Treatment of Type 2 Diabetes in Childhood Using a Very-Low-Calorie Diet

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OBJECTIVE — Pharmacologic agents currently approved for use in children with type 2 diabetes (metformin and insulin) are less than optimal for some patients. We evaluated the use of a ketogenic, very-low-calorie diet (VLCD) in the treatment of type 2 diabetes.

RESEARCH DESIGN AND METHODS — We conducted a chart review of 20 children (mean age 14.5 ± 0.4 years) who consumed a ketogenic VLCD in the treatment of type 2 diabetes. Several response variables (BMI, blood pressure, HbA_{1c}, blood glucose, and treatment regimens) were examined before, during, and up to 2 years after the diet and compared with a matched diabetic control group.

RESULTS — Before starting the diet, 11 of 20 patients were treated with insulin and 6 with metformin. Mean daily blood glucose values fell from 8.9 ± 1.1 to 5.5 ± 0.38 mmol/l ($P < 0.0001$) in the first 3 days of the VLCD, allowing insulin and oral agents to be discontinued in all but one subject. BMI fell from 43.5 ± 1.8 to 39.3 ± 1.8 kg/m^2 ($P < 0.0001$) and HbA_{1c} dropped from 8.8 ± 0.6 to 7.4 ± 0.6% ($P < 0.005$) as the diet was continued for a mean of 60 ± 8 days (range 4–130 days), and none required resumption of antidiabetic medications. Sustained decreases in BMI and insulin requirements were observed in patients remaining on the VLCD for at least 6 weeks when compared with those of the control group.

CONCLUSIONS — The ketogenic VLCD is an effective short-term, and possibly long-term, therapy for pediatric patients with type 2 diabetes. Blood glucose control and BMI improve, allowing the discontinuation of exogenous insulin and other antidiabetic agents. This diet, although strict, has potential as an alternative to pharmacologic therapies for this emerging subset of diabetic individuals.

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The prevalence of obesity in adolescence has increased dramatically within the past two decades, with at least 12% of adolescents defined as overweight (BMI above the 95th percentile for age and sex) (1). The U.S. National Diabetes Commission and the Nurse's Health Study have both found a direct relationship between weight gain and the risk for diabetes (2,3). Excessive weight among adolescents threatens to become a major public health problem, as the emergence of type 2 diabetes in this age-group has risen exponentially (4). A number of groups have reported a profound increase in the incidence of type 2 diabetes among minority children in North America (5–9). Among African-American adolescents, this subset of diabetes is frequently associated with morbid obesity and hypertension (8,10). This condition is characterized by the absence of islet cell antibodies, normal to elevated fasting C-peptide levels, acanthosis nigricans, and a parental history of type 2 diabetes (11). At the time of presentation, many of the signs of type 1 diabetes (weight loss, polyuria, and polydipsia) may be lacking, while variable degrees of ketosis and even ketoacidosis are quite common (12). Obesity and puberty appear to combine with genetic predisposition to result in disease presentation (13).

The approach to treatment of pediatric type 2 diabetes is complicated by the fact that there are currently few data comparing the relative efficacies of diet, exercise, insulin, and other drug therapies. Furthermore, pediatric patients require more aggressive, efficacious therapies than adults in light of their increased risk for macrovascular and microvascular complications from longer diabetes exposure (12). As the treatment of choice for type 1 diabetes, exogenous insulin has traditionally been used in all forms of diabetes that occur in childhood (14). However, exogenous insulin therapy is frequently complicated by overeating and excessive weight gain (15). As the antecedents of type 2 diabetes appear to be insulin resistance and hyperinsulinemia, therapies that result in weight reduction and a lowering of ambient insulin concentrations might afford the best opportunity to avoid the development of a vicious cycle. The efficacy and safety of pharmacologic therapies that improve insulin resistance (thiazolidinediones and metformin) in comparison with insulin remain unclear in pediatric patients (12).

