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The Effects of a High-protein, Low-fat, Ketogenic Diet on Adolescents With Morbid Obesity: Body Composition, Blood Chemistries, and Sleep Abnormalities

Steven M. Willi, MD*; Mary Joan Oexmann, MS, RD‡; Nancy M. Wright, MD*; Nancy A. Collop, MD$; and L. Lyndon Key, Jr, MD*

ABSTRACT. Objective. To evaluate the efficacy and metabolic impact of a high-protein, low-carbohydrate, low-fat ketogenic diet (K diet) in the treatment of morbidly obese adolescents with initial weights of >200% of ideal body weight.

Methods. Six adolescents, aged 12 to 15 years, weighing an average of 147.8 kg (range, 120.6–198.6 kg) and having an average body mass index of 50.9 kg/m² (39.8–63.0 kg/m²), consumed the K diet for 8 weeks. Daily intake consisted of 650 to 725 calories, which was substantially in the form of protein (80–100 g). The diet was very low in carbohydrates (25 g) and fat (25 g). This was followed by 12 weeks of the K diet plus two carbohydrates (30 g) per meal (K+2 diet).

Main Outcome Measures. Anthropometric data and blood and urine were collected at enrollment, during week 1, and at 4-week intervals throughout the course of the study. Resting energy expenditure was measured by indirect calorimetry. Body composition was estimated using dual-energy x-ray absorptiometry, bioelectrical impedance analysis, and urinary creatinine excretion at enrollment and on completion of each phase of the diet. Nocturnal polysomnography and multiple sleep latency testing were conducted at baseline and repeated after an average weight loss of 18.7 kg to determine sleep architecture, frequency and duration of apneas, and daytime sleepiness.

Results. Subjects lost 15.4 ± 1.4 kg (mean ± SEM) during the K diet and an additional 2.3 ± 2.9 kg during the K+2 diet. Body mass index decreased 5.6 ± 0.6 kg/m² during the K diet and an additional 1.1 ± 1.1 kg/m² during the K+2 diet. Body composition studies indicated that weight was lost equally from all areas of the body and was predominantly fat. Dual-energy x-ray absorptiometry showed a decrease from 51.1% ± 2.1% body fat to 44.2% ± 2.9% during the K diet and then to 41.6% ± 4.5% during the K+2 diet. Lean body mass was not significantly affected. Weight loss was accompanied by a reduction in resting energy expenditure of 5.2 ± 1.8 kcal/kg of fat-free mass per day. Blood chemistries remained normal throughout the study and included a decrease in serum cholesterol from 162 ± 12 to 121 ± 8 mg/dL in the initial 4 weeks of the K diet. An increase in calcium excretion was accompanied by a decrease in total-body bone mineral content. A paucity of rapid eye movement sleep and excessive slow-wave sleep were seen in all subjects at enrollment. Weight loss led to an increase in rapid eye movement sleep (P < .02) and a decrease in slow-wave sleep (P < .01) to near normal levels.

Conclusions. The K diet can be used effectively for rapid weight loss in adolescents with morbid obesity. Loss in lean body mass is blunted, blood chemistries remain normal, and sleep abnormalities significantly decrease with weight loss. Pediatrics 1998;101:61–67; adolescents, body composition, ketogenic diet, morbid obesity, sleep apnea.

ABBREVIATIONS. OSA, obstructive sleep apnea; CPAP, continuous positive airway pressure; K diet, ketogenic diet; K+2 diet, ketogenic diet plus two carbohydrate sources per meal; IBW, ideal body weight; BLA, bioelectrical impedance analyzer; DEXA, dual-energy x-ray absorptiometry; REE, resting energy expenditure; IGF-1, insulin-like growth factor-1; IGFBP-3, IGF binding protein-3; MSLT, multiple sleep latency test; EEG, electroencephalogram; REM, rapid eye movement; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Despite the strong emphasis on thinness in our society, more children than ever are obese. Data collected from several national health surveys show that obesity is growing in incidence at an alarming rate.1–3 This same survey data demonstrated an 80% increase in the prevalence of super-obesity (defined as triceps skinfold measurements in the highest 95th percentile) between 1963 and 1980.4

