Paradoxical Weight Loss With Extra Energy Expenditure at Brown Adipose Tissue in Adolescent Patients With Duchenne Muscular Dystrophy

Shigeko Satomura, Ichiro Yokota, Katsunori Tatara, Etsuo Naito, Michinori Ito, and Yasuhiro Kuroda

We examined the energy expenditure in patients with Duchenne muscular dystrophy(DMD) to evaluate the cause of the paradoxical weight loss observed in large numbers of adolescent patients before any obvious impairment of their swallowing function. In the morning, resting energy expenditure (REE)/m^2 was almost the same as that in normal controls despite a reduction in fat-free mass (FFM); thus, REE/m^2/FFM was significantly increased in patients (median, 21.2 kcal/m^2/FFM kg; range, 17.7 to 44.2, $P = .012$). A thermographic examination in the morning showed an obvious elevation of the body surface temperature on the back. This phenomenon was consistent with a paradoxical fall in the low frequency (LF)/high frequency (HF) ratio at night analyzed using the inter-RR spectrum by 24-hour electrocardiogram, which indicated relative activation of the sympathetic nervous system. The urinary secretion of norepinephrine at night was also significantly greater in patients (median, 0.119 μg/kg/h; range, 0.061 to 0.219, $P = .011$). These results suggest that paradoxical activation of the sympathetic nervous system may accelerate the production of heat in brown adipose tissue (BAT) and increase the level of energy consumption in patients, and that adolescent DMD patients may require greater caloric intake than expected to maintain body weight, which is important to improve the prognosis of their respiratory function.

DUCHENNE MUSCULAR DYSTROPHY (DMD) is caused by a defect of the muscle membrane protein whose gene is located at chromosome Xp21.[1,2] This disease decreases the amount of body muscle year by year beginning in early childhood. Patients are unable to walk at about 8 years of age, and almost all of them move from a manual to an electrically powered wheelchair by 15 years of age.[3,4] During the second decade of life, the digestive power (swallowing function) decreases, and they tend to prefer soft and water-rich foods.[5-7]

DMD patients show a remarkable increase in fat mass instead of a reduction in skeletal muscle, which leads to excess weight gain beginning at around 8 years of age. This phenomenon has been considered to be the result of a reduction in energy expenditure due to the loss of skeletal muscle, which is the main source of energy consumption.[8] The use of automatic wheelchairs further reduces their daily energy expenditure. Their weight increases yearly, reaches a peak level at about 13 years of age, and then begins to decline in some patients.[9] Interestingly, this weight loss begins before any obvious impairment of their swallowing function and therefore cannot be explained solely by a reduction in caloric intake. It is important for DMD patients to maintain their weight level during adolescence because weight loss can make their respiratory condition worse, and thus shorten their life.[7,10]

In this study, we examined the energy expenditure in adolescent DMD patients to evaluate the cause of this paradoxical weight loss before any obvious impairment of swallowing function.

SUBJECTS AND METHODS

Subjects

Eight patients were examined in this study. Their ages and the results of their physical examinations at the time of this study are summarized in Table 1. The body weight fluctuation in each control subject was within 0.5 kg during study period. Body fat mass was measured by a bioelectrical impedance analysis using an Impimeter SS-110 (Sekisui Chemical Corp, Tokyo, Japan). In this method, the bioelectrical impedance between bilateral wrists was measured and converted to body fat mass (%). The interassay coefficient of variation (CV) was 2.0%, and the test-retest correlation coefficient was 0.97. The stage of activity of daily life (ADL) was 8 in all patients, which means that they required full assistance in their daily activities.[11] None of the patients had any difficulty in respiratory function for daily activity at the time of the examination. Their daily caloric intake was planned to be between 1,600 and 1,700 kcal/d based on a calculation of their daily activities, and all of them were able to feed themselves. Six healthy young male volunteers also participated in this study as normal controls.

Figure 1 shows the longitudinal changes in body weight in each patient examined in this study. Each patient began to become overweight beginning at around 8 years of age and reached their maximum body weight at around 13 to 15 years. In most cases, their body weight gradually declined despite a reduction in daily activity and maintenance of caloric intake.

