL), indicating the need for insulin therapy. Her glutamic acid decarboxylase antibody was 23.0 U/mL (reference range: 0–1.4 U/mL). On the basis of these results, the patient was diagnosed with T1DM. Therefore, intensive insulin therapy was initiated. Her parents were instructed in how to count carbohydrates in order to determine the appropriate insulin dose for her meals. We explained that carbohydrate counting was used to adjust the bolus insulin dose to the amount of carbohydrate required to provide an ordinal balanced diet, similar to that of healthy children. At discharge, her height was 95.3 cm (SDS 1.12) and her body weight was 15.55 kg (SDS 1.54). Her father's height was 178 cm, and her mother's height was 162 cm (her target height was 163.5 cm, with a target range of 155.5 cm–171.5 cm (10)). Her HbA1c level ranged between 5.7% and 6.7%, and she did not develop ketoacidosis after discharge. In addition, occasional mild hypoglycemia was noted but not severe hypoglycemia. Severe growth retardation was observed at 4 yr and 8 mo of age (Fig. 1) (11). Her height and body weight were 98.5 cm (SDS –1.33) and 18.1 kg (SDS 0.72), respectively. Her height growth velocity was only 1.7

cm/yr (SDS –7.02). At that time, her bone age was 3.5 yr of age. Her insulin-like growth factor-I (IGF-I) level was very low (32 ng/mL, SDS –2.73). Dyslipidemia and ketosis were detected (Table 1). However, her thyroid hormone levels were within normal ranges (Table 1). An arginine stimulation test showed a peak GH level of 1.22 ng/mL (normal > 6.0 ng/mL). A magnetic resonance imaging scan of the brain showed no abnormalities.

Her mother disclosed that carbohydrate restriction (< 60 g/d) had been implemented, after discharge, to reduce the variability of her blood glucose level because the fluctuation in the patient's blood glucose level made her parents anxious. Her parents had read a book that recommended carbohydrate restriction. To stabilize her blood glucose level, the parents implemented carbohydrate restriction. The restriction was initiated, without consulting us, because her parents assumed that we would not agree to a carbohydrate-restricted diet. To ensure sufficient energy, her parents provided her with a greater amount of fat and protein, such as mayonnaise, fish, meat, eggs, cheese, and bread made from soy flour. Since her parents were unwilling to disclose information regarding the restriction and unwilling to see a dietician at that time, we could not evaluate the precise energy intake or energy balance during carbohydrate restriction. Her total insulin dose was 7–8 units/d (0.39–0.44 units/kg/d). We prompted her parents to discontinue carbohydrate restriction, and after reading articles on ketogenic diets that inhibit linear growth, they began to gradually ease the restriction. At 5 yr and 4 mo of age, her energy intake was estimated to be 1,395 kcal/d, with 46% derived from carbohydrates (approximately 157 g/d), 39% from fat, and 15% from protein. Her parents refused re-examination using the GH stimulation test; therefore, we could not confirm whether she had a GH deficiency (GHD). However, her IGF-I level increased to 61 ng/mL (–1.80 SD) at 5 yr and 5 mo of age. Her height growth velocity significantly improved (Fig. 1) to 5.62 cm/yr (SDS –1.22) at 5 yr and 8 mo of age and 7.54 cm/yr (SDS 2.05) at 6 yr and 8 mo of age. Ketosis and dyslipidemia gradually normalized by 5 yr and 11 mo of age. The patient reached an adult height of 159.3 cm (SDS 0.55) at 14 yr of age.

Discussion

Our patient showed that implementing a carbohydrate-restricted diet can severely retard the linear growth of a child with T1DM. Although the impact of carbohydrate restriction on the height growth velocity in children with T1DM is controversial (6–9), four children exhibited severe height growth retardation during carbohydrate restriction (Table 2) (8, 9). Two showed apparent improvements in height growth velocity after discontinuing carbohydrate restriction (9), which is consistent with the result for our patient. The other two children were still undergoing restriction at the last examination (8). In our patient and in previously reported cases, the duration of growth retardation