The ketogenic, very-low-calorie diet (VLCD), or protein-sparing modified fast, is a "low-insulin diet" that has previously been used in children (16). Recently, we have shown (17) that this diet induces rapid weight loss and improves sleep apnea while preserving lean body mass in nondiabetic obese children. In obese adults with type 2 diabetes, the diet has been shown to safely induce rapid weight loss while decreasing hyperinsulinemia (18) and improving blood pressure (19,20). As the safety and efficacy of VLCDs in pediatric type 2 diabetic patients is currently unknown, we evaluated the ability of this diet to reduce weight and improve hyperglycemia while decreasing the dependence on antidiabetic medications. Short- and long-term effects

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Abbreviations: VLCD, very-low-calorie diet.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Subject and control baseline data*

	All subjects attempting diet	Subjects on diet >6 weeks	Control subjects
n	20	15	
Age (years)	14.5 ± 0.4	14.9 ± 0.4	14.9 ± 0.5
Sex (M/F)	5/15	5/10	5/10
Duration of diabetes (months)	21.0 ± 4.9	24.6 ± 6.5	24.1 ± 4.7
HbA_{1c} (%)	8.8 ± 0.6	8.8 ± 0.8	8.9 ± 0.8
Weight (kg)	120.5 ± 5.9	122.4 ± 6.6	118.0 ± 6.2
BMI (kg/m^2)	43.5 ± 1.8	44.2 ± 2.3	43.7 ± 2.8
Arterial pressure (mmHg)	89 ± 3	89 ± 3	88 ± 3
Mean insulin dose (units/kg)	0.36 ± 0.09	0.31 ± 0.10	0.30 ± 0.09
Number on insulin	11	8	8
Number on oral agents	6	5	4

Data are means ± SE.

of the diet were assessed via comparison with a matched group of subjects with type 2 diabetes.

RESEARCH DESIGN AND METHODS

We reviewed the charts of all children ($n = 20$, mean age 14.5 ± 0.4 years) (Table 1) with type 2 diabetes consecutively admitted to our hospital for the introduction of a high-protein, low-fat, ketogenic VLCD as either primary or secondary treatment for this condition. Subjects were selected due to their associated morbid obesity (i.e., BMI >30 kg/m^2), and data were collected from March 1997 to December 2002. The diagnosis of diabetes was based on either oral glucose tolerance testing or a HbA_{1c} ≥7.0% (21), and typology was confirmed by fasting C-peptide levels ≥0.6 ng/ml and negative islet cell antibody testing (12). Five subjects were male, and all were African American. Due to the untested nature of this diet in adolescents with poorly controlled type 2 diabetes (mean HbA_{1c} 8.8 ± 0.6%, range 5.8–14.0%), patients were admitted to the inpatient General Clinical Research Center for 3–5 days to initiate the ketogenic VLCD. All subjects were obese, with mean weight 120.5 ± 5.9 kg and BMI 43.5 ± 1.8 kg/m^2 (Table 1). Before starting the diet, 11 of 20 subjects were treated with insulin at a mean dose of 0.66 ± 0.10 unit · kg^{-1} · day^{-1}, and 1 subject was taking metformin in addition to insulin. Of the remaining nine patients not taking insulin, five were taking metformin and only four did not require any pharmacologic therapy.

A group of children with type 2 diabetes, followed concurrently in our diabetes clinic, were selected on the basis of baseline data for comparison through a paired analysis. For each study subject, we determined all possible type 2 diabetic patients who could be matched for age, race, and sex with similar follow-up frequency throughout a 2-year period. Baseline data from the comparison group (including duration of diabetes, medications, HbA_{1c}, and BMI; all at an age matched to the individual subject) were collected and served as the basis for pairing with study subjects (without using the same control twice) (Table 1). Subjects and diabetic control subjects were followed with regular outpatient clinic visits to monitor changes in weight, blood pressure, HbA_{1c}, and antidiabetic regimen. Changes in outcome variables were compared in each subject at baseline, during the first 3 days of the diet, at the end of the diet, and periodically thereafter for up to 24 months. To further assess the impact of the diet as a diabetes treatment, we analyzed the changes in BMI, diabetes regimen, and HbA_{1c} in subjects completing at least 6 weeks of the diet ($n = 15$) and in the matched comparison group. Except during the VLCD intervention, an American Diabetes Association diet and standard pharmacologic therapy were applied in both groups with similar treatment goals.

