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Bone Mineral Content and Bone Mineral Density Are Lower in Older than in Younger Females with Rett Syndrome

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Abstract

Although bone mineral deficits have been identified in Rett syndrome (RTT), the prevalence of low bone mineral density and its association with skeletal fractures and scoliosis has not been characterized fully in girls and women with RTT. Accordingly, we measured total body bone mineral content (BMC) and bone mineral density (BMD) using dual energy x-ray absorptiometry in a cross-sectional group of 50 females, ages 2-38 y, with RTT. Methyl-CpG-binding 2 (*MECP2*) mutations, skeletal fractures, and scoliosis were documented. The prevalence of BMC and BMD z-scores <-2 SD was 59% and 45%, respectively. Although absolute BMC and BMD increased significantly with increasing age, BMC and BMD z-scores were significantly lower in older than in younger females. The prevalence of fractures and scoliosis was 28% and 64%, respectively. Low BMD z-scores were positively associated with fractures and scoliosis. Deficits in BMD were identified across a broad range of *MECP2* mutations. This study identified associations among low bone mineral density, fractures, and scoliosis, and underscored the need for better understanding of the molecular mechanisms of *MECP2* in the regulation of bone mineral metabolism.

Keywords

bone mineral density; skeletal fractures; scoliosis; genotype-phenotype correlations; body composition; anticonvulsants

Bone mineral deficits complicate the clinical course of Rett syndrome (RTT) (1-3), an X-linked neurodevelopmental disorder caused by mutations in the methyl-CpG binding 2 (*MECP2*) gene (4). Consequently, girls with RTT are at increased risk for skeletal fractures (1,3). The etiology of bone mineral deficits is unknown, although impaired ambulation and anticonvulsant therapy have been implicated as causally related factors (3). We have shown that bone mineral deficits are present, despite adequate dietary calcium (Ca) intake, increased intestinal Ca absorption, and the absence of vitamin D deficiency or hyperparathyroidism (5). Our studies (5,6) and that of Haas *et al*. (1) documented early, profound deficits of total body bone mineral content (BMC) and bone mineral density (BMD) in girls with RTT compared with unaffected girls and children with other neurological disorders. Haas *et al*. (1) showed that total body BMC did not improve with advancing age, while our study suggested that the accretion of total body BMC throughout childhood was possible (5). All of these studies were limited because of the small number and narrow age range of the participants (1,5,6). They also captured total body BMC and BMD

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when less emphasis was placed on the nutritional and physical rehabilitation of females with RTT.

In the present study, we expanded the number and age range of the participants and used body composition and ambulation as proxies for nutritional status and physical activity to better understand the prevalence of bone mineral deficits and the relation between bone mineral deficits, *MECP2* mutations, and occurrence of bone-related disorders in RTT. We hypothesized that: 1) the early decrease in BMC and BMD persists over time in a cross-sectional cohort of females with RTT, 2) bone mineral deficits occur across a range of *MECP2* mutations, and 3) the reduction in BMC and BMD correlates with the occurrence of fractures and scoliosis. We anticipated that this study would facilitate the development of strategies to promote bone mineral health in RTT.

SUBJECTS AND METHODS

Subjects

Fifty females who met the clinical criteria for RTT were enrolled (7). *MECP2* mutations, if known, were recorded. All participants were female because males with *MECP2* mutations have a different phenotype and rarely meet the diagnostic clinical criteria (8). The eligible age range was 0-40 y, with individuals divided among groups of 5-y intervals. Individuals were excluded if they received oral Ca supplements 6 months prior to study, had previous therapy with bis-phosphonates, had hypocalcemia, hyperparathyroidism, vitamin D deficiency, or had scoliosis requiring spinal rod placement, the latter because metal interferes with the ability of DXA to provide an accurate assessment of spine BMD.

Parents gave permission for the participation of their daughters in the research study. Assent was waived for the participants because of their cognitive impairment. The Institutional Review Board for Baylor College of Medicine approved the study protocol.