Obesity in childhood is strongly linked to its persistence into adulthood. Obese adolescents have a 70% chance of becoming obese adults.5 The long-term risks of obesity in adolescence include increased mortality from diabetes, hypertension, coronary heart disease, and cancer.6,7 The relative risks of these complications have been correlated to the degree of obesity.8

The more immediate complications of obesity include trauma to the weight-bearing joints, obstructive sleep apnea (OSA), and gallbladder disease.9,10 OSA is a potentially lethal disorder in which breathing stops for >10 seconds at a time. Treatment options for this condition include continuous positive airway pressure (CPAP), uvulopalatopharyngoplasty, and tracheostomy.11 CPAP is an effective short-term solution. However, it is poorly tolerated in children.12 Weight loss reduces the duration and frequency of apnea in adults13 and may offer a more attractive long-term solution to sleep apnea than either of the surgical interventions.14 However, its ef-
ficacy has never been demonstrated in a group of obese children.

The prognosis for treatment of adolescent obesity is generally poor.6 The very low calorie ketogenic diet (K diet), introduced in the 1980s, is perhaps the most successful dietary approach to weight loss in this group.6 The low-fat, low-calorie diet is a mainstay of nutritional intervention for moderate to severe obesity. This is especially the case in childhood when the metabolic consequences of severely restrictive diets on normal growth must be taken into consideration. The K diet can be supplemented with two carbohydrates at each meal (K+2 diet) to provide a low-fat, low-calorie diet that is not ketogenic.

The primary purpose of this study was to evaluate the metabolic consequences of weight loss using the K and K+2 diets in a group of adolescents with morbid obesity. Another goal was to monitor body composition changes during weight loss to determine if the diets effectively preserved lean body mass. Finally, we wanted to determine if the rapid weight loss could decrease sleep abnormalities observed in adolescents with morbid obesity.

METHODS

Recruitment and Study Design

Six morbidly obese (>200% of the ideal body weight [IBW]) adolescents (age 12–15) were recruited through the Medical University of South Carolina Pediatric Endocrinology Clinic to participate in this 20-week study. IBW is based on the medium frame as defined by the Metropolitan Life Insurance Tables.17 Informed consent was obtained from the subjects and their legal guardians. Subjects agreed to engage in moderate, aerobic exercise three times a week and to consume the K diet for 8 weeks, followed by 12 weeks of the K+2 diet.

Subjects were admitted to the General Clinical Research Center every 4 weeks throughout the study. The first admission lasted 4 days to conduct the baseline evaluation and initiate the K diet. The purpose of the second admission was to monitor progress on the K diet by repeating blood tests, a single 24-hour urine collection, and anthropometric studies. Subjects were admitted at 8 weeks to further monitor progress and initiate the K+2 diet. Anthropometric and biochemical data were repeated at 12, 16, and 20 weeks. Sleep studies were performed at baseline, 8 weeks, and 20 weeks. Throughout the study, subjects were required to maintain a written record of their compliance with exercise, dietary intake, nutritional supplements, and urine ketone tests.

Dietary Intervention

The dietary intervention consisted of two phases. The initial phase included a high-protein, low-fat, K diet. The K diet provided 645 to 725 calories and consisted of simple foods containing 80 to 100 g of protein and 25 g each of carbohydrate and fat. Subjects consumed 13 oz of lean meats, 3 cups of low-calorie vegetables, and ad lib diet gelatin dessert. Foods were evenly distributed throughout the day. As this diet is deficient in certain vital nutrients and may induce electrolyte loss through osmotic diuresis, subjects were encouraged to take >200 mEq of sodium chloride and a minimum of 8 cups of very low-calorie fluid each day. Subjects were also provided with daily dietary supplements including 30 mEq of potassium chloride, 1.0 g of elemental calcium (as calcium carbonate), and two multivitamins with minerals (Upshur-Smith Labs, Minneapolis, MN). Pill counts were completed every 4 weeks to assure compliance with the nutrient supplements.

After 8 weeks on the K diet, the second stage of the dietary intervention began with subjects consuming the same basic diet with the addition of two carbohydrate exchanges per meal (K+2 diet). The exchange list contained portions of food equal to 15 g of carbohydrate (breads, starchy vegetables, and fruits). The potassium supplement was discontinued while the two multivitamins with minerals and calcium supplements were continued throughout the study.

