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Energy balance in congenital generalized lipodystrophy type I

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Abstract

Congenital generalized lipodystrophy type 1 (CGL-1) is characterized by an absence of adipose tissue and decreased serum leptin levels. Low leptin levels in CGL-1 support the claim that subjects are hypermetabolic and hyperphagic. The present study examines this claim. We determined 24-hour energy expenditure (24-h EE) (kilocalories) (n = 2) and resting metabolic rate (RMR) per kilogram of lean body mass (LBM) (n = 3) in CGL-1 and in 18 healthy control subjects. The 24-h EEs of control and subjects with CGL were compared with respect to kilocalories required per day relative to kilograms of LBM and with respect to RMR relative to kilograms of LBM. Fasting leptin, adiponectin, and 24-hour ghrelin levels were also measured in subjects with CGL-1. The 24-h EE per kilogram of LBM for the subjects with CGL-1 falls on the same regression line observed for this relationship in the controls. The RMR per kilogram of LBM in subjects with CGL-1 also was similar to that in controls. Both 24-h EE and RMR were quite increased when reported per kilogram of total body weight. Subjects with CGL-1 also have decreased fasting leptin and adiponectin hormone levels and no premeal ghrelin rise. People with CGL-1 have similar RMR and daily caloric requirements as healthy controls when these parameters are expressed as a function of LBM. Appetite-regulating hormone levels in CGL-1 suggest that multiple factors act to control appetite in these individuals.

1. Introduction

Congenital generalized lipodystrophy (CGL) is an autosomal recessive disorder characterized by the absence of adipose tissue and leptin deficiency. Berardinelli [1] first described CGL in 1954 in 2 children with hepatomegaly, marked muscular development, and milky serum. In 1968, we [2] reported a variant form of CGL in an African American family with a similar phenotype that, in addition, featured cystic bone lesions. More than 30 years later, the CGL variant associated with bone disease was classified as CGL type 1 (CGL-1), resulting from mutations in the gene for AGPAT2 (1-acylglycerol-3-phosphate *O*-acyltransferase 2), located at 9q34 [3-5]. AGPAT2, also known as *LPAATβ gene* (lysophosphatidic acid acyltransferase *β*), catalyzes the formation of phosphatidic acid, a critical component of phospholipids and triglyceride synthesis. The CGL variant initially described by Berardinelli [1] and later by Seip [6] is consistent with characteristics seen in CGL type 2 (CGL-2). Congenital generalized lipodystrophy type 2 results from mutations in the gene for seipin (at 11q13) that encodes an integral membrane protein of the endoplasmic reticulum [7,8].

Both CGL variants have been reported to be associated with increased energy intake and increased resting metabolic rate (RMR) with respect to total body weight (TBW) [9]. The metabolic demands of individuals with congenital leptin deficiency [10] are consistent with the continuous pattern of

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food intake [1,11-16] and low serum leptin levels reported in people with CGL [17]. Energy requirements are predominantly determined by lean body mass (LBM) because triglyceride stores in adipose tissue are metabolically inactive. Because adipose tissue is effectively absent in CGL, LBM accounts for a higher proportion of the TBW in these individuals. Therefore, energy expenditure in CGL reported as a function of TBW [9] may have been previously overestimated. To determine energy requirements in CGL-1, we compared the daily caloric intake and RMR (as a function of LBM) in CGL-1 and healthy control subjects.

2. Research design and methods

2.1. Subjects

Eighteen weight-stable control subjects (10 male and 8 female subjects) and 3 subjects with CGL-1 were examined. The study was approved by the Human Subjects Institutional Review Committee of the University of Washington, and informed consent was obtained from all subjects after the nature of the procedures were explained to them. Subject 1-4, a 55-year–old man, has a muscular appearance, bone cysts, acromegaloid features, type 2 diabetes mellitus, hypertension, coagulopathy, and hyperlipidemia (subject III-1 in Brunzell et al [2]). His 60-year–old brother (subject 1-1) has a history of type 2 diabetes mellitus, hypertension, a muscular appearance, and acromegaloid features (subject III-4 in Brunzell et al [2]). An additional CGL-1 subject, a 33-year–old African American female (subject 3-1) not related to the other subjects, has type 2 diabetes mellitus, hypertension, a muscular appearance, acromegaloid features, bone cysts, history of acute pancreatitis (due to hypertriglyceridemia), and bipolar disorder. Subjects with CGL-1 were either homozygotes or compound heterozygotes for mutations in the AGPAT2 gene (Table 1).