Resting Energy Expenditure and Thermography

Resting energy expenditure (REE) was measured in 8 patients and 6 normal controls in the early morning after an overnight fast. The room temperature was adjusted between 25°C and 26°C, and the humidity was 50% to 60%. The previous evening, they ate the same meals, slept at 9:00 PM, and woke up at 6:00 AM. REE was then measured by an open-circuit system using a Calorie Scale (Chest Company, Tokyo, Japan). Briefly, the subject was covered by a head hood in the resting supine position, and the respiratory metabolic rate was then calculated based on the volume of oxygen consumed and carbonic acid gas produced during the 15-minute examination. The accuracy of the oxygen and carbonic acid gas analyzer was ± 3%. The interassay CV of REE values in this system was 4.0%, and the test-retest correlation coefficient was 0.98.

Intrascapular surface temperature was measured in the same patients

From the Department of Pediatrics, School of Medicine, University of Tokushima, Tokushima, and the Department of Pediatrics, National Tokushima Sanatorium, Tokushima, Japan.

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Address reprint requests to Ichiro Yokota, MD, Department of Pediatrics, Tokushima University School of Medicine, Kuramoto-cho 3, Tokushima 770-8503, Japan.

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Table 1. Ages and Results of Physical Examinations in DMD and Controls

	DMD								Control					
Case	1	2	3	4	5	6	7	8	1	2	3	4	5	6
Age (yr)	22	22	18	17	18	24	21	16	28	23	25	25	21	24
Height (cm)	152	162	160	157	159	158	165	152	174	168	162	169	165	178
Body weight (kg)	27.0	50.0	34.9	59.9	62.7	28.6	40.6	40.8	62.0	54.0	64.9	57.9	57.2	74.5
BSA (m^2)	1.07	1.50	1.25	1.62	1.66	1.12	1.36	1.31	1.73	1.59	1.71	1.65	1.62	1.92
BMI (kg/m^2)	11.7	19.1	13.7	24.3	24.9	11.6	15.1	17.7	20.5	19.1	24.8	20.3	20.9	23.4
FFM (kg)	23.2	27.1	28.2	41.6	24.3	23.9	33.5	32.2	52.7	45.9	55.1	50.6	50.8	63.5
Body fat rate (%)	14.2	45.8	19.3	30.5	61.2	16.6	17.4	21.0	15.0	15.0	15.2	12.7	11.2	14.8
ADL (stage)	8	8	8	8	8	8	8	8						

Abbreviations: BSA, body surface area; BMI, body mass index; FFM, fat-free mass; ADL, activity of daily life.

and controls using a thermometer (Model thermotracer TH 1106, Nippon Electric San-ei company, Tokyo, Japan). The minimum detectable difference in temperature was 0.025°C. In each case, the patients and normal controls were paired and examined under the same conditions as described above. Two normal control subjects were examined twice for a paired analysis. The intrascapular surface temperature was measured every 5 minutes for 20 minutes. The thermogram data were analyzed as a thermo-distribution histogram map with a resolution of 0.17°C to 0.35°C. Under these conditions, the interassay CV and test-retest correlation coefficient were 0.5% and 0.97%, respectively.