Procedures

All females with RTT were admitted overnight to the General Clinical Research Center, Texas Children's Hospital, for 1) review of their medical history, 2) physical examination, and 3) determination of their stature and body habitus, bone age, and total body and regional bone mineral status. Individual *MECP2* mutations were classified as missense, early truncation, late truncation, and large deletion mutations (10). A history of fractures, seizures and anticonvulsant use, the ability to ambulate, and the presence of scoliosis were documented.

Height was measured using a fixed stadiometer or horizontal length board with a movable foot piece (Harpenden, Crymych, Great Britain). Weight was measured using an electronic balance (Scale-Tronix, Inc., Wheaton, IL). BMI was calculated as weight divided by height squared. Height, weight, and BMI measurements were converted to z-scores based on the National Center for Health Statistics normative data (11). Body fat, as a proportion of body weight, was estimated from triceps, biceps, subscapular, and suprailiac skinfold thickness (12). The bone age of females, age 20 y or less, was calculated from an x-ray of the right hand using reference standards (13).

Whole body, hip, and spine BMC and BMD were measured by dual-energy x-ray absorptiometry (DXA) (Delphi-A System, Hologic, Inc., Madison, WI) using standardized scan protocols. Midazolam (0.2 mg/kg/dose) was administered intravenously immediately before the scan to prevent repetitive involuntary movements that could invalidate the analysis. The data from 10 body regions were summed to provide values for total body BMC and BMD; lean body mass; and body fat using body composition software (Delphi-A System, Version

11.2, Hologic, Inc., Waltham, MA). The *in vivo* precision for BMC and BMD measurements is 2-3% for children and young adults (9).

Bone mineral status was expressed as BMC, which reflects bone mass, and BMD, which reflects a calculated measure of areal density, not a true volumetric density (14). Because areal density is dependent on bone size, thinning of the bone cortex and a smaller outer diameter of bone may result in diminished areal BMD, whether or not true volumetric density is diminished. To correct for changes in bone size as a function of age and body size, total body BMC and BMD were converted to z-scores based on values measured in a reference population (9). The reference database includes DXA scans for more than 2200 healthy children for whom ethnic, racial, and gender distributions are approximately equal. These data were used to develop a predictive algorithm for normative total body BMC and BMD based on age, gender, ethnicity, race, and height (6). For individuals whose ages exceeded 20 years, adult references provided with the DXA instrument were used. A significant bone mineral deficit was defined as total body BMD z-score <-2 SD (15).

Statistical Analysis

Sample size was determined from an analysis of females, age 5-12 y, with RTT (6) whose BMC averaged 458 ± 111 g and unaffected girls, ages 6-10 y, 11-14 y, and 15-18 y whose BMC averaged 775 ± 233, 1346 ± 312, and 1979 ± 289 g, respectively (9). Seven individuals within each 5-y age category allowed us to detect differences in BMC between females with RTT and the reference population of 1 SD at a significance of 0.05 and power of 0.8.

Descriptive statistics were calculated using Minitab software (Version 11.0, Minitab Statistical Software, Inc., State College, PA). One-sample t-tests were used to detect differences in height, weight, BMI, BMC, and BMD z-scores between the RTT cohort and reference population (9,11). Linear regression was applied to characterize relations: 1) between methods used to estimate the proportion of body fat in the RTT cohort; 2) among the variables: lean body mass, body fat, bone age, total body BMC, total body BMD, and age, and 3) among the variables spine, hip, and total body BMC and BMD. Two-sample t-tests were used to detect differences in lean body mass, body fat, and BMC between girls with RTT and the reference population at age-specific intervals (9). Two-sample t-tests were used to detect differences in BMC and BMD z-scores within the RTT cohort, based on gene mutations, occurrence of fractures and scoliosis, seizure and medication history, and ambulatory status. Chi-squared analysis was used to detect differences in the occurrence of fractures and scoliosis between individuals with and without bone mineral deficits. Significance was determined at $P<0.05$.