The controls were matched to the subjects with CGL-1 by LBM. In control subjects, the measurements of LBM and daily caloric intake were performed in 10 healthy male and 8 healthy female subjects. Studied previously, these individuals had a mean age of 44 (±14) years, a mean LBM of 66 kg (±17), a mean weight of 104 kg (±20), and a mean height of 175 cm (±10) [18].

2.2. Genotype analysis

For exons 2 to 6 at 9q34, the following amplification primer pairs were designed based on the sequence of the human AGPAT2 gene in GenBank:

Exons 2 to 4. Fragment size = 1.1 kilobases.
AGPAT2 I1F: 5′ CAGCCTCGGCTGCGGGATCTG 3′
AGPAT2 I4R: 5′ CACCTGCTGCCTTAAGCCAGCCTC 3′
Exon 5. Fragment size = ~255 base pairs.
AGPAT2 I4F: 5′ CCCATGGCAGCAGCGAAGGC 3′
AGPAT2 I5R: 5′ CTCCGTGACTGTAGGGTCAGGC 3′
Exon 6. Fragment size = ~ 300 base pairs
AGAPT2 I5F: 5′ CGAGGCCAGGGGCAGCAGGCTG 3′
AGAPT2 I6R: 5′ CCAGCCATCGGCTTCCACCTG 3′

Fragments of exons 2 to 4 were initially denatured at 94°C followed by 35 cycles of denaturation at 94°C for 15 seconds, annealing at 66°C for 2 minutes, and polymerization at 72°C for 4 minutes. Exons 5 and 6 fragments were initially denatured at 94°C followed by 35 cycles of denaturation at 94°C for 15 seconds, annealing at 64°C for 30 seconds, and polymerization at 72°C for 30 seconds, followed by a final step of 4 minutes at 72°C.

The polymerase chain reaction products were gel-purified, the DNA was extracted using the Qiagen MinElute Gel Extraction kit (catalog no. 28604, Germantown, MD) and both strands of DNA were directly sequenced using the Applied Biosystem (Foster City, CA) Bigdye Terminator kit and protocol. The amplification primers were used in sequencing reactions.

2.3. AGPAT2 activity

Blood was obtained after a 12-hour fast in EDTA tubes, and peripheral blood mononuclear cells were isolated and plated on culture dishes. The AGPAT activity from peripheral blood mononuclear cell lysates was assayed as previously described [19]. Total activity of the different AGPAT isoforms is predominantly based on AGPAT1 and AGPAT2 activity. Total AGPAT enzyme activity was obtained by incubation in the presence of dimethyl sulfoxide (8 μmol/L); AGPAT2 activity was obtained after incubation with a specific AGPAT1 inhibitor, CT 11493 (10 μmol/L). For each patient sample, one control sample (of healthy, non-

Table 1
Metabolic measurements and AGPT2 mutations in subjects with CGL-1

Subject	Sex	Age	% Body fat	Weight (kg)	Height (cm)	BMI (kg/m^2)	Leptin * (ng/mL)	Adiponectin † (μg/mL)	HbA_{1c} (%)	Mutations in AGPT2	
1-1	M	60	5.6	73.0 ‡	178	23.0	0.9	0.85	11.5	IVS4-2A→G	R 68X
1-4	M	55	6.9	94.0	177	30.0	1.3	0.45	7.8	IVS4-2A→G	R 68X
3-1	F	33	4.9	73.1	162	27.9	1.2	0.20	9.5	IVS4-2A→G	P112L

BMI indicates body mass index; HbA_{1c}, glycosylated hemoglobin.
* Normal values: 2 to 5.6 ng/mL for men and 3.7 to 11.1 ng/mL for women.
† Normal values: 1.5 to 10.3 μg/mL.
‡ Patient has left total leg amputation.