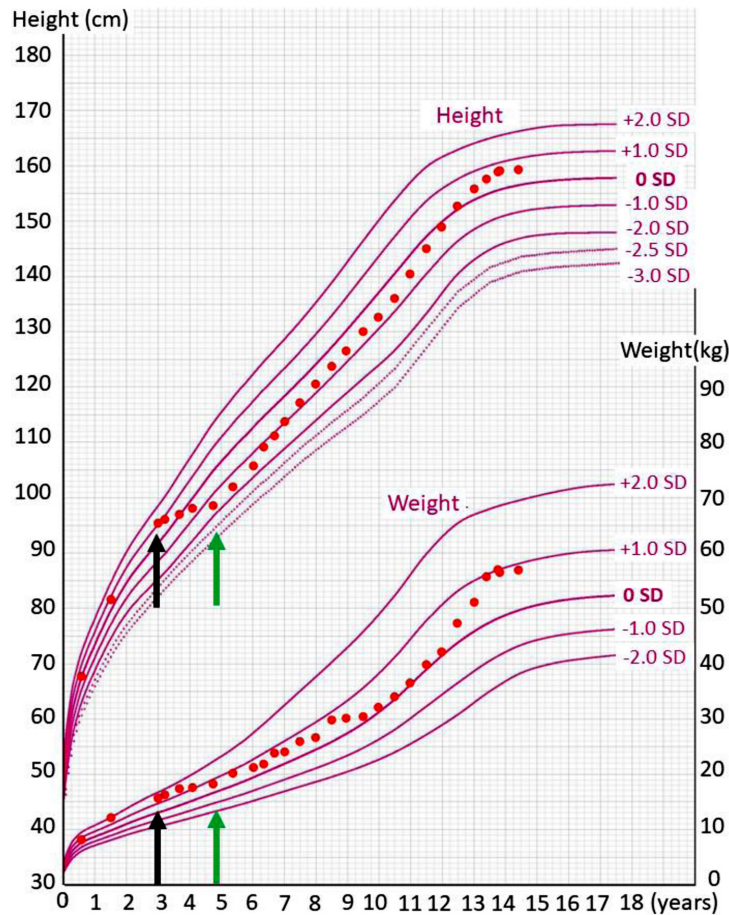


Fig. 1. Standard deviation for the patient’s height and weight. The black arrows show the discharge. The green arrows show the initiation of easing carbohydrate restriction.

Table 1. Endocrinological and biochemical data at the age of 4 yr and 8 mo

		Reference range
IGF-1 (ng/mL)	32	48–238
TSH (μIU/mL)	1.71	0.31–3.9
FreeT ₃ (pg/mL)	2.52	2.29–4.35
FreeT ₄ (ng/dL)	1.06	1.01–1.98
Anti-thyroid peroxidase antibody (IU/mL)	22.2	0.00–16.0
Thyroglobulin antibody (IU/mL)	16	0.00–28.0
Total protein (g/dL)	7.3	6.2–7.9
Albumin (g/dL)	5	4.0–5.0
Triglyceride (mg/dL)	123	35–114
Total cholesterol (mg/dL)	519	130–220
LDL cholesterol (mg/dL)	408	< 140
HDL cholesterol (mg/dL)	86	> 39
Total ketone body (μmol/L)	4,607	28–120
3-Hydroxybutyric acid (μmol/L)	696	0–74

The values above and below the reference ranges are boldfaced.

coincided with the duration of carbohydrate restriction (9). This suggests that implementing a carbohydrate-restricted diet in children with T1DM can impair height growth velocity. Thus, a carbohydrate-restricted diet should not be implemented in children with T1DM, at least without carefully monitoring their growth trajectories. However, it was difficult to clarify whether

carbohydrate restriction alone caused growth retardation in our patient, because her meals during carbohydrate restriction were not accurately evaluated. Thus, we cannot ignore the possibility that other problems caused by the implementation of the carbohydrate-restricted diet, such as energy or protein deficiencies, caused the height growth retardation.