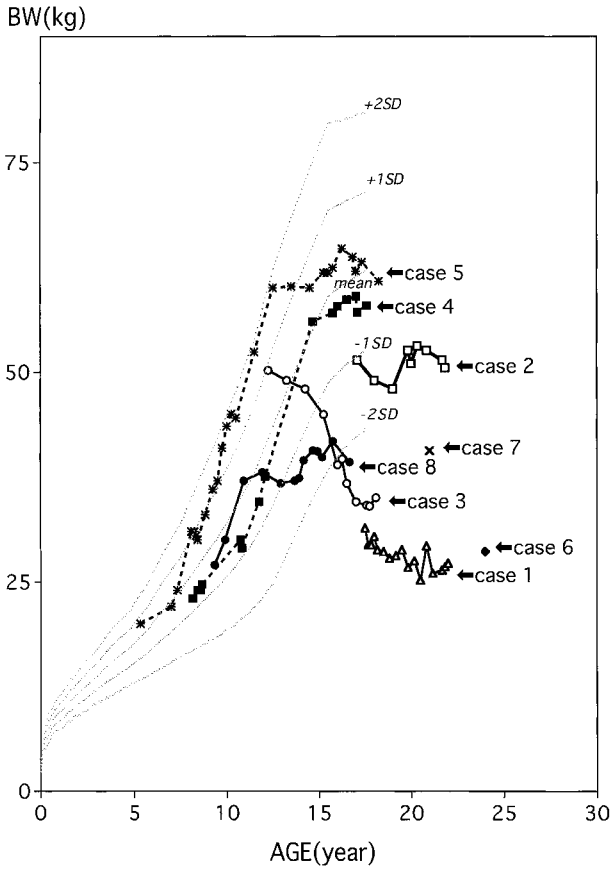

Fig 1. Longitudinal changes in body weight in 8 DMD patients. Each arrow indicates the body weight of each patient at the time of this examination. Records of changes in body weight were not available in 2 patients (cases 6 and 7). The weak dot lines indicate the + 2 SD, + 1 SD, mean, −1 SD and −2 SD of the curve for body weight gain in Japanese boys, respectively.

Analysis of Inter-RR Spectrum by 24-Hour Electrocardiogram

Electrocardiograms were obtained from 5 patients (patients 1, 2, 3, 4, and 5) and 5 normal controls (controls 1, 2, 3, 4, and 5) using a 24-hour ambulatory electrocardiograph recorder (model DMC 4502, Nihon-Khoden Corp, Tokyo, Japan). For 24 hours, patients and normal controls followed their usual daily activities in the hospital and at school. Frequency domain measurements were obtained by power spectrum analysis, as previously described.[12] Power spectra components were analyzed using a Holter analyzer (SM-3000 system, Fukuda-Denshi Corp, Tokyo, Japan). In this analysis, each 1 hour was defined as 1 period. In each period, each power spectrum was independently analyzed. RR intervals before and after ectopic beats over 3 seconds were excluded from the analysis. The frequency domain was analyzed by Fast Fourier transformation (FFT) and mainly consisted of 2 parts. Low frequency (LF) power was defined as the power spectrum between 0.04 to 0.15 Hz, which mainly represents sympathetic nervous system function. High frequency (HF) power was defined as that between 0.15 to 0.4 Hz, which represents parasympathetic nervous system function in the heart. Thus, the LF/HF ratio indicates the balance between the sympathetic and parasympathetic nervous systems.[13]

Urinary Catecholamine Secretion at Night

Nocturnal urinary catecholamine secretion (norepinephrine [NE], epinephrine [EP], dopamine [DA]) was measured in 5 patients (patients 1, 2, 3, 4, and 5) and 6 control subjects. The urine collected from 9:00 PM to 7:00 AM was stored in 7 mL of 6 N hydrochloric acid and measured by radioimmunoassay (Otsuka Assay Laboratories, Tokushima, Japan). The results were expressed as μg/kg/h.

Statistical Analysis

Differences between groups were evaluated by Mann-Whitney's U test. Wilcoxon signed-ranks test was used to evaluate the difference of temperature values in intrascapular lesion. A value of $P < .05$ was considered significant. Data are presented as the median and the range. All analyses were conducted with StatView software (version 4.5 for Macintosh, SAS Institute Inc, Cary, NC)

RESULTS

In DMD patients, REE/m^2 ranged between 507 and 1,026 kcal/m^2/day (median, 716 kcal/m^2/d), whereas in normal controls, this ranged between 557 and 985 kcal/m^2/d (median,

Table 2. REE in DMD and Controls

	DMD								Control					
Case	1	2	3	4	5	6	7	8	1	2	3	4	5	6
BMR/m^2 (kcal/m^2/d)*	1,078	1,413	1,275	1,534	1,638	1,068	1,346	1,269	1,572	1,502	1,592	1,587	1,517	1,797
REE/m^2 (kcal/m^{21}/d)†	1,026	554	605	735	507	861	697	893	557	985	700	704	765	795
REE/m^2 FFM (kcal/m^2/kg)‡	44.2	20.4	21.5	17.7	20.9	36.0	20.8	27.2	10.6	21.5	12.7	13.9	15.1	12.5

Abbreviations: BMR, basal mertabolism rate; REE, resting energy expenditure; FFM, fat-free mass.