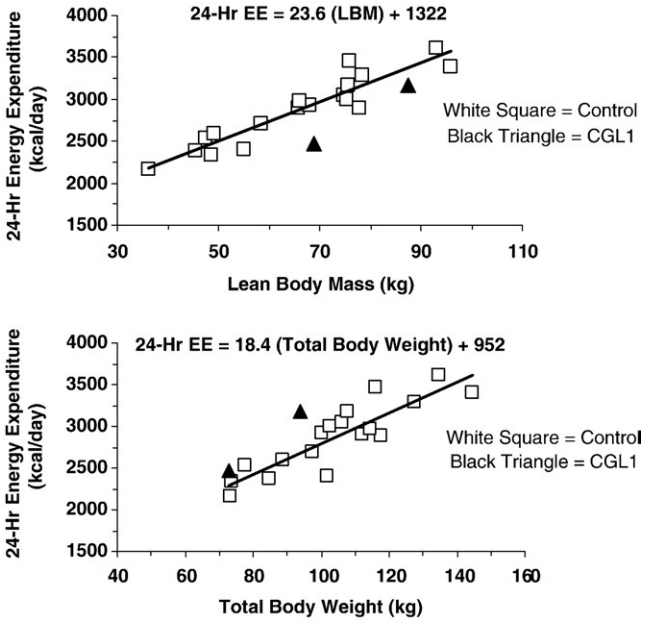

Fig. 1. A, Lean body mass vs 24-hour energy expenditure. B, Total body weight vs 24-hour energy expenditure.

CGL, middle-aged men) was processed on the same day in the same assay. All samples were assayed in duplicate.

2.4. Diets

Each control and CGL-1 subject was admitted to the General Clinical Research Center at the University of Washington Medical Center. The controls were admitted in 1988, whereas individuals with CGL-1 were admitted in 2004. All subjects were limited to weight-maintaining liquid formula diets divided into 3 or 5 equal servings between 8:00 AM and 8:00 PM. No other meals were provided. In addition, subjects' physical activity levels were limited to activities of daily living and short walks. In the studies, 45% to 55% of the total calories was derived from carbohydrates (maltodextrose), 30% to 40% from fats (corn oil and butterfat), and 15% from proteins (nonfat milk). Liquid formula containers of all subjects were rinsed with water and drank to ensure an accurate measurement of daily caloric intake. Complete vitamin and iron supplements were provided.

Body weight was measured each morning on a metabolic scale immediately upon arising with the same limited clothes on each occasion.

2.5. Lean body mass

Lean body mass was measured by underwater weighing with pulmonary N2 washout or by dual-energy x-ray absorptiometry scan (GE Lunar Prodigy, Chalfont St. Giles, UK). Measurements of LBM by underwater weighing and dual-energy x-ray absorptiometry scan are highly correlated [20,21].

2.6. Resting metabolic rate

Resting metabolic rate was measured in the same way for all controls and CGL-1 subjects. The calculation of RMR was performed by hood indirect calorimetry in the morning as subjects awakened and before they arose from bed as previously described [18]. All hood calorimetry instruments used were calibrated for both gas sensor and total airflow.

2.7. Daily energy expenditure and RMR as functions of TBW and LBM

Lean body mass is highly correlated with energy metabolism [22-24], and 24-hour energy expenditure is reported per unit of LBM when comparing individuals of different body compositions. As previously reported, we measured the daily caloric intake of 18 healthy individuals as a function of LBM and TBW (Fig. 1A, B) [18]. Similarly, in the same cohort, the relationship between RMR as a function of LBM and TBW was measured (Fig. 2A, B).

For study subjects, their LBM determined their daily energy expenditure by using the linear regression equation correlating LBM and 24-hour energy expenditure in controls (Fig. 1A). For subjects 1-1 and 1-4, their weight was maintained for 5 and 8 days, respectively, with a weight stability of +40 g/d mean change for subject 1-1 and +50 g/d mean change for subject 1-4. In addition, all individuals with CGL were limited only to activities of daily living. Slight adjustments of 5% to 10% initially were made to 24-hour caloric intake to achieve weight stability. Therefore, discounting significant caloric losses, at a steady weight, the 24-hour energy expenditure is approximated by the 24-hour caloric intake over the period of weight stability for each individual with CGL (24-hour caloric intake = 24-hour energy expenditure).

