Growth of children on the ketogenic diet

Eileen P G Vining* MD, Associate Professor of Neurology and Pediatrics;
Paula Pyzik BA, Research Coordinator;
Jane McGrogan BS RD, Dietician;
Heather Hladky BS BSN, Nurse Coordinator;
Akash Anand BS, Research Assistant;
Steven Kriegler PhD, Research Assistant and Statistician, The Pediatric Epilepsy Center;
John M Freeman MD, Lederer Professor of Pediatric Epilepsy, The Johns Hopkins Medical Institutions, Baltimore, MD, USA.

**Correspondence to first author at* Meyer 2-147, JHH, 600 N. Wolfe Street, Baltimore, MD 21287, USA.
E-mail: evining@jhmi.edu

This is a prospective cohort study of 237 children (130 males, 107 females) placed on the ketogenic diet for control of intractable epilepsy (mean age at starting diet 3 years 8 months; age range 2 months to 9 years 10 months); average length of follow-up was 308 days. There were 133 children on the diet at 1 year and 76 at 2 years. Height and weight measurements were converted into age- and sex-appropriate *z* scores. There was a rapid drop in weight *z* scores in the first 3 months. After this initial period, the weight *z* score remained constant in children who started the diet below the median weight for their age and sex, although *z* scores continued to decrease in children starting above the median. There was a small decrease in height *z* scores in the first 6 months (<0.5); however, there were larger changes by 2 years. There was no difference based on sex for either height or weight. The ketogenic diet generally provides sufficient nutrition to maintain growth within normal parameters over a defined period. Very young children grow poorly on the diet and should be followed-up carefully over long periods of use.

After decades of sporadic application, use of the ketogenic diet has been revitalized in the treatment of intractable childhood epilepsy (Freeman et al. 1998, Nordli et al. 2001, Wheless et al. 2001). Designed to mimic fasting by producing sustained ketosis, the diet provides 90% of caloric intake as fats, with adequate protein and minimal amounts of carbohydrates. The caloric intake is usually limited to about 75% of the recommended dietary allowance. With its increased, and perhaps more prolonged, use it becomes more important to understand the diet's full impact on the child's well-being. It has been clearly demonstrated to have an excellent therapeutic efficacy with respect to seizure control (Lefevre and Aronson 2000), but at what cost? In the earliest days of its use, physicians and parents expected the child to be on the diet for a short time (usually no more than two years) while complete seizure control was achieved and maintained. The children would then be weaned off the diet and it was expected that they would continue to be seizure free. Historically, about 30% of children who started the diet followed this pattern. We are less certain about the duration of treatment of other children whose seizures were less well controlled. Today, few children have such complete success with seizure control, which may be related to the availability of more antiepileptic medications and the selection of children with more intractable epilepsy. However, more than 50% of those who start the diet have had more than 50% improvement at 1 year and 25 to 50% have more than 90% improvement at 1 year (Freeman et al. 1998). These are children who have received virtually all of the new medications and some have even undergone surgery. These children have found a major improvement in the quality of their life through the diet, at least with respect to seizure control. However, their parents, and often their physicians, are anxious about the long-term impact of the diet. Their questions include: is nutritional status being severely compromised? What effects will this have on the child's long-term health? Does the diet need to be so stringent? Is it safe to stay on the diet for many years, especially when no other viable alternative has appeared? As more children are being treated for longer periods of time, the effect of the diet on the overall health and growth of children must be addressed. This study is part of the ongoing prospective evaluation of children who have been treated with the ketogenic diet at Johns Hopkins Medical Institutions, Baltimore, USA.