*P = .028.

†P = .70.

‡P = .012.

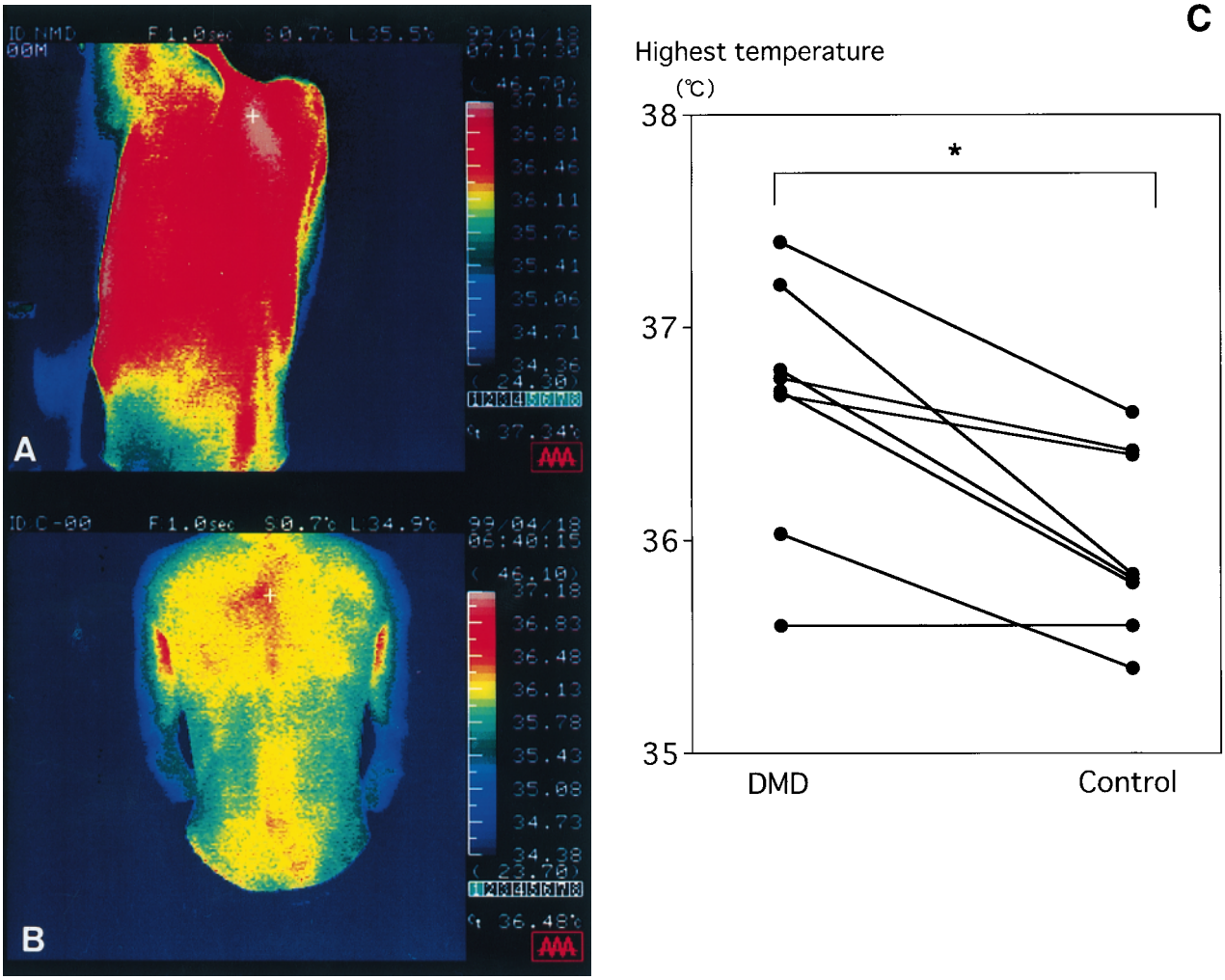

Fig 2. Typical results for the distribution of body surface temperature obtained by thermography. Patients (A) and normal controls (B) were paired and examined under the same conditions. The intrascapular surface temperature was measured every 5 minutes for 20 minutes. Their thermogram data were analyzed as a thermo-distribution histogram map with a resolution of 0.17°C to 0.35°C. The range of surface temperature corresponding to each color is indicated on the right side of each figure. Higher temperatures are indicated by red, and lower temperatures are shown in blue. The cross indicates the point with the highest temperature. (C) Shows a comparison of the highest temperature values. Eight paired analyses were plotted. The highest temperature in DMD patients (median, 36.73°C; range, 35.60 to 37.40) is significantly higher than that in controls (median, 35.80°C; range, 35.40 to 36.60; P = .018)