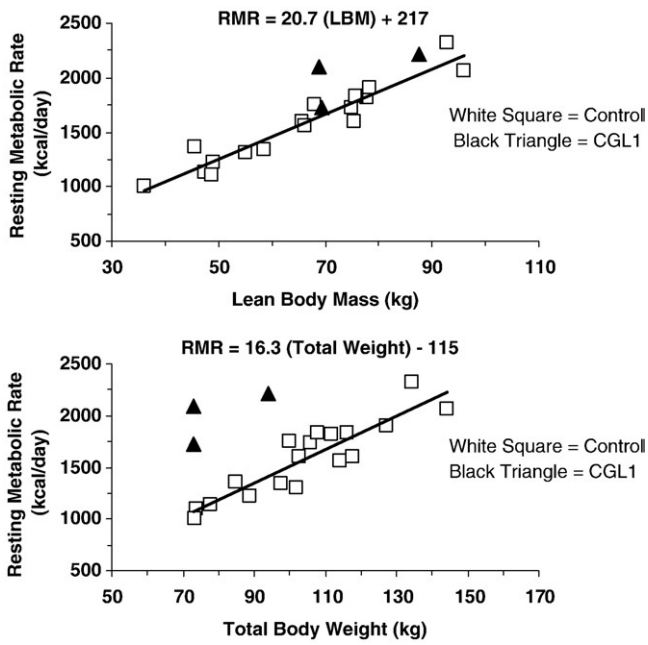

Fig. 2. A, Lean body mass vs RMR. B, Total body weight vs RMR.

2.8. Statistics

For controls, we calculated the mean and standard deviation of their age, TBW, LBM, height, and plasma ghrelin levels. We used linear regression to determine the correlation between 24-hour energy expenditure with LBM and TBW (Fig. 1A, B). We used the same method to determine the correlation between RMR with LBM and TBW (Fig. 2A, B).

2.9. Serum markers for appetite and insulin resistance

Serum leptin and adiponectin levels were measured by Northwest Lipid Research Laboratory in Seattle. The leptin assay uses ^{125}I-labeled human leptin and a human leptin antiserum to determine the level of serum leptin levels. The lowest level of leptin that can be detected by this assay is 0.5 ng/mL when using a 100-μL sample size. Each sample is analyzed in duplicate. The adiponectin assay is based on a commercial radioimmunoassay kit and uses ^{125}I-labeled murine adiponectin and a multispecies antiadiponectin serum. This is a double antibody assay using polyethylene glycol–aided precipitation. The assay has a sensitivity of 1 ng/mL when using a 100-μL sample size. Each sample is analyzed in duplicate. The 24-hour ghrelin assays were measured as previously described [25]. The 24-hour ghrelin levels were determined in the CGL subjects after 3 weeks of meals served at the same time of the day to each subject (8:00 AM, 12:00 PM, and 5:30 PM). The mean 24-hour ghrelin levels for previously described 10 weight-stable control subjects (9 women and 1 man) with the same meal times (8:00 AM, 12:00 PM, and 5:30 PM) were used for comparison [25]. Glycosylated hemoglobin levels were measured by the University of Washington Medical Center Clinical Laboratories.

3. Results

3.1. AGPAT2 activity and genotypes

The AGPAT2 activity in the 3 CGL patients was reduced by 70% to 76% compared with that in normal controls (Fig. 3)

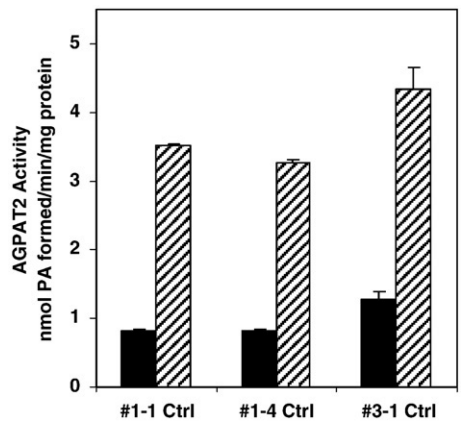

Fig. 3. The AGPAT2 activity in CGL-1 (solid bars) and control (striped bars) subjects.