Diet

The diet, identical to one that we previously used to treat morbid obesity (17), consisted of a high-protein, low-fat, low-carbohydrate VLCD. Between 680 and 800 calories were presented daily as simple foods containing 80–110 g protein (1.5 g/kg lean body mass) and <30 g each of carbohydrate and fat. Subjects consumed ~13 oz of lean meats, 3 cups of low-calorie vegetables, and ad libitum low-calorie foods containing Nutrasweet. Because this diet is not nutritionally complete and may cause electrolyte loss via osmotic diuresis, subjects were required to consume >200 mEq sodium chloride and a minimum of 8 cups carbohydrate-free fluid daily. The diet was also supplemented with 30 mEq potassium chloride, 1,200 mg elemental calcium as calcium carbonate, and two multivitamins with minerals and iron each day. The subjects and their parents were instructed in the home preparation of the diet and discharged when moderate or large ketones were present in at least two consecutive urine tests. Subjects were encouraged to follow the ketogenic VLCD until they had reached a predefined treatment goal (usually a 10% reduction in BMI and normalization of HbA_{1c}) and were asked to inform us immediately if they planned to discontinue the diet so we could evaluate appropriate diabetes therapy. During the VLCD, outpatient compliance and safety were monitored through a daily log of blood glucose readings and urine ketone tests, as well as monthly clinic checks of weight, blood glucose control (home glucose meter downloads and HbA_{1c}), and electrolyte levels (comprehensive metabolic panels). Upon discontinuation of the VLCD, patients were asked to consume a standard American Diabetes Association diet intended for modest weight reduction. As ketosis waned within 24 h of this transition, the electrolyte and mineral supplements were discontinued.

Blood pressure

Blood pressure measurements were made on the right arm with subjects in a relaxed, sitting position (Dinamap VS Monitor 8100; Dinamap, Tampa, FL) and are reported as the mean of three readings. Cuff size was based on measurements of right arm circumference and length. Mean arterial pressure was compared over time as a reflection of systolic and diastolic changes influenced by the diet. As all subjects were obese (BMI >30 kg/m^2), hypertension was defined by the adult criteria of systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg.

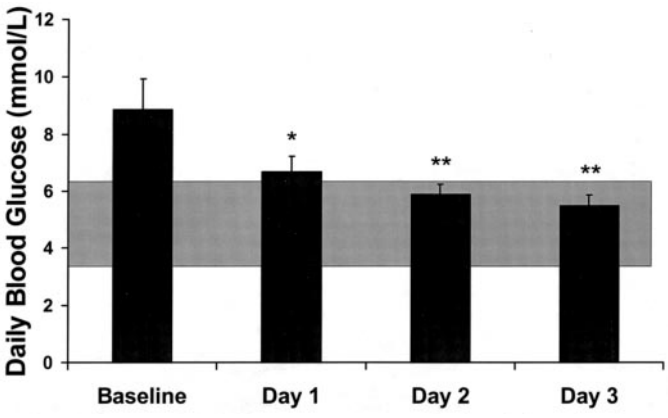

Figure 1—*Acute effects of the VLCD on mean blood glucose values from a five-point profile (q.a.c., q.h.s., and 2:00 A.M.). Glucose levels fell consistently from baseline through day 3 of the diet despite discontinuation of oral agents at baseline and a total weaning of insulin in all but one subject by day 3 of the diet. *P < 0.01, **P < 0.001 vs. baseline. The shaded area represents the normal range.*

Anthropometric measurements

Weight and height measurements were performed by a limited number of highly skilled technicians. Initial weights were determined using a single electronic scale (Detecto, Cleveland, OH) on the inpatient unit with subjects wearing light clothing without shoes or socks. Follow-up clinic weights were measured using a scale of the same make and model, with subjects in light clothing with shoes and socks removed. All heights were measured with a single Harpenden stadiometer.

Glycemic control

Oral antidiabetic medications were discontinued on the first day of the diet. Blood glucose values (Accucheck; Boehringer Mannheim, Indianapolis, IN) were strictly monitored on a five-point profile throughout the admission (premeal, bedtime, and 2 A.M.), and insulin was weaned as preprandial blood glucose levels fell below 5.5 mmol/l (100 mg/dl). Metabolic profiles were monitored during the 3–5 day hospitalization to ensure that patients were not at risk for developing electrolyte disturbances or ketoacidosis. HbA_{1c} was measured using an automated, immunochemical technique (DCA 2000; Miles, Tarrytown, NY) (normal range 4.2–6.3%).

Statistical analysis

All results are presented as means ± SE. Comparisons of BMI, HbA_{1c}, mean arterial pressure, and blood glucose in the same subject over time were made using one-way ANOVA with repeated measures or paired Student's *t* tests as appropriate. Changes in BMI and HbA_{1c} were examined for correlation to length of time on the diet using Pearson's analysis and graphed with a linear regression fit. Changes in hypertensive status and diabetes regimen were assessed using χ^2 analysis. The long-term changes in BMI, mean insulin dose, and HbA_{1c} were compared with those of a control group by performing repeated-measures ANOVA with post hoc Bonferroni Multiple Comparison tests.