734.5 kcal/m^2/d) (Table 2). Although the reduction of skeletal muscle was expected to reduce energy expenditure, REE/m^2 in DMD was comparable to that in normal controls ($P = .70$). To correct for differences in body composition, REE/m^2/fat-free mass (FFM) was examined. This value in DMD (median, 21.2 kcal/m^2/FFM kg; range, 17.7 to 44.2) was significantly greater than that in normal controls (median, 13.3 kcal/m^2/FFM kg; range, 10.6 to 21.5, $P = .012$).

Figure 2 shows the typical results for the distribution of body surface temperature. In normal subjects (Fig 2B), the surface temperature was highest at the intrascapular region and then gradually decreased in concentric circles. In contrast, the surface temperature of the backs of DMD patients (Fig 2A) was clearly elevated. While the surface temperature was increased in DMD, the highest temperature was again observed at the intrascapular region. Similar results were obtained in each of the 8 paired analyses. Thus, the highest temperature in DMD patients (median, 36.73°C; range, 35.60 to 37.40) was significantly higher than that in controls (median, 35.80°C; range, 35.40 to 36.60, $P = .018$) (Fig 2C).

Figure 3 shows the inter-RR spectra by 24-hour electrocardiogram analyzed by the FFT method. In normal controls, each component shows circadian variability. HF components were elevated at night and in the early morning. Therefore, the LF/HF ratio decreased at night and increased during daytime. In DMD patients, however, HF components at night and in the early morning were lower than those in controls and showed no circadian variability. The LF/HF ratio in DMD patients tended to show less variability and was higher than those in controls throughout the day. One patient showed an inverse circadian pattern of LF/HF components: low during the day and high at night.

The urinary secretion of catecholamine at night, especially NE, was significantly increased in DMD patients ($P = .011$) (Table 3).