RESULTS

Characteristics of the RTT Cohort

The age range of the RTT cohort was 2-38 y (Table 1). The racial and ethnic distribution was predominantly Caucasian. *MECP2* mutations were identified in 90% of the cohort, the most common being missense and early truncation mutations. Height, weight, and BMI z=scores were <2SD in 50%, 48%, and 28%, respectively of the RTT cohort. Mean z-scores for height, weight, and BMI, were significantly lower than those of the reference population (11). Fractures and scoliosis occurred in 28% and 64% of the cohort, respectively. Fifty percent of the cohort used anticonvulsants and 74% were ambulatory at the time of study.

Bone Mineral Content and Density Measures

Total body BMC and BMD z scores were <-1 SD in at least three-fourths of the RTT cohort and <-2 SD in approximately one-half of the RTT cohort (Table 2). Mean z-scores for total body BMC and BMD were significantly lower in the RTT cohort than in the reference

population (9). After adjusting for age, BMD, but not BMC, of African-American females with RTT tended to be greater than their Caucasian, Hispanic, and Asian counterparts (0.857 ± 0.081 vs. 0.786 ± 0.090, 0.789 ± 0.079, and 0.758 ± 0.082 g/cm ^{2}, respectively; $p<0.07$). Total body BMC [$BMC_{(g)} = 32 \pm 87\ age_{(y)} - 1.4\ age_{(y)}^2$; $p<0.001$, $r = 0.87$] and BMD [$BMD_{(g/cm2)} = 0.54 + 0.025\ age_{(y)} - 0.0004\ age_{(y)}^2$; $p<0.001$, $r = 0.85$] increased with advancing age. However, within each comparative age group, total body BMC was significantly lower in the RTT cohort than in the reference population (Figure 1a) (9). Total body BMC (Figure 2a) and BMD (Figure 2b) z-scores decreased significantly over the age range of the RTT cohort. Hip BMC (Figure 3a) and BMD (Figure 3b) were associated significantly with total body BMC and BMD, respectively. Spine BMC ($p<0.001$, $r = 0.94$) and BMD ($p<0.001$, $r = 0.96$) were associated with total body BMC and BMD, respectively. Bone age was similar to chronological age in individuals younger than age 20 y ($p< 0.001$, $r = 0.97$).

Body Composition Measures

Lean body mass and body fat comprised 66 ± 7% and 31 ± 7% of body weight, respectively, in the RTT cohort (Table 2). The proportion of body fat obtained by DXA correlated positively with that obtained from the thickness of four skinfolds ($p< 0.001$, $r = 0.80$). Lean body mass [$\text{Lean body mass}_{(kg)} = 3.74 \pm 1.69\ age_{(y)} - 0.03\ age_{(y)}^2$, $p<0.001$, $r = 0.85$] and body fat [$\text{body fat}_{(kg)} = 0.33 \pm 1.09\ age_{(y)} - 0.02\ age_{(y)}^2$; $p<0.01$, $r = 0.56$] increased with advancing age. However, within each age group, the lean body mass (Figure 1b), but not body fat (Figure 1c), was significantly lower in the RTT cohort than in the reference population (9). When expressed as a proportion of body weight, body fat was higher for girls with RTT, age 3-5 y (30 ± 4% vs. 21 ± 5%, $p<0.001$) and 6-10 y (33 ± 7% vs. 23 ± 8%, $p<0.01$) than that of the respective reference groups, but not for girls with RTT, age 11-14 y (23 ± 12% vs. 27 ± 8%) and 15-18 y (32 ± 9% vs. 27 ± 6%) (9). When adjusted for age, the accretion of bone mineral content was associated positively with the lean body mass ($p<0.001$, $r = 0.97$), but not body fat.

Mutational Analysis

Total body BMC and BMD z-scores were not significantly different among the classes of gene mutations.

Anticonvulsants and Ambulation

Total body BMC and BMD z-scores were significantly lower in those who had seizures than in those who did not (Table 3). Total body BMC and BMD z-scores were significantly lower in those who received anticonvulsants previously, but not at the time of study, than in those who did not. Total body BMC and BMD z-scores did not differ between females who ambulated independently and those who walked with assistance or never walked.