Method

All patients under 10 years of age starting the Johns Hopkins Ketogenic Diet Program for the first time between 27 September 1994 and 1 May 2000 and whose parents gave informed consent to participate in our prospective study of the efficacy of the ketogenic diet were included in this study. The protocol was approved by the Joint Committee on Clinical Investigations on Human Subjects. Two-hundred and thirty-seven patients (age range 2 months to 9 years 10 months, mean age of 3 years 8 months) were started on the diet during this period. Baseline height and weight were measured and follow-up measurements were obtained from parental reports and clinical appointments at Johns Hopkins. In order to study the possible effect of the diet on children at different ages, we divided the participants into four groups based on their age at entry to the study: 0 to <1 years, 1 to <4 years, 4 to <7 years, and 7 to 10 years. Heights and weights were converted to *z* scores for age using the Epi Info 2000

software package which contains the National Center for Health Statistics growth curves (The Centers for Disease Control and Prevention, Atlanta, GA). The *z* score represents an individual's height or weight in terms of the standard deviations from the mean. Thus, a child who was exactly at the average height for age and sex would have a *z* score of 0, and a child in the 97.5th centile would have a *z* score of +2 (i.e. 2SD above the mean). Changes in growth were analyzed using linear regression and the cross-panel version of the generalized estimating equation in the Stata7 program (Stata Inc., College Station, TX).

In order to examine the effect of the diet on children with less neurological disability, we examined a subgroup that excluded children who entered the study with severe physical and cognitive impairments. For this analysis we added two additional variables: the ambulatory variable was based on whether the children were weight bearing or could pull themselves to standing. The second variable was based on whether the child could communicate in any way, including signing. We restricted this subgroup to children who were older than 2 years of age upon entry so that language could be ascertained.

Caloric range for the cohort ranged from 25 to 116Kcal/kg/day with an average of 64Kcal/kg/day. Initial calculations

Table I: Baseline characteristics

Characteristics	*Age group, y*				
	0 to <1	*1 to <4*	*4 to <7*	*7 to 10*	*Total*
Age, mean (SD) y	0.65 (0.24)	2.39 (0.94)	5.53 (0.92)	8.29 (0.77)	3.7 (2.7)
Children (*n*)	24	102	65	46	237
Sex, (M:F)	13:11	56:46	35:30	26:20	130:107

Table II: Initial diet information

Age (y)	*Diet ratio (fat:protein + carbohydrates)*			
	Mean Kcal/day (SD)	*3:1 (%)*	*3.5:1 (%)*	*4:1 (%)*
0–<1	621 (116)	17 (71)	4 (16)	3 (13)
1–<4	886 (159)	28 (27)	3 (3)	71 (70)
4–<7	1175 (202)	4 (6)	0 (0)	61 (94)
7–10	1312 (225)	8 (17)	3 (7)	35 (76)