Table 2
Predicted and measured 24-hour energy expenditure and RMR in subjects with CGL-1

Subject	1-1	1-4	3-1
Predicted 24-h EE/kg of LBM	2948	3387	–
Measured 24-h EE	2466	3170	–
% Deviation from predicted 24-h EE/kg of LBM	−16.4	−6.4	–
Predicted 24-h EE/kg of TBW	2295	2682	–
% Overestimation of predicted 24-h EE/kg of total weight	7.5	18.2	–
Predicted RMR/kg of LBM	1643	2053	1656
Measured RMR/kg of LBM	1725	2218	2095
% Deviation of measured RMR from predicted RMR	5.0	8.0	26.5
Predicted RMR/kg of TBW	1075	1417	1077
% Overestimation of predicted RMR/kg of total weight	60.5	56.5	94.5

[26]. There was no compensatory increase in AGPAT1 (data not shown). Subjects 1-1 and 1-4, who were compound heterozygotes for the IVS4-2A to G and R68X mutations, have similar AGPAT2 activity. In addition, AGPAT2 activity was reduced by 70% in subject 3-1, who is a compound heterozygote for the IVS4-2A to G and the novel mutation P112L.

3.2. Twenty-four–hour energy expenditure and LBM

There is a higher correlation in controls between daily energy expenditure and LBM (r^2 = 0.88, P < .001) than between daily energy expenditure and TBW (r^2 = 0.77, P < .001) (Fig. 1A, B). When 24-hour energy expenditure is expressed as a function of LBM, the 2 CGL-1 subjects (1-1 and 1-4) fall near the regression line formed by the 18 control subjects (Fig. 1A, Table 2). When the daily energy expenditure is expressed as a function of TBW, values for the subjects with CGL-1 fall above the regression line formed by control subjects (Fig. 1B, Table 2).

3.3. RMR and LBM

The correlation is stronger in controls between RMR and LBM (r^2 = 0.92, P < .001; RMR = 20.7[LBM] + 217) than RMR and TBW (r^2 = 0.83, P < .001) (Fig. 2A, B). When the RMR of 3 CGL-1 subjects (1-1, 1-4, and 3-1) is compared with that of 18 controls as a function of LBM, the values for 2 of the 3 subjects fall near the regression line formed by the control subjects (Fig. 2A, Table 2). In contrast, when the RMR is expressed as a function of TBW, the measured values for all subjects with CGL-1 are well above the regression line formed by control subjects (Fig. 2B, Table 2).

3.4. Leptin, ghrelin, and adiponectin

Fasting leptin and adiponectin levels in the CGL individuals were very low (Table 1). In addition, the 24-hour profile of ghrelin in subjects 1-1 and 1-4 were more

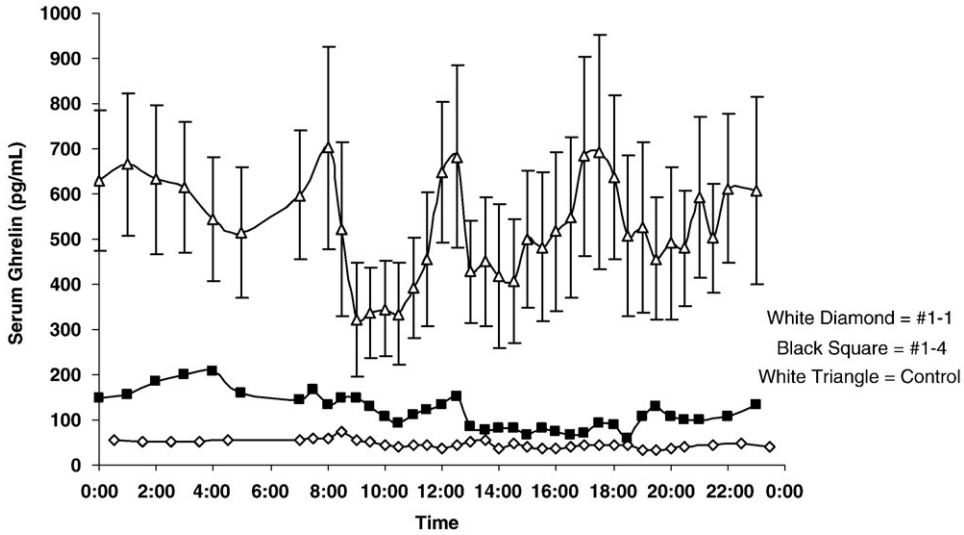

Fig. 4. The 24-hour plasma ghrelin levels in subjects with CGL-1 and the mean 24-hour ghrelin levels in 10 control subjects, with error bars representing 2 standard deviations.

than 2 standard deviations below that of the mean for previously described controls (Fig. 4) [25]. The subjects with CGL-1 also did not have the expected premeal spike or postmeal decline in ghrelin levels observed in controls.