Body Composition Measurements

Weights were determined using a single electronic scale (Detecto, Cleveland, OH) at 8 AM after voiding and before breakfast. Clothing was weighed separately and subtracted accordingly. Lean body mass was assessed from measurements of creatinine excretion.18 On a monthly basis, a bioelectrical impedance analyzer (BLA) was used to determine body composition for fat, water, and lean mass (RUL Systems, Detroit, MI). Lean body mass was estimated from formulae derived for use in children.19 In addition, body composition was measured by a dual-energy x-ray absorptiometry (DEXA) scanner (DPX, Lunar Radiation Corporation, Madison, WI, software 3.2) in subjects at baseline, 8 weeks, and 20 weeks. This method is precise, and the radiation exposure is minimal.20 The DEXA scans were not performed on one of the subjects because of the weight limitation of the equipment.

Indirect Calorimetry

Resting energy expenditure (REE) was determined between 8 and 9 AM in the fasted state from oxygen consumption corrected for the respiratory quotient and the daily nitrogen excretion. Oxygen consumption and carbon dioxide production were measured using a Beckman MMC Horizon Metabolic Cart (Beckman Instruments, Fullerton, CA).

Laboratory Parameters

At enrollment, after 4 days of the K diet, and every 4 weeks thereafter, complete blood chemistries as well as electrolytes, hematologic profile, and lipid profile were performed after an overnight fast. In addition, 24-hour urine samples were collected to assess nitrogen and electrolyte balance. Insulin-like growth factor-1 (IGF-1), IGF binding protein-3 (IGFBP-3), and serum leptin (OB protein) levels were measured at baseline and on completion of each phase of the diet.

Sleep Studies

At baseline, subjects were evaluated with nocturnal polysomnography, followed by a multiple sleep latency test (MSLT). These studies were repeated 48 hours after transition to the K+2 diet and on completion of the study. Nocturnal polysomnography testing consisted of multiple leads including electrocardiogram, electroencephalogram (EEG), electromyogram, chest wall pneumography, and pulse oximetry. Apnea was defined as a complete or near-complete interruption in respiration with EEG arousal and/or hypoxemia. OSA was quantitated using an apnea index, which is equal to the average number of episodes per hour. Sleep architecture was evaluated by analysis of the distribution of rapid eye movement (REM), slow-wave, and non-slow-wave activity during the nocturnal sleep study. The MSLT, a daytime test, evaluates time to sleep onset during each of four 20-minute sleep opportunities presented at 2-hour intervals. A mean sleep latency of ≤5 minutes is defined as excessive daytime sleepiness in adults.21 Baseline sleep study parameters were compared with those after maximal weight loss.

Statistical Analysis

All results are presented as means ± SEM. Comparison of REE and biochemical parameters in the same subject at each phase of study were made by one-way analysis of variance with repeated measures. Paired Student’s t tests and Mann-Whitney analysis were used to compare baseline sleep architecture and serum proteins (IGF-1, IGFBP-3, leptin) to those after weight loss. Regression analysis was used in an evaluation of body composition methods, and in a comparison between measures of obesity and serum leptin levels.

RESULTS

Weight Loss

Table 1 demonstrates that subjects lost 15.4 ± 1.5 kg (mean ± SEM) during the initial 8 weeks of the K diet. One subject regained weight during the following 12 weeks of the K+2 diet, while the remaining
five lost 4.9 ± 1.9 kg. Overall, weight loss was not statistically significant in the K+2 phase. The decrease in body mass index was significant during the K diet, but not during the K+2 diet. In a paired analysis of this small sample, weight loss was significantly greater during the K diet than during K+2 diet (P = .01).

Body Composition

Estimates of lean body mass from the various methods used are seen in Table 2. Results of the DEXA scans correlated well with both BIA measurements (Pearson’s r = 0.95; P < .0001) and estimates of lean body mass from creatinine excretion (r = 0.92; P < .0001). The correlation between estimates derived from BIA and creatinine excretion was not as strong (r = 0.77; P = .0002). In general, estimates from BIA were greater than from DEXA or urinary creatinine. This was especially true for measurements before weight loss.

Results of DEXA in each phase of treatment are seen in Fig1. Changes in lean body mass, as estimated from DEXA and urinary creatinine, were not significant over the term of treatment. These data demonstrate that the weight lost during the K diet was predominantly from fat.