Skeletal Fractures and Scoliosis

An age effect was apparent for both fractures and scoliosis in the RTT cohort; females with fractures (20.3 ± 6.7 vs. 13.6 ± 10.1 y, $p<0.01$) and/or scoliosis (18.0 ± 8.9 vs. 11.0 ± 9.5 y, $p<0.01$) were older. Fractures were found in 50% of females with, but only in 7% of those without, bone mineral deficits ($X^2 = 11.3$, $p<0.001$). Total body BMC and BMD z-scores were significantly lower in those with than without fractures (Table 3). Fractures ranged from one to five per individual and occurred at variable sites. Scoliosis was found in 77% of those with, and in 52% of those without, bone mineral deficits ($X^2 = 3.3$, $p<0.07$). Total body BMD, but not BMC, z-scores were significantly lower in those with than without scoliosis (Table 3).

DISCUSSION

The natural history of bone mineral deficits and bone-related disorders has not been characterized fully in females with RTT. In this cross-sectional study, low BMD was common, occurring in 45% of the RTT cohort. However, the variability across the age range studied precluded our ability to identify individual susceptibility. Although absolute BMC and BMD increased with advancing age, BMC and BMD z-scores were lower in older than in younger females. Skeletal fractures and scoliosis also were common, occurring in 28% and 64%, respectively, of the RTT cohort, and were associated with lower total body BMC and BMD. Bone mineral deficits were identified across a broad range of *MECP2* mutations. These findings highlight the importance of early diagnosis of bone mineral deficits in RTT and underscore the need to better understand the molecular mechanisms of *MECP2* in the regulation of bone mineral metabolism.

BMC in healthy, prepubertal and postpubertal children increases annually by 11 ± 2% and 4 ± 0.5%, respectively (16). In the present study, the rate of increase in total body BMC and BMD in females with RTT was substantially lower than that of healthy, unaffected girls, ages 8-16 y (9), but paralleled changes observed in children with other neurological disabilities (15,17). Others have reported deficits in cortical bone thickness, radial bone density, and tibial bone strength, measured by skeletal radiographs, densitometry, and ultrasonography in girls with RTT (3,18,19). Histomorphometric studies of trabecular bone in girls with RTT suggest that deficits in BMD may be the consequence of decreased bone formation rather than increased resorption because the number and metabolic activity of osteoblasts are decreased, while the number of osteoclasts may be normal or diminished (20). Thus, bone mineral deficits in RTT may be a manifestation of growth failure rather than a degenerative disorder (17).

Although bone mineral deficits were apparent at an early age, we found marked variability in total body BMC and BMD among the RTT cohort. Genetic factors are thought to be responsible for 70% of the variance in bone mass (21). However, the variability in total body BMC or BMD in the RTT cohort could not be explained by their mutations because the small number of subjects within each group precluded phenotype-genotype correlations. Others have suggested that R133C and T158M mutations confer a protective effect against bone mineral deficits (19), but we did not observe such an effect. In the present study, deficits in lean body mass, but not body fat, paralleled bone mineral deficits (22). Being African-American, as in unaffected individuals, tended to protect against low bone density (9). BMC and BMD z-scores were lower in individuals who had seizures and received anticonvulsants, both known risk factors (15).

Ambulation protects against bone mineral deficits in children with neurological disorders (23). In children with cerebral palsy, programs using upright stands, load-bearing physical activities, or vibrating platforms improved vertebral, femoral neck, and tibial BMD (24-26). In our study, however, total body BMC and BMD z-scores were not significantly different between those who ambulated independently and those who walked with assistance or never walked. The explanation for this finding was not readily apparent although, in contrast to other studies (23), body size did not differ between our ambulatory and non-ambulatory groups. Despite our findings, we routinely emphasize physical therapy for females with RTT to improve their functional abilities (27).