RESULTS — The diet was followed for a mean of 60 ± 8 days (range 4–130 days). All subjects stopped the diet voluntarily, and none experienced nausea, vomiting, dehydration, or other side effects, such as orthostatic dizziness, muscle cramps, fatigue, or halitosis, previously reported in pediatric studies (22).

Blood pressure

Mean arterial pressure fell from 88.6 ± 2.6 to 82.8 ± 1.9 mmHg within the first 3 days of the diet ($P < 0.05$). While five of the subjects had hypertension at baseline, none remained hypertensive by day 3 of the diet or at diet completion ($P < 0.05$).

Glycemic control

In the first 3 days of the diet, the mean daily blood glucose fell from 8.9 ± 1.1 to 5.5 ± 0.38 mmol/l (Fig. 1) and all but one patient was able to discontinue all antidiabetic therapy. These improvements in blood glucose were sustained while on the diet, as was evident from the changes in HbA_{1c}, which decreased from an average of 8.8 ± 0.6% at baseline to 7.4 ± 0.6% by diet completion ($P < 0.005$). A larger reduction in HbA_{1c} was found in those subjects who followed the diet for a longer period of time ($r = -0.57$, $P < 0.01$; Fig. 2*B*, solid line). Not surprisingly, this correlation was present only in sub-

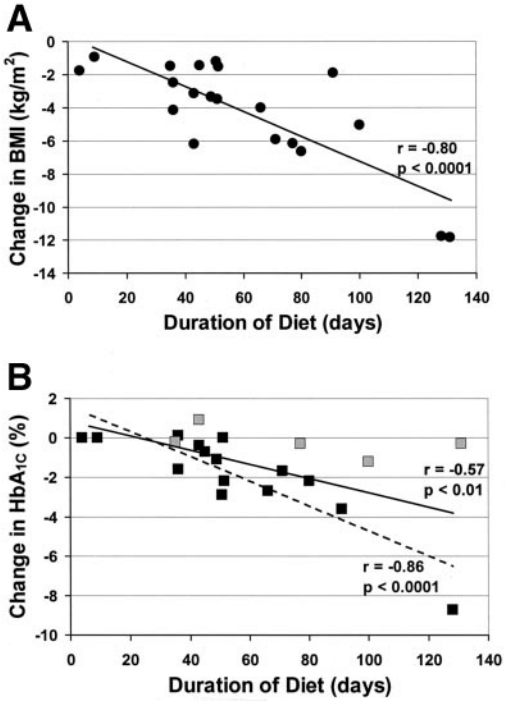

Figure 2—*Effects of the VLCD on BMI and HbA_{1c} from baseline to the end of the diet.* A*: A strong linear correlation exists between length of time on the diet and change in BMI (r = −0.80, P < 0.0001).* B*: A similar effect on glycohemoglobin was observed only in patients with initial elevations in HbA_{1c}. ■, subjects with baseline HbA_{1c} >6.5%; ▨, subjects with baseline HbA_{1c} <6.5%. The solid line represents the linear regression for all subjects (r = −0.57, P < 0.01). The dashed line represents the linear regression for subjects with baseline elevations in HbA_{1c} (r = −0.86, P < 0.0001).*