4. Discussion

Lean body mass is the most significant determinant of daily energy balance in individuals restricted to activities of daily living. In this study, there is a high correlation between LBM and daily caloric intake in control subjects. Because CGL is associated with near absence of adipose tissue, which normally is composed mainly of metabolically inactive triglyceride mass, the energy parameters of these individuals have to be determined in terms of their relatively increased proportion of fat-free mass. Therefore, to control for the different amounts of adipose tissue in control and CGL subjects, their energy requirements are corrected for LBM to facilitate accurate comparisons.

Three main reasons appear to be responsible for the hypothesis that CGL subjects are hypermetabolic and hyperphagic (ie, ingesting an excessive number of calories). First, in the past, energy balance in subjects with CGL has been reported in terms of TBW instead of LBM [9]. Second, because of a lack of adipose tissue and therefore an inability to store sufficient long-term energy, subjects with CGL are observed to be eating frequent meals. Finally, congenital lipodystrophy is associated with markedly low serum leptin levels [17], which would be predicted to lead to increased food intake [10].

Because individuals with CGL do not gain weight with their apparent hyperphagia [9], subjects with both types of CGL have been described as hypermetabolic. However, the RMR may have been overestimated in CGL-2 when reported with respect to total weight; and it appears to be normal in CGL-1, in whom individual metabolic rate data have not been reported [27]. When RMR values for CGL-1 are recorded with regard to TBW (rather than LBM), as previously reported in subjects with CGL, they are up to 95% higher than the standard values for healthy controls (Table 2). The relation of RMR with LBM for the controls (RMR = 20.7[LBM] + 217) in this study is remarkably similar to that reported by Mifflin et al [24] (n = 238 men, RMR = 22.5[LBM] + 209; n = 245 women, RMR = 20.8 [LBM] + 360). Their data add validity to our data in a much smaller cohort for RMR. In the present study, the RMR in 2 of 3 CGL-1 subjects fell within 10% of predicted values for control subjects with similar LBM. Determination of RMR requires overnight fasting, and the only CGL-1 subject who appears to have an increased metabolic rate, subject 3-1, has bipolar disorder and was noncompliant with the requirement for overnight fasting.

In the past, both abnormally high and normal measurements of resting metabolism have been reported in undifferentiated CGL. Schwartz et al [28] first reported RMR data in CGL and found them to be normal. More recently, Savage et al [29] attributed the increased RMR in a group of subjects with various lipodystrophies to their relatively higher LBM. Studies by Petersen et al [13] and Oral et al [30], who measured basal metabolic rate before and after leptin therapy, reported no change and a mean decrease from 1920 to 1580 kcal/d, respectively [13,30]. Klein et al [31] reported an RMR of 30% above normal in their single subject. Seip [9] reported elevated levels in 4 CGL subjects, with values as high as 73% above normal. However, the data on hypermetabolism in these studies either are an average for a group of subjects that includes different types of

lipodystrophy or are based on subjects who have characteristics associated with CGL-2. The current study reports that individuals with CGL-1 have normal metabolic rates.

Several studies describe energy use in lipodystrophy. One study found statistically insignificant increases in energy expenditure, whereas others reported energy use in lipodystrophic subjects but did not include control values [15,16,31,32]. Furthermore, these studies do not distinguish between different types of lipodystrophy [15,16,31,32] and report the daily energy use as a mean value for the entire group [16,31,32]. The best example of this is Seip's [9] examination of 7 individuals with CGL whom he describes as hyperphagic. However, in addition to not reporting energy balance in terms of LBM, daily caloric intake results are provided for only a pair of subjects. In fact, as the phenotypic heterogeneity between the 2 types of CGL has become more apparent [12,33], Seip's subjects appear to have CGL-2. Still, because energy use is most accurate when reported as a function of LBM, these energy balance values are exaggerated. Three other individuals with CGL in the same study are described as having a "voracious appetite"; but no caloric measurements are presented, so the degree of overeating is unclear. In fact, many assertions of hyperphagia in CGL are not based on discernible measurements of energy intake by investigators, but rather by observation of continuous feeding behavior or the subjects' own perception of eating habits [1,11-14]. Therefore, the premise that CGL-1 is associated with increased daily caloric intake is based primarily on studies of different types of lipodystrophy, overestimated results, and investigator observation.