Low BMD is thought to contribute to fracture risk, although prospective measures of BMD in the lumbar spine of children with cerebral palsy did not predict subsequent fracture risk (29). In healthy girls, each 1 SD reduction of total body BMD doubles the risk for new fractures (30). The annual fracture rate for healthy females 6 years of age and older is 3 per 100 person-y (28) and for girls with spastic quadriplegia, 2.7 per 100 person-y (29). In the present study,

one to five skeletal fractures occurred in 28% of the RTT cohort, resulting in a fracture rate of 3.6 per 100 person-y. Scoliosis occurred in 64% of the RTT cohort, a value in the range of other reports (31-34). However, we may have underestimated the prevalence of scoliosis and the severity of low bone mineral density in females with RTT because we excluded females with spinal rod placement. Nevertheless, for future DXA applications, the correlation among spine, hip, and total body BMC and BMD in the RTT cohort is of practical importance for those in whom repetitive movements or spinal rod placement preclude total body scans. The associations among low BMC and BMD, fractures, and scoliosis suggest that bone mineral metabolism is important for bone mineral health.

In summary, bone mineral deficits and bone-related disorders were common in RTT. Bone mineral deficits were greater in older than in younger females with RTT. Fractures and scoliosis were associated with lower BMC and BMD. Although factors commonly associated with protection from, or increased risk of, bone mineral deficits were identified, a better understanding of molecular mechanisms that regulate the interaction between *MECP2* and bone mineral metabolism is crucial to the development of therapeutic strategies for RTT.

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Abbreviations

BMC, bone mineral content; BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry; MECP2, methyl-CpG-binding protein 2; RTT, Rett syndrome.

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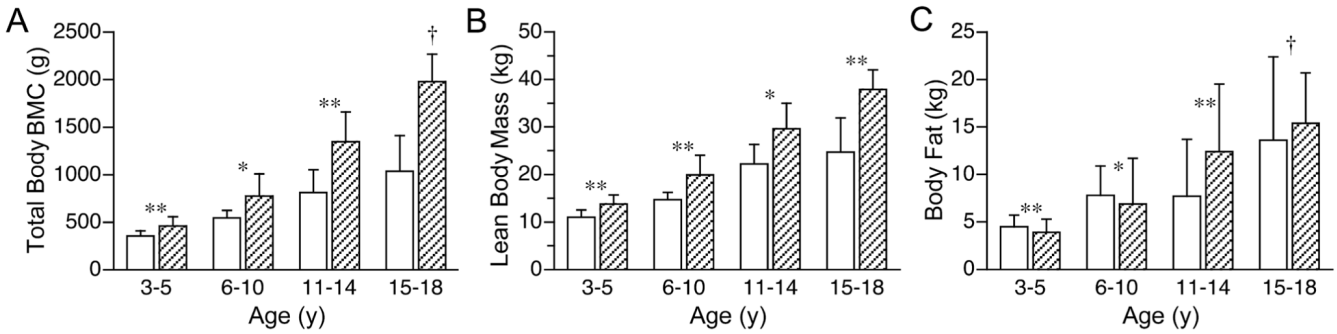

Figure 1.

Body composition of girls (n = 50) with Rett syndrome (□) and an age-matched reference population (▨): (a) total body BMC, (b) fat-free mass, (c) body fat; *p<0.05, **p<0.01, † p<0.001.