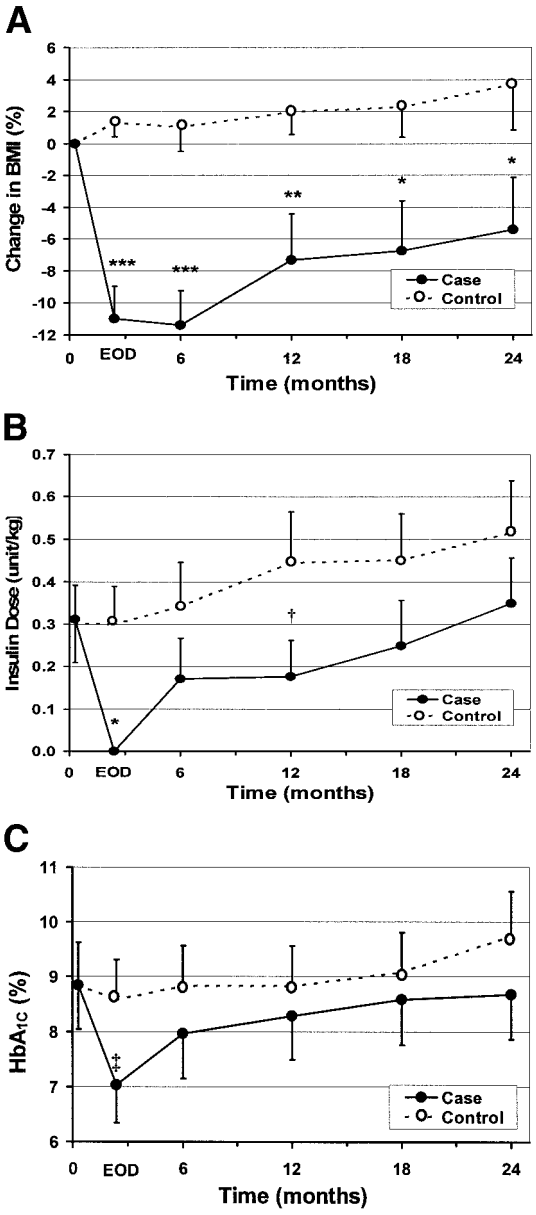

Figure 3—*Long-term effects of the VLCD on BMI* (A)*, insulin dose* (B)*, and* HbA_{1c} (C)*. In comparison with a matched control group* (○ *with dashed lines), subjects compliant with the VLCD for >6 weeks* (● *with solid lines) experienced sustained decreases in BMI* (*P < *0.05,* **P < *0.01,* ***P < *0.001 vs. baseline and control), but only transient reductions in insulin requirements* (†P < *0.01 vs. baseline and control) and glycohemoglobin* (‡P < *0.05 vs. baseline only).*

jects who had baseline levels ≥6.5% ($r = -0.86$, $P < 0.0001$; Fig. 2*B*, dashed line). Notably, all subjects who remained compliant for at least 8 weeks achieved HbA_{1c} levels in the normal range. Unfortunately, these effects on HbA_{1c} were not sustained, as the VLCD-treated subjects demonstrated a gradual rise in HbA_{1c} (Fig. 3*C*).

Weight loss

All subjects lost weight while on the diet, and 11 of 20 lost >10 kg. Although weight loss was variable, subjects lost an average of 11.4 ± 1.9 kg by the end of the diet ($P < 0.0001$), representing 9.3 ± 1.6% of total body weight. Likewise, BMI decreased from 43.5 ± 1.8 to 39.3 ± 1.7 kg/m^2 ($P < 0.0001$). As was the case with HbA_{1c}, those subjects who followed the diet for a longer period of time experienced a greater decrease in BMI ($r = -0.80$, $P < 0.0001$) (Fig. 2*A*). Furthermore, the change in HbA_{1c} was correlated with percentage weight loss, as subjects who lost more weight experienced a greater fall in HbA_{1c} ($r = 0.49$, $P < 0.02$). Long-term follow-up of patients on the diet for at least 6 weeks showed that BMI was still significantly reduced 2 years after diet initiation (44.2 ± 2.3 vs. 41.2 ± 2.1 kg/m^2, $P < 0.05$). When compared with a matched control group, the change in BMI was significantly different throughout the 2-year follow-up period (Fig. 3*A*). Although VLCD patients did regain some weight after the initial drop in BMI, their rate of weight gain was similar to that of the control group. Over the 2 years of observation, the control group experienced a 3.7% increase in BMI, compared with a net 5.4% reduction in the VLCD-treated group.

Pharmacologic treatment

Before starting the diet, all oral antidiabetic agents were discontinued. Improved blood glucose control allowed insulin to be discontinued in all but one subject (who was not compliant), and no other subjects required resumption of medications during the course of the diet. As seen in Fig. 3*B*, the insulin dose was lower in the subjects than that of their matched controls. However, this difference only reached statistical significance at the end of the diet and at the 12-month follow-up. The groups were no different with respect to their use of metformin (data not shown).