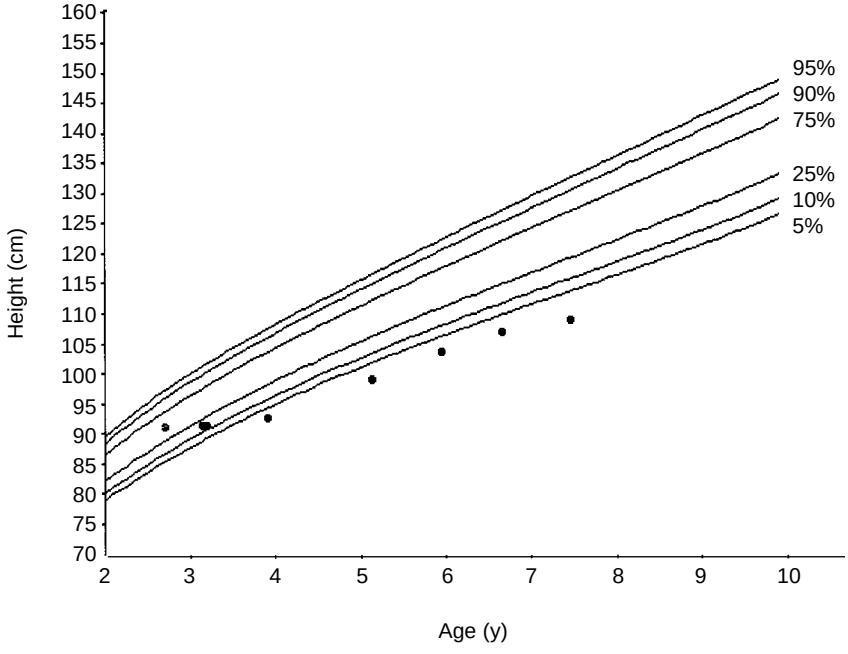

Figure 1: *Individual growth data. Patient A was a female who started diet at age 2 years 8 months and her height was 91cm. This corresponds to 46th centile of height for age, and a z score of –0.07. She discontinued diet at age 7 years 6 months. At that time she was 109cm which corresponds with 0.07th centile and a height for age z score of –2.48. We performed regression analysis on difference variable of (–2.48) – (–0.07) = –2.41.*

were based on the children's age, initial assessment of their nutritional status, and their expected energy demands. The diet is planned so that weight gain or loss is carefully controlled. The target goal for the more neurologically typical children was the 50th centile of weight for height. For children who were not ambulatory or weight bearing, the target weight for height was the 25th centile. This was reduced further to the 10th centile if the child was severely neurologically compromised. There was a presumption that less mobile and active children require fewer calories for maintenance. In addition, the weight-for-height ratio (nutritional status) was also considered in these initial calculations. For instance, a child less than 1 year of age might initially have the diet calculated to contain 75Kcal/kg/day. However, if that child's weight-for-height ratio was high (i.e. the child was proportionally too heavy), the prescribed calories would be adjusted downward. The caloric content and ratio of the diet were readjusted throughout treatment to respond to identified problems in weight gain or loss, and in a continuing attempt to optimize the ketosis and control of seizures for the individual child. The majority of children were fed using regular table foods. Bottle-fed children were fed a ketogenic formula, as were those who had gastrostomy tubes. All diets were supplemented with calcium and vitamins (Swink et al. 1997, Freeman et al. 2000).

Results

Baseline characteristics of the children are described in Table I and their initial diet information is presented in Table II. Some of the children in this study have been included in our other outcome studies. In general, the population in this study appeared to have responded quite similarly to our previously published populations. Of the 237 children who began the diet, 102 (43%) had discontinued the diet by 1 year. The reasons for doing so included: ineffective (n=42), too restrictive (n=21), illness (n=17), seizure free (n=4), lost to follow-up (n=3), other (n=15). We found the following levels of seizure control in the 135 children who were still on the diet at 1 year: seizure free, n=34 (25%), >90% seizure reduction, n=37 (27%), 50 to 90% seizure reduction, n=44 (33%), and <50% seizure reduction, n=20 (15%).

In order to examine whether children grow normally on the ketogenic diet, we compared them with the national population of children in the USA by converting each measurement of height and weight into a z score for children of the same age and sex. In order to help conceptualize this measurement and calculation process, individual data for one child are presented in Figure 1. The difference in z score versus the time on the diet was then analyzed by age group, as well as whether the child had a starting weight or height above the median for age (z score >0) or below the median for age (z score <0). As these changes were not linear over time, the regression model we used consisted of three 'splines' or lines of different slopes. These were from zero to 100 days, 100 to 730 days, and after 730 days (Table III). Table III shows the number of children in each spline as well as the number of measurements made on these children. Clearly some children had a number of measurements made during each time period.

Although the data were fit as straight lines over time, we took the values of these lines at five clinically relevant time points and plotted them as bar charts. The results are shown in Figures 2 and 3 for weight and height respectively. All groups of children had a lower z score for weight after 3 months on the diet (p<0.01). As the diet is calculated for the needs of each child, long-term changes in the weight z score depended upon whether the child was above or below the median weight for age upon entering the study (p<0.01). As we did not plan for children entering below the median to lose weight, as expected, their z scores were relatively stable after 3 months. However, in children who started above the median, weight control was planned and they exhibited a