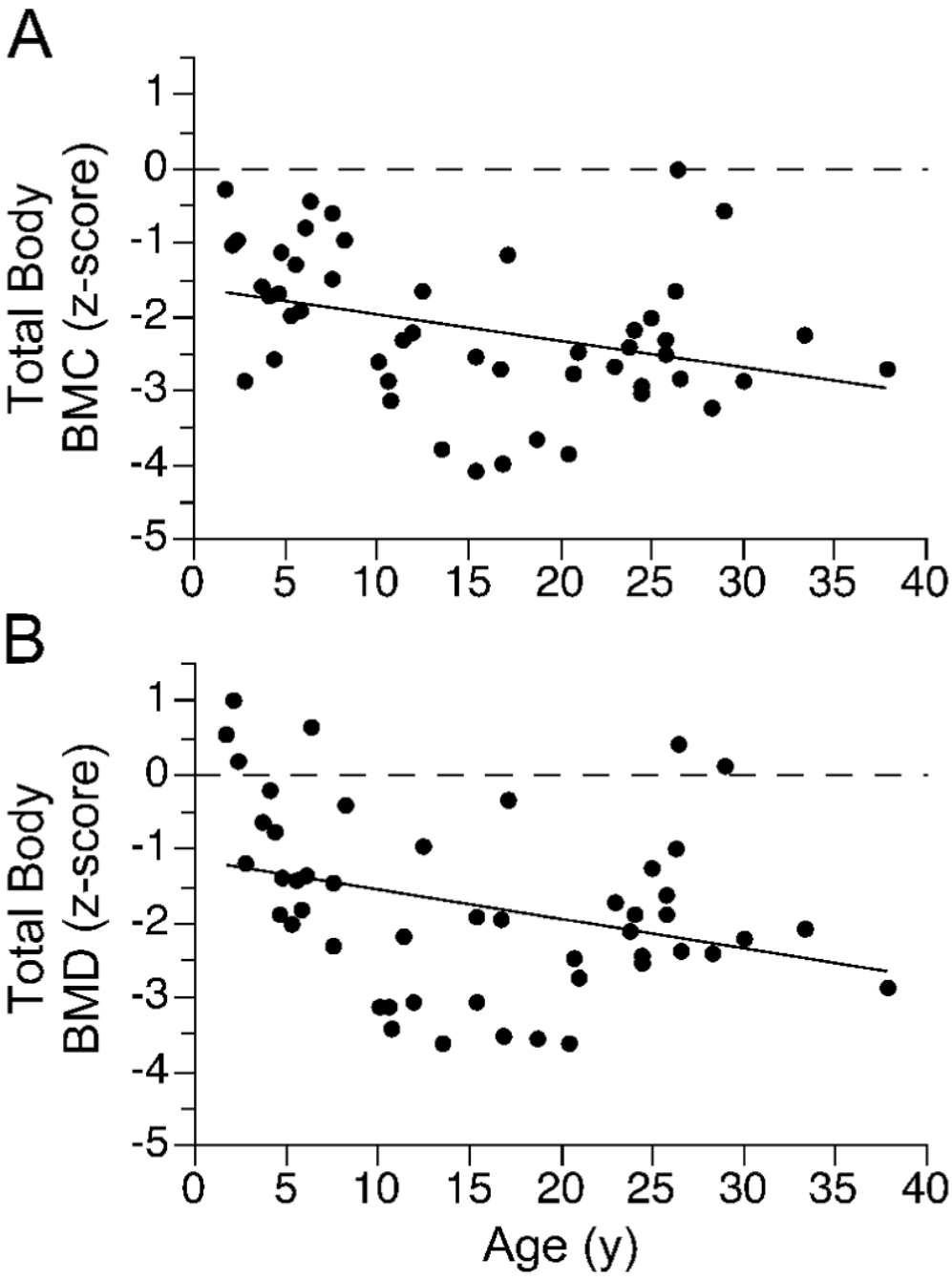

Figure 2.
Relation between total body BMC or BMD and age in girls and women (n = 50) with Rett syndrome: (a) total body $BMC_{(z\text{-}score)} = -0.85 - 0.17\ age_{(y)} + 0.004\ age^2_{(y)}$; $p<0.01$, $r = -0.45$; (b) total body $BMD_{(z\text{-}score)} = -0.12 - 0.22\ age_{(y)} + 0.005\ age^2(y)$; $p<0.01$, $r = -0.46$.