CONCLUSIONS

— The profound increase in adolescent obesity has been implicated in the concomitant emergence of type 2 diabetes in this population (4), and it has been suggested that a sedentary lifestyle, in conjunction with easy access to a calorie-dense diet, aggravates obesity and type 2 diabetes in this population (23–25). As a result, clinicians must explore treatment plans that combat society's trends toward inactivity and excessive dietary energy and fat consumption. While changes in diet and exercise pattern are currently recommended as "first-line" therapies for diabetes and obesity (26,12), successful diabetes management without oral medications or insulin occurs in <10% of adult patients with diabetes over time (12). As data demonstrating the effectiveness of oral hypoglycemic agents in pediatric type 2 diabetes are very limited (27), insulin remains a major pharmacologic therapy for this condition. Unfortunately, this approach may increase the risk of obesity and obesity-related complications.

Weight reduction is one of the most effective therapies for obese patients with type 2 diabetes. The ketogenic VLCD is a "low-insulin diet" that has been shown to safely induce rapid weight loss while preserving lean body mass in nondiabetic

obese children (16,17,22). The VLCD causes similar weight loss in obese adults with type 2 diabetes while improving endogenous insulin secretion and lowering HbA_{1c} (28). To date, the effects of this diet remain untested in a population of pediatric type 2 diabetic subjects.

A number of the results of the present study are analogous to findings from similar studies in adults with type 2 diabetes and in obese children. Weight loss, the most outwardly apparent benefit of the VLCD, is a good example. Our subjects lost an average of 11.4 kg during the diet (5.8 kg/month), which is comparable with that in nondiabetic adolescents (17,22,29) and, in fact, exceeds that of most studies in diabetic adults (19,28,30–32). These results were achieved in a predominantly outpatient setting and without the benefit of a behavioral therapy component. Although this diet constitutes a dramatic change in dietary habits for this patient population, we suspect that our subjects' compliance may have been facilitated by this rapid weight loss, along with their decreased reliance on insulin injections and other antidiabetic medications. There is an additional appetite-suppressant effect of ketosis, which accompanies the diet and may also contribute to the success of this therapy. Despite the predisposition toward ketoacidosis observed in African-American children with type 2 diabetes (11,33), we observed no ketoacidosis during this diet, while all but one of our subjects was able to discontinue insulin treatment. However, we were very careful to exclude type 1 diabetes through the absence of multiple islet cell antibodies (ICA, insulinoma-associated protein 2, and anti-GAD) and persistence of C-peptide production.

Our results with regard to decreased dependence on antidiabetic medications, improved HbA_{1c}, and blood glucose were even more profound than those found in similar studies (18,32,34) treating obese adults with type 2 diabetes. After the reintroduction of carbohydrates into the diet, improvements in blood glucose were less impressive and similar to long-term studies in adults (28,35), which show intermediate levels of blood glucose control in the face of continued withholding of antidiabetic medications. Only one of our subjects required pharmacological treatment throughout the dietary intervention. Of note, this subject had long-standing poor metabolic control and required a high insulin dose at the outset. She was poorly compliant with all but the inpatient portion of the treatment (as assessed from weight loss, urine ketone tests, and home blood-glucose monitoring).

All subjects were encouraged to follow the diet until they had reached a predefined treatment goal, usually a 10% reduction in BMI and normalization of HbA_{1c}. The duration of dietary adherence was clearly a major determinant of success, with all subjects achieving normal HbA_{1c} levels within 8 weeks of sustained compliance. The majority of these patients remained in good control without requiring antidiabetic medications for at least 1 year after discontinuing the diet, suggesting that the diet may have some lasting effects. The possibility of sustaining these therapeutic effects in children with intermittent VLCD, as has been demonstrated in adults (19), awaits further study.

In summary, we report the first experience with a VLCD in the treatment of type 2 diabetes in childhood. During the ketogenic VLCD, patients exhibited improvements in blood glucose and HbA_{1c}, with reductions in weight and blood pressure, while still decreasing their reliance on antidiabetic medications. In addition to these acute clinical improvements, this treatment option appears to cultivate more sustained benefits on BMI. As this was not a prospective, randomized, controlled trial, we cannot rule out the distinct possibility that the long-term effects of the VLCD were due to differences between the VLCD-treated and control groups at baseline or during follow-up. We suspect that the lasting effects of the VLCD may be induced by changes in dietary habits, as has been suggested in some adult studies (28,36). Thus, the VLCD has the potential to improve diabetes control over the short term and perhaps empower diabetic individuals over the long term. Prospective studies using the VLCD in this population are needed to confirm our findings and determine optimal dietary protocols, the facilitative role of behavioral interventions, and long-term clinical outcomes.

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