Table III: Number and grouping of data points in model

		Weight: number of children in each spline (nr of measurements)		
Age (y)	*Starting z score*	*0–100 days*	*100–730 days*	*730+ days*
<0	Below median	8 (28)	7 (40)	1 (1)
	Above median	16 (76)	15 (128)	5 (20)
1–<4	Below	54 (147)	47 (278)	27 (78)
	Above	48 (147)	42 (229)	15 (43)
4–<7	Below	24 (58)	22 (89)	7(24)
	Above	41 (94)	30 (127)	12 (30)
7–10	Below	25 (67)	21(117)	6 (13)
	Above	21(54)	16 (79)	3 (21)
		Height: number of children in each spline (nr of measurements)		
Age (y)	*Starting z score*	*0–100 days*	*100–730 days*	*730+ days*
<0	Below median	10 (32)	9 (49)	0 (0)
	Above median	14 (72)	13 (119)	6 (21)
1–<4	Below	49 (142)	44 (258)	21 (63)
	Above	53 (152)	45 (249)	21(58)
4–<7	Below	29 (65)	24 (103)	10 (31)
	Above	36 (87)	28 (113)	23 (56)
7–10	Below	23 (65)	18 (114)	7 (20)
	Above	23 (56)	19 (82)	2 (14)

continuing decrease in weight z score as time progressed.

In terms of the height or stature measurements, the children grew well for the first 6 months compared with the national average, with only a small drop in the z score of less than 0.5. In contrast to weight, however, there was a continuing decline in height z score among all groups by 2 years ($p<0.01$). As with weight, there was a significant difference between children who started above the median compared with those who started below the median ($p<0.001$). However, none of the age groups lost more than two z scores (i.e. 2SDs of the mean) for height or weight by two years. The number of patients available after this time point was limited, but there is a suggestion that the younger children actually fell more than 2SDs below the mean in height or stature change (i.e. they grew poorly) at three years. There were significant differences between age groups for both height and weight, with the older children growing better ($p<0.01$ for both height and weight), but no difference based on sex ($p=0.73$ for height, $p=0.54$ for weight).

As studies have found that children with cerebral palsy (CP) do not grow as well as normally developing children (Shapiro et al. 1986; Stallings et al. 1993a, b; Samson-Fang and Stevenson 1998), we performed a subgroup analysis to see if a more significant underlying neurological disability could account for poor growth in children on the ketogenic diet. The subgroup analysis consisted of 156 children of more than 2 years of age at the time of starting the diet. There were 32 children who were not communicating (speaking or using signs) or ambulatory (walking or standing erect). These were the most neurologically compromised. There were 17 children who were ambulatory but not communicating. The remaining 107 children were both communicating and ambulatory, with no children who communicated but were not ambulatory. As expected, there was a significant difference between ambulatory and non-ambulatory children in their weight change ($p<0.001$) with the non-ambulatory children showing a greater decline in z score. This difference was significant only in the first 100 days of the diet ($p<0.01$) and not afterwards ($p=0.53$). The communication variable was also significantly related to change in weight z score ($p<0.001$). But in contrast with the ambulatory variable, it was significant both before 100 days ($p<0.01$) and after 100 days ($p<0.001$), again with the non-communicating children showing a greater decline in z score. When both of these variables were included in the model, the communication variable was significant ($p<0.05$) and the ambulatory variable was not ($p=0.67$), suggesting that the communication variable is a better predictor for poor weight gain. In striking contrast to the change in weight