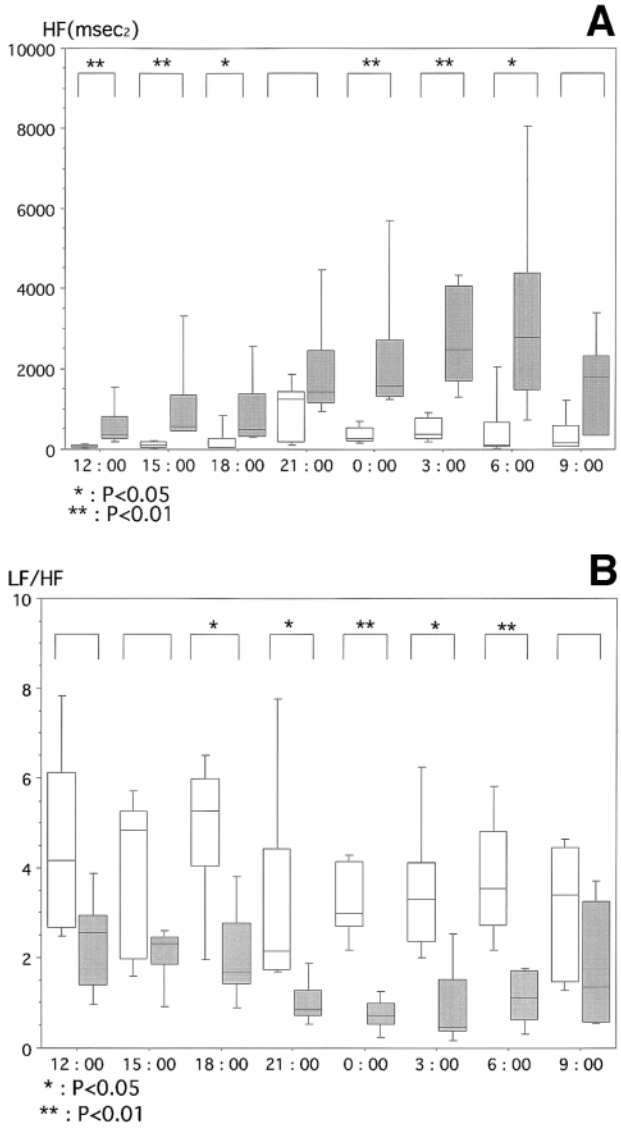

Fig 3. Inter-RR spectrum in a 24-hour electrocardiogram analyzed by the FFT method. The open rectangle and bar shows the result of DMD patients and the shaded rectangle and bar shows that of normal controls. The rectangle or bar indicates the range of 75 or 90 percentile value, respectively. The horizontal line in each rectangle indicates median value. In normal controls, each component shows circadian variability. HF components were elevated at night and in the early morning (A). Therefore, the LF/HF ratio decreased at night and increased during daytime (B). In DMD patients, however, HF components were lower than those in controls at night and in the early morning and showed no circadian variability (A). The LF/HF ratio in DMD patients tended to show less variability and was higher than that in controls throughout the day (B).

DISCUSSION

Skeletal muscle accounts for a large proportion of energy consumption and produces heat, which is important for maintaining body temperature. In DMD patients, the amount of skeletal muscle decreases with aging during childhood.[3,4] This likely results in reduced basal energy expenditure and relatively excess caloric intake. In fact, DMD patients show a remarkable increase in fat mass deposition during the prepubertal stage.[9] However, REE/m^2 in the adolescent DMD patients examined in this study was not significantly less than that in normal controls, and REE/m^2/FFM was actually higher in DMD patients. This result is consistent with previous examinations,[14,15] but the origin of the paradoxical energy expenditure in DMD patients has not been well clarified. In our study, a thermographic study showed that DMD patients had a significantly higher body surface temperature at rest, indicating that the consumption of a large amount of energy as heat elevated REE to a level indistinguishable from that in normal controls.

Brown adipose tissue (BAT) is another important organ for supplying heat. Continuous activation of the sympathetic nervous system accelerates the expression of the uncoupling protein-1 gene and the differentiation of BAT, which leads to increased heat production.[16-18] In DMD patients, dominant activation of the sympathetic nervous system even at night, as evaluated by a higher LF/HF ratio, has been observed.[13] This result is consistent with the remarkable increase in the urinary secretion of catecholamine.[19] These results suggest that in

Table 3. Urinary Catecholamines Secretion at Night in DMD and Controls

	DMD					Control					
Case	1	2	3	4	5	1	2	3	4	5	6
NE (μg/kg/h)*	0.074	0.061	0.119	0.219	0.170	0.032	0.024	0.044	0.038	0.064	0.029
EP (μg/kg/h)†	0.008	0.004	0.006	0.027	0.008	0.003	0.002	0.006	0.002	0.008	0.004
DA (μg/kg/h)‡	0.856	0.350	0.771	2.129	0.824	0.232	0.246	0.395	0.502	0.485	0.332
SUM (μg/kg/h)§	0.938	0.415	0.896	2.375	1.002	0.267	0.272	0.445	0.542	0.557	0.365

Abbreviations: NE, norepinephrine; EP, epinephrine; DA, dopamine.

*$P = .011$.

†$P = .068$.

‡$P = .029$.

§$P = .029$.

DMD patients, activation of the parasympathetic nervous system becomes weaker and loses its circadian rhythm with aging, and compensatory paradoxical activation of the sympathetic nervous system causes heat production in BAT even at night and early morning; this may result in a greater-than-expected increase in the level of energy consumption.

The origin of paradoxical activation of the sympathetic nervous system in DMD patients is unclear and needs to be clarified in future studies. One possibility is that it may be due to latent deterioration of cardiac function.[20]

Since our results indicate a greater-than-expected acceleration of energy expenditure at rest, adolescent DMD patients may expend more energy than expected from their daily activity levels. It is important for such patients to maintain their body weight to prevent the deterioration of respiratory function and to prolong their life. Thus, this extra caloric consumption should be taken into account when we seek to establish adequate levels of calories for adolescent DMD patients.

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