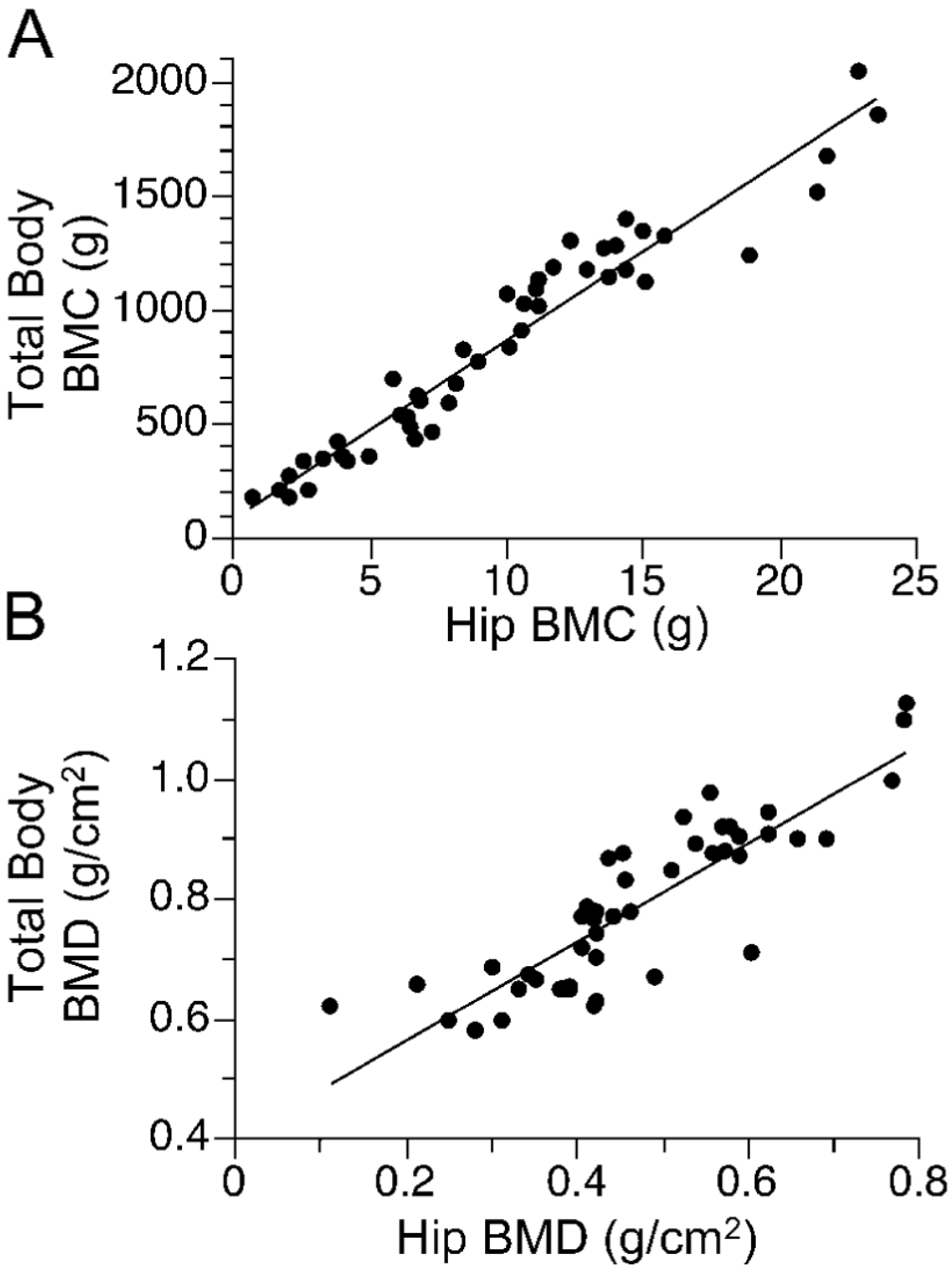

Figure 3.
Relation between total body and hip BMC or BMD in girls and women (n = 50) with Rett syndrome: (a) total body $BMC_{(g)}$ = 89 + 78 hip $BMC_{(g)}$; $p<0.001$, r = 0.97]; (b) total body $BMD_{(g/cm2)}$ = 0.40 + 0.82 hip $BMD_{(g/cm2)}$; $p<0.001$, r = 0.86.