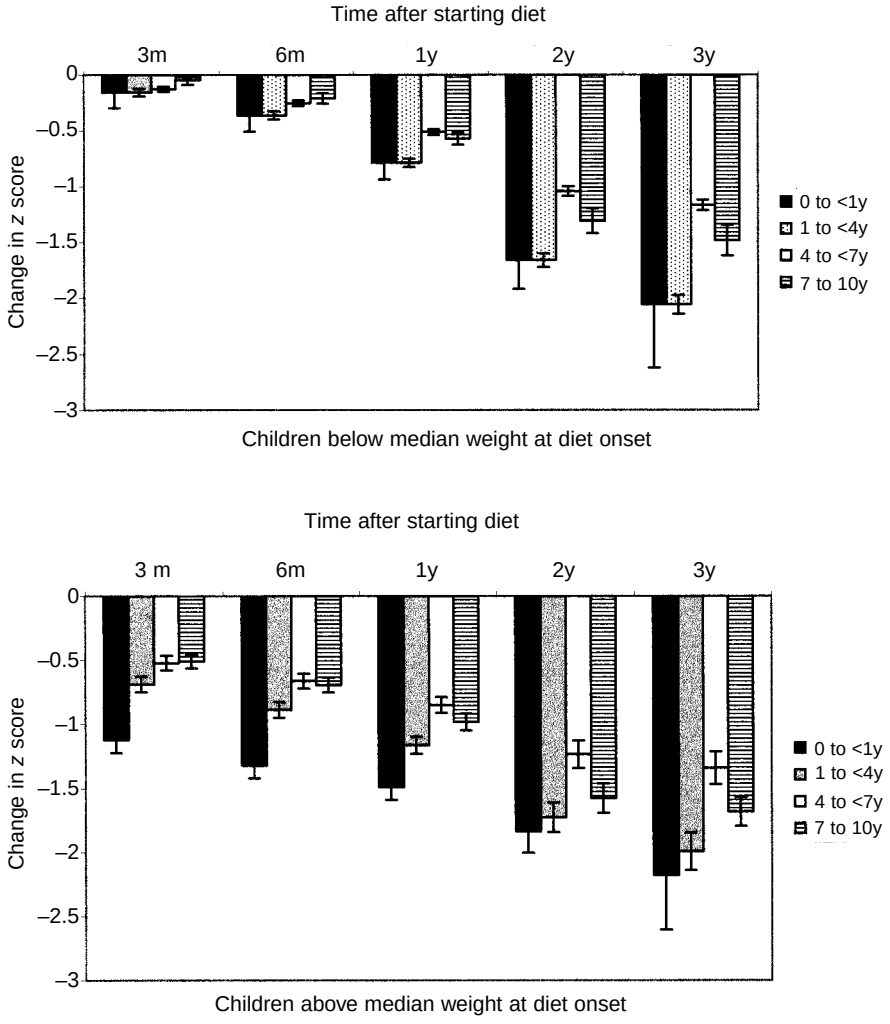

Figure 2: *Change in weight z score over time.*

z scores, the change in height z scores was not significantly related to either being ambulatory ($p=0.18$) or communicating ($p=0.11$). Data for the group of children who were both ambulatory and communicating are presented in Figure 4. This group, when compared with the group at large, appears to experience a less adverse impact on weight and height.

Discussion

Only short-term information on growth in a limited number of patients has previously been available (Couch et al. 1999). This study provides information about the impact of the diet on growth over a more protracted and clinically relevant period during which both weight change and linear growth can be assessed. At 1 year it is clear that, as intended with the initial and subsequent diet plans, the weights of the children on the diet have not increased substantially and children are, therefore, at lower centiles. They have managed to gain minimal weight and have maintained their weight within the normative values for age. This is true for even the youngest children (less than 1 year of age), although they gain weight less well, compared with the national standards, than children initiating the diet at older ages. While this is expected, as our traditional prescription of the diet (calculating caloric intake at 75% of the recommended daily allowance) is intended to restrict weight gain, this study provides data which show that particularly careful monitoring of the young children on the diet is critical. Our center is very experienced in using the diet even in the youngest, most vulnerable children and it is possible that stability of weight and growth might be a greater problem when the diet is used by groups with less understanding of the difficulties involved in managing these more fragile patients. Although we have rigidly restricted weight gain, we do not know that such stringent weight control is actually necessary for the success of the diet. The linear growth of the children (increase in height or stature) which is probably a more valid indicator of nutritional adequacy over time, appears less adversely impacted over a 1-year period. This is particularly true for the oldest children who appear to grow taller almost normally.