Table 2. Characteristics of cases with severe height growth velocity impairment

Case No. in the literature	de Bock M <i>et al.</i> , 2018		Franceschi R <i>et al.</i> , 2020		This study
	Case 4	Case 5	Case 1	Case 2	
Sex	F	M	M	F	F
1) Age at diagnosis of T1DM	4 yr	2 yr	5 yr 4 m	6 yr 6 m	2 yr 11 m
Height at diagnosis of T1DM	93.5 cm ^a	84 cm ^b	114 cm	130 cm	95.3 cm
Height SDS at diagnosis of T1DM	-2.0 SD	-1.36 SD	0.04 SD	1.93 SD	1.12 SD
2) Age at physical examination during carbohydrate restriction	11.3 yr	4 yr	6 yr 5 m	8 yr	4 yr 8 m
Height during carbohydrate restriction	123.9 cm	95.9 cm	114 cm	133 cm	98.5 cm
Height SDS during carbohydrate restriction	-3.28 SD	-2.36 SD	-1.06 SD	0.89 SD	-1.33 SD
Height gain from 1) to 2) (cm/yr)	30.4/7.3	11.9/2	0/1.1	3/1.5	3.2/1.8
Continuing carbohydrate restriction at the last visit	YES	YES	NO	NO	NO
Nutrient intake during carbohydrate restriction					
Carbohydrate intake during the restriction	NA	45 g/d	30 g/d	40 g/d	<60 g/d
Carbohydrate (%)	39	6	12	17	NE
Protein (%)	19	27	27	30	NE
Fat (%)	42	67	61	53	NE
Energy shortage	+	+	+	+	NE
Percentage of energy intake for expected energy requirement (%)	76	86	70	60	NE
Adverse event except for growth retardation during carbohydrate restriction	-	dyslipidemia	-	-	dyslipidemia

NA, not available; NE, not evaluated; SDS, Standard deviation score. ^a examined 4 wk after diagnosis, ^b examined 2 wk after diagnosis.

We assumed that one of the causes of our patient's growth retardation was the reduced carbohydrate intake, which could be aggravated by T1DM. A ketogenic diet in patients with epilepsy is analogous to a carbohydrate-restricted diet in patients with T1DM. Although the impact of a ketogenic diet on growth is controversial, some reports have indicated a negative impact (12–14), which our patient's parents read about. In 22 children without T1DM, a ketogenic diet resulted in a height growth velocity decrease from a median SDS of -0.6 ± 2.2 SD to a median SDS of -4.1 ± 2.2 SD (13). Thus, carbohydrate restriction may adversely affect the growth of children with or without T1DM. Moreover, T1DM may exacerbate growth retardation in children under carbohydrate restriction compared with those without T1DM. Our patient experienced a more severe decline in height growth velocity during carbohydrate restriction (SDS -7.02) compared to patients with epilepsy on a ketogenic diet (SDS -4.1 ± 2.2 SD) (13). Children with T1DM are prone to growth failure and have low a IGF-I level, which is likely to be related to poor glycemic control (1, 15). Recent studies have shown that intensive insulin therapy improves glycemic control, height growth velocity, and IGF-I level in children with T1DM (1, 16, 17). Although the height outcome in T1DM remains controversial, growth disturbances have been minimized or even normalized (16, 18). Thus, a sufficient insulin dose is crucial for appropriate height growth velocity in children with T1DM as lowering the insulin dose due to carbohydrate restriction may impair growth. Our patient's family used carbohydrate counting to determine the insulin dose for

each meal and the resulting carbohydrate restriction may have led to a low insulin dose. Patients with T1DM tend to have a lower serum IGF-I level due to an inadequate intraportal insulin concentration because insulin modulates hepatic GH receptor expression (17, 18). Taken together, an inadequate exogenous insulin dose due to carbohydrate restriction in children with T1DM can cause a more significant decline in the intraportal insulin concentration. This might result in a much lower IGF-I level and a greater height growth velocity retardation than in children without T1DM implementing carbohydrate restriction. Additionally, as insulin signaling in chondrocytes promotes chondrocyte differentiation and proliferation, decreased insulin signaling in the chondrocyte insulin receptor is likely to retard growth (19). Therefore, the low insulin dose administered to our patient may have reatarded growth due to decreased insulin signaling in chondrocytes. Further studies are necessary to determine whether carbohydrate restriction has a more negative effect on growth in children with T1DM than in those without T1DM.

Other potential causes of growth retardation in our patient were energy or protein shortages due to the implementation of a carbohydrate-restricted diet. A carbohydrate-restricted diet can lead to energy shortages and growth retardation. It is unclear whether the patient's energy intake was sufficient during carbohydrate restriction. We did not evaluate the exact energy intake and energy balance of her diet during the restriction period because her family refused the evaluation. We did not evaluate prealbumin- or