Biochemical Parameters

Within 72 hours of starting the K diet, urine testing revealed the presence of small to moderate amounts of ketone bodies. Ketosis was quickly suppressed with the daily addition of 90 g of carbohydrate during the K+2 diet. With few exceptions, no alterations in serum chemistries were observed in subjects during either phase of the protocol. Uric acid increased transiently from 8.15 ± 0.49 to 10.53 ± 0.56 mg/dL after 4 days of the K diet (P < .05) and returned to normal within 4 weeks. Serum potassium decreased from 4.3 ± 0.2 to 3.9 ± 0.1 mEq/L (P < .05) during the 8 weeks of the K diet, despite the use of potassium supplements (30 mEq/day).

Serum lipid profiles demonstrated a profound effect of the ketogenic diet (Fig 2). A decrease in total cholesterol (from 162 ± 12 to 121 ± 8 mg/dL) was noted within the first month of treatment (P < .01). Furthermore, the effect was shared among low-density lipoprotein (LDL) and high-density lipoprotein (HDL) fractions. This combined effect on cholesterol fractions left the LDL:HDLC ratio unchanged at 2.5.

Fasting serum IGF-I levels (317 ± 13 ng/mL) be-

<table>
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<th>Subject No.</th>
<th>Age/Sex</th>
<th>Initial</th>
<th>Change in Weight</th>
<th>Change in BMI</th>
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<tr>
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<td>Weight (kg) BMI (kg/m²)</td>
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<td>K+2 Diet</td>
</tr>
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<tr>
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<td>-4.5</td>
</tr>
<tr>
<td>3</td>
<td>13/M</td>
<td>122.0 43.4</td>
<td>-13.4</td>
<td>-12.9</td>
</tr>
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<td>4</td>
<td>14/M</td>
<td>198.6 63.0</td>
<td>-20.1</td>
<td>-0.7</td>
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<tr>
<td>5</td>
<td>15/M</td>
<td>176.7 55.2</td>
<td>-16.2</td>
<td>-4.3</td>
</tr>
<tr>
<td>6</td>
<td>15/F</td>
<td>120.6 39.8</td>
<td>-10.9</td>
<td>+11.1</td>
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<td></td>
<td>Mean ± SEM</td>
<td>147.8 ± 13.6</td>
<td>50.9 ± 3.4</td>
<td>-15.4 ± 1.5</td>
</tr>
</tbody>
</table>

Fig 1. Composition of body fat, lean, and mineral mass as measured by dual-energy X-ray absorptiometry before and after dietary interventions. Asterisks represent statistically significant changes from baseline (P < .05).

<p>| TABLE 1. Demographic and Anthropometric Data From Subjects Throughout the Study |
|------------------------------------------|------------------|------------------|------------------|------------------|</p>
<table>
<thead>
<tr>
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<th>Age/Sex</th>
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<td>120.6 39.8</td>
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<tr>
<td></td>
<td>Mean ± SEM</td>
<td>147.8 ± 13.6</td>
<td>50.9 ± 3.4</td>
<td>-15.4 ± 1.5</td>
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TABLE 2. Changes in Lean Body Mass During Weight Loss

<table>
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<th>Subject Number</th>
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<th>After K+2 Diet</th>
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<td></td>
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<td>BIA</td>
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<td>53.9</td>
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<td>66.5</td>
<td>71.8</td>
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<td>4</td>
<td>101.1</td>
<td>74.4</td>
<td>97.1</td>
</tr>
<tr>
<td>5</td>
<td>92.8</td>
<td>90.0</td>
<td>89.2</td>
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<tr>
<td>6</td>
<td>61.5</td>
<td>72.8</td>
<td>66.8</td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td>67.2 ± 6.9</td>
<td>80.1 ± 6.5</td>
<td>66.4 ± 5.7</td>
</tr>
</tbody>
</table>

Change in lean body mass +1.4 ± 0.5 -4.0 ± 0.9 +0.5 ± 1.6 +0.5 ± 0.4 -1.0 ± 0.8 -2.1 ± 1.2
fore treatment were significantly lower than age-matched control values (P < .01). The K diet effected an increase in serum IGF-I levels to 415 ± 54 ng/mL (P < .05). IGFBP-3 levels (2.9 ± 0.3 mg/L) were also lower than controls (P < .01) and remained constant despite weight loss. Leptin levels were loosely correlated with weight (Pearson’s r = 0.61; P < .05) and body fat content (r = 0.64; P < .05). Of note, however, leptin levels were considerably lower than found in similarly obese adults and showed no consistent decline with weight loss.