Recognizing that the nutritional well-being of children with neurological disability is directly related to health status (use of health care resources, use of medications, respiratory problems, etc; Liptak et al. 2001), our findings of poorer weight gain in our more severely affected children raises additional

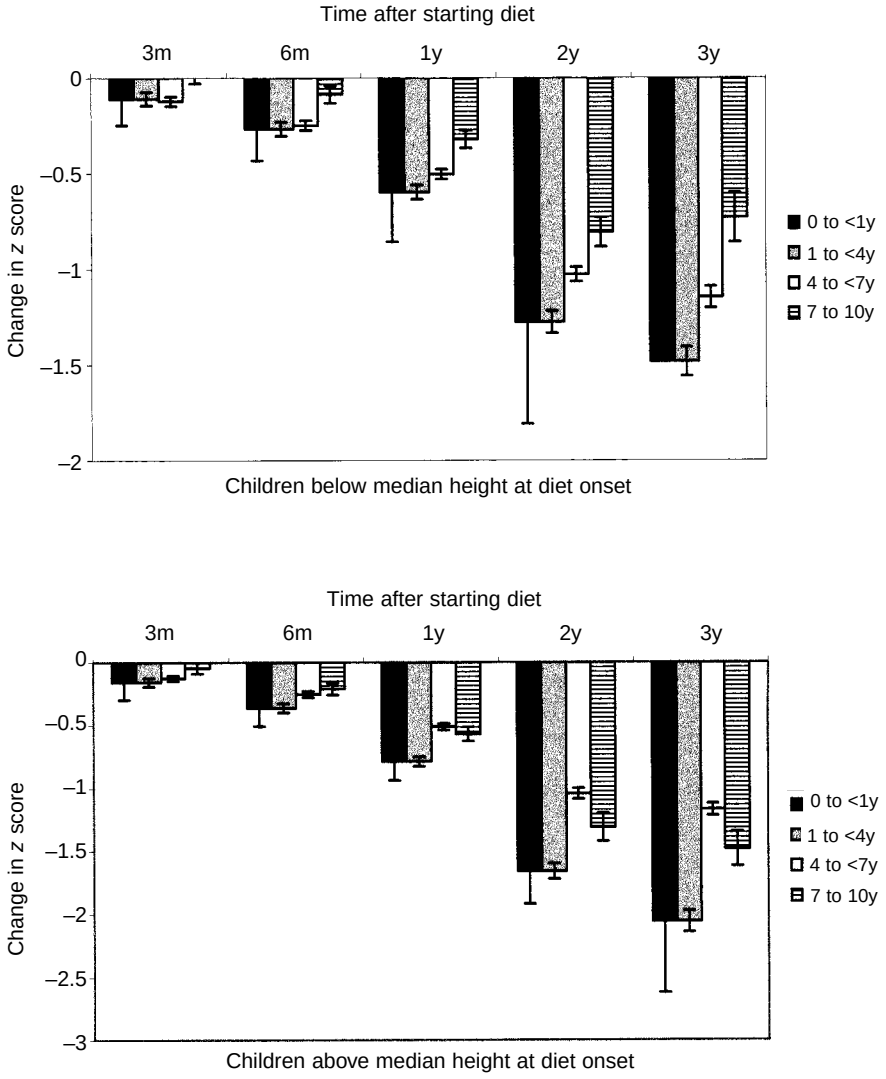

Figure 3: *Change in height z score over time.*

concerns for their well-being. We must continue to address the difficulties in understanding the caloric demands of a child who has greatly increased tone, even though there is limited mobility. Although we did not demonstrate that their linear growth was more adversely impacted, this may be due to problems in measurements in children with CP. It is often difficult to measure height/length reliably in these children because of contractures and disorders of tone. Measurements other than recumbent length may assess nutritional state more adequately (Stallings et al. 1993b, Kong et al. 1999, Zemel et al. 2001) and should probably be used in future studies.