retinol-binding proteins. All four previously reported cases that displayed severe growth retardation, both in height and weight, consumed less energy than the estimated requirement (ranging from 60% to 86% of the recommended amount) (Table 2) (8, 9). It is possible that only patients with energy deficiency during carbohydrate restriction develop growth retardation, as previously reported. Our patient also showed poor weight gain (Fig.1), suggesting an energy shortage and/or insulin insufficiency. However, implementing carbohydrate restriction, on its own, may lead to a risk of shortage of energy (8, 9). Our patient may have consumed less energy than required during carbohydrate restriction, resulting in growth retardation. As for protein insufficiency, we cannot deny the possibility of a shortage of protein in our patient during carbohydrate restriction because of the lack of precise information on protein intake during the restriction. However, it was less likely that there was a severe shortage of protein because the patient's family attempted to serve protein and fat instead of carbohydrate. The four previous cases with severe retardation of height growth velocity during carbohydrate restriction did not have a shortage of protein (8, 9), suggesting that implementing a carbohydrate-restricted diet does not readily lead to a shortage of protein.

Our patient has a low IGF-I level during carbohydrate restriction, which could lead to retardation of the growth in height. The reduction in the IGF-I level in this patient could also have several potential causes. First, one of the potential causes is the low insulin concentration in the portal vein due to restricted carbohydrate intake, as discussed above. A eucaloric very-low-carbohydrate diet can reduce IGF-I synthesis by reducing insulin concentration in the portal vein, even in patients with acromegaly (20). Second, the reduction in the IGF-I level might have been caused by energy and protein shortage in our patient, as energy shortage together with a protein shortage can reduce the IGF-I level (21). Third, our patient showed a blunted response in the GH stimulation test, whereas patients with T1DM usually have GH resistance, indicating a decreased IGF-I level and an elevated GH level (18). However, it is uncertain whether our patient had GHD, as we did not conduct another GH stimulation test after discontinuation of carbohydrate restriction. Nevertheless, her height growth velocity and IGF-I level improved noticeably after terminating the restriction, suggesting that she did not have a GHD. One patient with T1DM implementing carbohydrate restriction was reported to have a poor GH response, which may have been caused by blunted pituitary GH release due to a high-fat diet (8). A study in healthy children showed that a high-fat diet may reduce exercise-induced GH release (22). Since our patient consumed a high-fat, low-carbohydrate diet, the high-fat diet may have impaired GH secretion, contributing to the low IGF-I level and impaired linear growth.

Another adverse effect of a carbohydrate-restricted

diet is a high cholesterol level. Our patient ate more fat like mayonnaise instead of carbohydrates, which might have contributed to the elevation of the cholesterol level. Hyperlipidemia has been reported in patients during carbohydrate-restricted diet (1, 5). As her serum albumin level did not decrease, it is unlikely that hypoalbuminemia caused by the low-protein diet resulted in decreased collagen osmolality and a high cholesterol level.

Although it was unclear whether the carbohydrate shortage itself or other factors, such as an energy shortage related to the restriction, caused growth retardation in our patient, implementing carbohydrate restriction dramatically retarded her growth. Therefore, children with T1DM should not restrict their carbohydrate intake, without careful monitoring. It is important to evaluate the growth of children with T1DM to identify inappropriate diets. For our patient, her parents started carbohydrate restriction without consultation. Similar to our patient, some children with T1DM and their families may initiate carbohydrate restriction without consulting a diabetologist (3). Insulin requirement is usually minimal during the honeymoon period which is the brief phase that patients experience the reduction of necessity of insulin dosage to normalize their blood glucose level after initiating insulin therapy (9); therefore, it may be more difficult for the attending physician to detect carbohydrate restriction, that was started immediately after T1DM diagnosis, by simply observing glucose control and insulin dose. As described in the 2022 guidelines, monitoring growth charts in children with T1DM at each clinic visit will assist in identifying changes in weight and height (2). To identify any inappropriate dietary restrictions in children with T1DM, careful evaluation of growth using growth charts is crucial.

When the parents were instructed in carbohydrate counting at the onset of the patient's T1DM, they were advised to adjust the insulin dose to her meal to allow her to eat almost freely. A previous guideline recommended that the amount and type of insulin should be adapted to the child's appetite and eating pattern (23). Recently, assessment of food intake and eating pattern by a pediatric dietician has been recommended (2). Regular assessment of energy intake and balance may be helpful in detecting inappropriate dietary restrictions.

In conclusion, implementing a carbohydrate-restricted diet in children with T1DM can significantly impair height growth velocity. Thus, severe carbohydrate restriction should not be recommended for children with T1DM without careful monitoring.

Conflict of interests: The authors have no conflicts of interest to declare.

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