Calcium balance was affected by the K diet. Urinary calcium excretion increased with the introduction of the K diet and quickly returned to normal in the K+2 phase (Fig 3). This rise in calcium excretion was accompanied by a small, but statistically significant decrease in total body bone mineral content (−0.15 ± 0.04 kg; P < .05). Mean serum calcium remained virtually unchanged at 10.0 through every phase of study except for a transient rise to 10.4 ± 0.14 mEq/L after the addition of carbohydrates (P < .05). These changes occurred in the face of a constant daily intake of calcium (1250 mg elemental calcium) and vitamin D (800 IU).

Indirect Calorimetry

Measurements of REE correlated well with weight (Fig 4; r = 0.67) and lean body mass (r = 0.55). To assess the effects of weight loss on REE without the complicating influence of body composition, REE measurements were corrected for lean body mass by DEXA. On initiation of the study, REE was 34.2 ± 2.3 kcal/kg of lean body mass. With weight loss, REE decreased to 28.9 ± 1.2 kcal/kg of lean body mass (P < .05).

Sleep Studies

One subject required CPAP treatment and another required a tracheostomy due to severe sleep apnea with profound hypoxemia. Neither subject required these interventions after achieving weight loss. Three other subjects had milder degrees of sleep apnea. Only one of the subjects did not have any apneic episodes. The mean apnea index decreased from 14.1 to 1.6 episodes per hour after an average weight loss of 18.7 kg. The number of subjects with excessive daytime sleepiness (MSLT ≤ 5 minutes) decreased from four, at enrollment, to one after weight loss.

Figure 5 illustrates the effect of weight loss on sleep EEG recordings in these morbidly obese subjects. Normal sleep architecture in this age group consists of 21% REM, 20% slow-wave activity, and 59% non-slow-wave activity. The average baseline distribution for the obese subjects was 13% REM, 41% slow-wave activity, and 45% non-slow-wave activity. After weight loss, the average distribution was 21% REM, 26% slow-wave activity, and 53%
non-slow-wave activity. Weight loss led to near normal-ization of sleep architecture with a significant increase in REM sleep \( (P < .02) \) and a decrease in slow-wave activity \( (P < .01) \).

**DISCUSSION**

Morbid obesity can be defined in many ways. For the purposes of this study, morbid obesity was defined as \( >200\% \) of IBW. We submit that this criterion is acceptable in light of the high incidence of weight-related abnormalities displayed in the present study as well as others.\(^6\)–\(^9\),\(^23\)–\(^25\).

Multiple dietary approaches have been used in the treatment of morbid obesity with varying degrees of success. Restriction of energy intake is essential. Di-ets can be classified as low-calorie (10–20 kcal/kg IBW) or very low-calorie (10 or less kcal/kg IBW).\(^26\)

With the very low-calorie ketogenic diet (K diet), weight loss is rapid. Patients may lose 18 to 22 kg in 12 to 15 weeks.\(^16\) Merritt et al\(^27\) found, as we have, that adolescents may approach positive nitrogen balance within 4 weeks of instituting this dietary approach. We observed no adverse events in our patients, but warn that careful monitoring of ketosis, blood pressure, and biochemical parameters are required for morbidly obese adolescents to safely con-sume the K diet.\(^28\)

Our results, with regard to weight loss, are consist-ent with those of others.\(^27\),\(^29\) Although our subjects lost significantly more weight on the K diet, greater efficacy should not be implied from these data. How-ever, the superiority of this dietary approach was recently shown in a randomized crossover study design.\(^29\) We demonstrate, furthermore, that the weight loss achieved with the K diet affects adipose tissue preferentially, and that preservation of lean body mass is possible. This was the case whether lean body mass was estimated from creatinine excretion or from body densitometry using DEXA. Bio-electrical impedance measurements reflected a greater loss of lean body mass. However, changes in total body fluid and electrolyte content, as a result of ketosis, may complicate these measurements. Although not clinically significant, the decrease in serum potassium observed during the K diet agrees with the assertion that changes in total body potassium do not accurately reflect shifts in lean body mass during weight loss.\(^30\) With the exception of transient elevations in uric acid, standard blood chemistries remained normal throughout both diets.