This study has a number of limitations. Data were collected in the routine management of these children and did not use the varied anthropometric measurements that are available. Although it was prospective, there were no constraints in place with respect to altering the diet (i.e. changing calories/kg/day in response to weight gain or loss). The study is population based and does not reflect both individual difficulties in sustaining growth, nor individual difficulties in diet restriction needed to maximize ketosis. It does not address the relation between growth/nutrition and ketosis itself. And it does not evaluate the impact of nutritional status on overall health, infection, renal stones, bone density, nor the nutritional content of these children's diets. Also, children with severe neurological dysfunction may grow poorly independent of nutrition, perhaps on the basis of inadequate growth hormone, and these children may be over-represented in the population that seeks treatment at our institution compared with other hospitals.

This evaluation does reassure us that this drastic dietary intervention appears to provide sufficient nutrition to allow for growth of these children. Older children who remain on the diet appear to grow almost normally. Future work requires an analysis of many of these parameters. The apparent trend of the *z* score to continue to decrease over time in most populations suggests that future work must carefully monitor these children in a continuing effort to provide adequate nutrition. Controlled strategies for following and managing the dietary intake of the youngest children and the most neurologically impaired children will need to be evaluated. Strategies to assess how long the diet should be used will also need to be considered. Finally, we will need to address the issue of 'catch-up' growth when these children discontinue the diet and compare their subsequent growth to their status before diet initiation. This study has provided the first comprehensive assessment of basic growth parameters in children treated with the ketogenic diet for a prolonged period of time. The myriad issues involving the nutritional components of this diet and its impact on other health factors, including the skeletal and cardiovascular system, remain to be addressed.

Accepted for publication 19th July 2002.