Decreased serum leptin levels are characteristic of CGL and consistent with the lack of adipose tissue. The adult subjects with CGL-1 in this study had low leptin levels, similar to those in published reports [17]. However, if daily energy intake in CGL-1 is not increased in the presence of very low leptin levels, then leptin alone may not determine food-seeking behavior, food intake, and energy utilization in this setting. The role of leptin as an appetite regulator in CGL-1 may be explained either by increased leptin sensitivity or by interaction of leptin with other regulatory factors (eg, insulin and/or ghrelin). Low serum leptin levels result in leptin hypersensitivity in congenital leptin deficiency [34] or after surgical removal of adipose tissue [35,36]. Studies of the latter intervention showed an unchanged or decreased level of appetite with liposuction. However, because of the very low levels of the serum leptin in CGL, even an exaggerated response to the hormone seems unlikely to prevent compensatory hyperphagia. In addition, if sensitivity to leptin action is increased in congenital lipodystrophy, the response would have to be tissue-specific because the gonadal response to leptin is reduced in CGL-1 [37]. Therefore, whereas the sensitivity to leptin signaling in the ovaries may exhibit no change, the hypothalamic response would have to be exaggerated. A more likely explanation for the lack of overeating in CGL-1 is that appetite relies on the interaction among multiple factors beyond just leptin. Insulin resistance in CGL-1, associated with decreased adiponectin levels in subjects of this study, may lead to hyperinsulinemia, which could counteract the appetite-stimulating affect of low serum leptin levels and result in appetite suppression in the central nervous system. Like leptin, central insulin infusion decreases food intake by modulating appetite-regulatory neuropeptides in the hypothalamus and other sites in the brain. Insulin may also affect another appetite stimulant, ghrelin. Persistent hyperinsulinemia in CGL-1 may explain the lack of preprandial increases in ghrelin levels because of insulin's known inhibitory action on ghrelin secretion (Fig. 4) [38]. The 24-hour ghrelin levels in subjects 1-1 and 1-4 are persistently low and do not manifest the normal mealtime spikes. It is possible that, without this stimulus for initiating meals, subjects with CGL-1 are inclined to graze for food, less driven to eat bolus meals at specific, habitual intervals. After meals, the subjects do not have the expected decrease in ghrelin levels. Interestingly, the 24-hour ghrelin levels for subject 1-1 resemble those in gastric bypass patients [25].

Taken together, the data suggest that all subjects with CGL-1 are not hyperphagic or hypermetabolic and also that, at the very least, past energy expenditure in CGL-2 may have been overestimated. In all, energy balance data for individuals with CGL-1 are scant. Based on our findings, although persons with CGL-1 eat more frequently than healthy individuals do, their energy intake is spread throughout the day and they consume the same number of total calories as do individuals with a more typical, meal-dominated eating pattern.

There are limitations to this study with regard to the small sample size and the timeline within which subjects and controls were studied. Control and study subject comparisons of measured LBM and RMR were completed at different times. However, the 2 techniques used in this study to determine LBM have a high correlation. In determining RMR, the hood calorimetric methods were very similar; and the machine was calibrated in the same way. To more accurately determine 24-hour energy expenditure, the study could have accounted for gastrointestinal (fat) and urinary (glucose) caloric losses. However, the energy loss from these sources is minimal (unpublished data) and does not account for the discrepancy between the measurements of 24-hour energy expenditure with regard to TBW vs LBM. In addition, potential sources of energy loss do not account for the wide discrepancy in RMR when measured with regard to TBW instead of LBM (Table 2).

More studies are needed in both types of CGL to clarify energy parameters and metabolism. Several larger studies have characterized larger groups of subjects with each type of CGL. However, this is one of few studies designed to evaluate metabolism specifically in one type of CGL. In the least, the results in this study suggest that data on energy use in other CGL subjects should be reexamined to treat these individuals more effectively.

Acknowledgment

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