Obesity in childhood leads to elevated total, LDL, and very low-density lipoprotein cholesterol, while lowering HDL cholesterol.\(^31\) This is an adverse lipoprotein profile with regard to the eventual development of cardiovascular disease.\(^32\) The beneficial effects of weight loss and reduced dietary fat on serum lipid profiles has been well-documented in adults. Reports in children suggest that weight loss produces a lowering of LDL and total cholesterol in proportion to the degree of initial elevation.\(^33\) The effects of the K diet on lipid profiles have, heretofore, not been systematically assessed. Our data suggests that this dietary approach acutely lowers LDL, HDL, and total cholesterol equally in a group of morbidly obese adolescents without hypercholesterolemia. The effects of this diet in hyperlipidemic children remain to be examined.

Bone mineral density decreased significantly during the ketogenic diet despite generous calcium and vitamin D supplementation. The onset of ketosis was accompanied by an increase in urinary calcium excretion, which returned to baseline soon after restoring carbohydrate intake. During the K+2 diet, bone mineral density increased slightly, and was no longer distinguishable from baseline in this small sample. This is the first study to suggest that bone mineral density is compromised by a ketogenic approach to weight loss, and that a more vigorous approach to calcium and/or vitamin D supplemen-tation is warranted.

A direct relationship between REE and lean body mass in adults has been established.\(^34\) A limited num-ber of similar studies in obese and nonobese children agree with the correlation between REE and lean body mass found in our subjects.\(^35\),\(^36\) The observation that REE (adjusted for lean body mass) decreases after weight loss is the first of its kind in adolescents. Recently, a similar observation was made in adults.\(^37\) The decreased basal metabolic rate in weight-reduced adolescents may contribute to the poor long-term efficacy of treatments for adolescent obesity.

The K diet has been shown to have little effect on growth velocity when used for 1 to 5 months.\(^38\) We found a small decrease in growth velocity; however, our subjects were late in puberty and most had already attained normal adult stature. A rise in IGF-I
levels with weight loss might have been predicted from the fact that growth hormone secretion is diminished in obese versus nonobese children. The change in growth factor levels with weight loss (a rise in IGF-I/no change in IGFBP-3) leads to an increase in the IGF-I/IGFBP-3 ratio (an index of free, biologically active IGF-I). Of note, a similar pattern is observed in subjects during treatment of poorly controlled diabetes.

The extent to which obesity contributes to OSA in children has not been determined. One study of obese children with a history suggestive of sleep-associated breathing disorders found polysomnographic abnormalities in 37% and a diagnosis of OSA in 24% using adult criteria. In a more recent study of 32 obese children referred for snoring or abnormal breathing during sleep, 59% were diagnosed with OSA. The incidence was even greater (68%) for children weighing >200% of their IBW. Our subjects were selected on the basis of their weight and desire for a weight loss program, without regard to the presence of OSA symptoms. The occurrence of OSA in the majority of our subjects is consistent with these previous studies.

Weight loss reduces the duration and frequency of apnea in adults. The present study demonstrates a decrease in apneic episodes and the return of sleep architecture to normal after weight reduction. This is the first evidence to suggest that weight loss may be effective in preventing the cardiopulmonary and neurocognitive sequelae of OSA. The significance of increased slow-wave sleep in this obese population is unclear. However, the majority of apneic events in our patients occurred during stages 3 and 4 sleep. We speculate that the association between obesity and excessive slow-wave sleep plays a role in the pathophysiologic mechanism of sleep events in our subjects.

We conclude that the low-calorie K diet is a safe and effective weight loss regimen for morbidly obese adolescents. The weight loss with this approach is rapid, consistent, and almost exclusively from body fat stores. Urinary calcium excretion is increased during ketosis and may lead to decreased bone mineral density, despite normal calcium intake. The K diet lowers serum cholesterol, restores IGF-I levels to normal, and leads to improved sleep function.

ACKNOWLEDGMENTS

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Submitted by Student
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