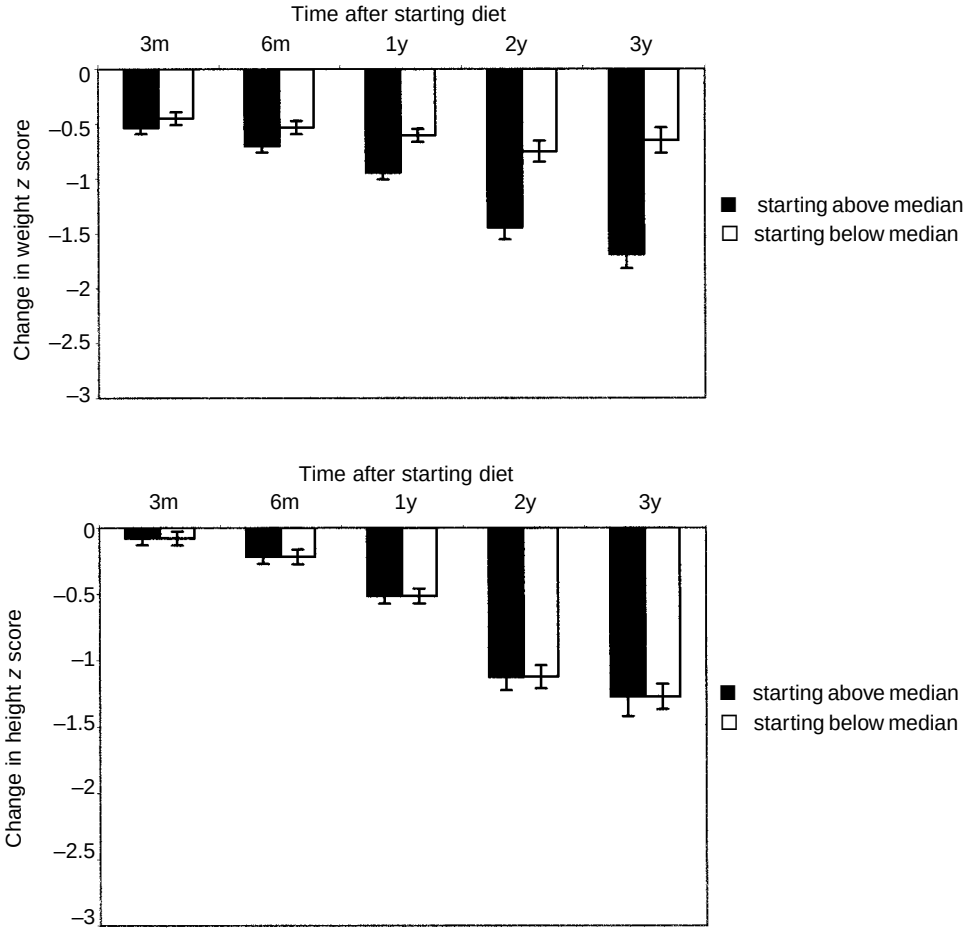

Figure 4: *Ambulatory and communicating children (n=107).*

Acknowledgement
Supported in part by the Sargent Family Foundation, the Charlie Fund, and the Pediatric Clinical Research Unit, supported by NIH/National Center for Research Resources grant M01-RR00052 to the Johns Hopkins University School of Medicine, Baltimore USA.

References

Couch SC, Schwarzman F, Carroll J, Koenigsberger D, Nordli DR, Deckelbaum RJ, DeFelice AR. (1999) Growth and nutritional outcomes of children treated with the ketogenic diet. *J Am Diet Assoc* **99:** 1573–5.

Freeman JM, Vining EPG, Pillas DJ, Pyzik PL, Casey JC, Kelly MT. (1998) The efficacy of the ketogenic diet – 1998: a prospective evaluation of intervention in 150 children. *Pediatrics* **102:** 1358–63.

Freeman JM, Kelly MT, Freeman JB. (2000) *The Ketogenic Diet: A Treatment for Epilepsy.* New York: Demos.

Kong CK, Tse PW, Lee WY. (1999) Bone age and linear skeletal growth of children with cerebral palsy. *Dev Med Child Neurol* **41:** 758–65.

Lefevre F, Aronson N. (2000) Ketogenic diet for the treatment of refractory epilepsy in children: a systematic review of efficacy. *Pediatrics* **105:** e46.

Liptak GS, O'Donnell M, Conaway M, Chumlea WC, Worley G, Henderson RC, Fung E, Stallings VA, Samson-Fang L, Calvert R, Rosenbaum P, Stevenson RD. (2001) Health status of children with moderate to severe cerebral palsy. *Dev Med Child Neurol* **43:** 364–70.

Nordli DR, Kuroda MM, Carrol J, Koenigsberger DY, Hirsch LJ, Bruner HJ, Seidel WT, DeVivo DC. (2001) Experience with the ketogenic diet in infants. *Pediatrics* **108:** 129–33.

Samson-Fang LJ, Stevenson RD. (1998) Linear growth velocity in children with cerebral palsy. *Dev Med Child Neurol* **40:** 689–92.

Shapiro BK, Green P, Krick J, Allen D, Capute AJ. (1986) Growth of severely impaired children:neurologic versus nutritional factors. *Dev Med Child Neurol* **28:** 729–33.

Stallings VA, Charney EB, Davies JC, Cronk CE. (1993a) Nutritional status and growth of children with diplegic or hemiplegic cerebral palsy. *Dev Med Child Neurol* **35:** 997–1006.

Stallings VA, Charney EB, Davies JC, Cronk CE. (1993b) Nutrition-related growth failure of children with quadriplegic cerebral palsy. *Dev Med Child Neurol* **35:** 126–38.

Swink TD, Vining EPG, Freeman JM. (1997) The ketogenic diet:1997. *Adv Pediatr* **44:** 297–329.

Wheless JW, Baumgartner J, Ghanbari C. (2001) Vagus nerve stimulation and the ketogenic diet. *Neurol Clin* **19:** 371–407.

Zemel BS, Riley EM, Stallings VA. (2001) Evaluation of methodology for nutritional assessment in children: anthropometry, body composition, and energy expenditure. *Annu Rev Nutr* **17:** 211–35.