Table 1

Characteristic features of girls and women (n=50) with Rett syndrome*

Age interval (y)	Age (y)	Height (cm)	Height z-score**	Weight (kg)	Weight z-score**	BMI (kg/m^2)	BMI z-score**
0-5 (n = 9)	3.4 ± 1.2	95.0 ± 9.7	-0.4 ± 1.2	13.5 ± 3.2	-0.9 ± 1.0	14.9 ± 1.5	-0.9 ± 1.4
5-10 (n = 8)	6.6 ± 1.1	113.5 ± 7.1	-1.0 ± 0.7	20.6 ± 4.7	-0.6 ± 0.9	15.8 ± 1.8	0.0 ± 1.0
10-14 (n = 7)	11.5 ± 1.2	132.7 ± 9.8	-2.2 ± 1.0	27.4 ± 7.1	-2.5 ± 1.4	15.4 ± 2.5	-1.5 ± 1.3
14-18 (n = 6)	16.0 ± 1.0	139.5 ± 8.7	-3.5 ± 1.3	37.4 ± 14.3	-4.6 ± 4.8	18.9 ± 5.8	-1.7 ± 3.3
18-24 (n = 7)	21.7 ± 2.1	139.3 ± 9.4	-3.7 ± 1.4	38.9 ± 7.1	-3.7 ± 1.8	18.9 ± 4.1	-2.0 ± 3.4
24-29 (n = 10)	26.1 ± 1.5	146.9 ± 8.4	-2.5 ± 1.3	45.9 ± 16.0	-2.5 ± 2.2	21.2 ± 6.8	-0.9 ± 1.7
29-37 (n = 3)	33.7 ± 4.0	142.8 ± 2.5	-3.1 ± 0.4	39.4 ± 8.4	-3.6 ± 2.1	19.3 ± 4.2	-1.3 ± 1.7

Race/Ethnicity (%)	
Caucasian	64
African-American	16
Hispanic	14
Asian	6
MECP2 mutation(%)†	
Missense	40
Early truncation	33
Late truncation	20
Deletion	7
Fractures (%)	28
Scoliosis (%)	64
Anticonvulsant use (%)	
Used any time throughout lifespan	70
Used at the time of study	50
Ambulation (%)	
Ever walked during lifespan	84
Walked independently at study	74

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Race/Ethnicity (%)	

[*] Expressed as mean ± SD where appropriate

[**] P<0.05, different from the National Center for Health Statistics data (12)

[†] Individuals with positive *MECP2* mutation (n = 45)

Table 2

Characteristic features of body composition of girls and women (n = 50) with Rett syndrome

Variable	Number of subjects*	Value**
Bone mineral content		
Total body (g)	49	850 ± 466
(z-score)	49	-2.2 ± 1.0†
(% <-1 SD)	49	84
(% <-2 SD)	49	59
Spine (g)	46	22 ± 13
Hip (g)	47	9.8 ± 5.8
Bone mineral density		
Total body (g/cm^2)	49	0.792 ± 0.140
(z-score)	49	-1.7 ± 1.2†
(% <-1 SD)	49	76
(% <-2 SD)	49	45
Spine (g)	46	0.597 ± 0.213
Hip (g)	47	0.471 ± 0.145
Lean body mass (kg)	46	19.6 ± 8.4
(% body weight)	46	66 ± 7
Body fat (kg) by DXA	46	10.1 ± 7.2
(% body weight)	46	31 + 7
Body fat (kg) by anthropometry‡	50	10.1 ± 6.5
(%body weight)	50	30.9 ± 4.5

*One individual unknowingly had metal devices in spine and hip; movement artifact prevented estimates of the components of body composition in some subjects

**Values expressed as mean ± SD where appropriate

†P<0.05, different from the reference population (10)

‡Determined from the sum of triceps, biceps, subscapular, and suprailiac skinfold thicknesses (13)

Table 3

Total body BCM and BMD z-scores versus the presence or absence of skeletal fractures, scoliosis, seizures, anticonvulsant use, and ambulatory status in girls and women (n = 50) with Rett syndrome

Variable	Number of subjects	BMC z-score*	BMD z-score*
Presence of seizures			
Yes	32	-2.4 ± 1.0**	-2.0 ± 1.1
No	17	-1.8 ± 0.9	-1.3 ± 1.2
Ever used anticonvulsants			
Yes	34	-2.4 ± 0.9†	-2.1 ± 1.0†
No	15	-1.5 ± 0.9	-1.0 ± 1.3
Currently using anticonvulsants			
Yes	25	-2.2 ± 1.2	-1.8 ± 1.3
No	24	-2.1 ± 0.8	-1.6 ± 1.1
Presence of scoliosis			
Yes	31	-2.4 ± 1.0	-2.0 ± 1.1**
No	18	-1.8 ± 1.0	-1.3 ± 1.3
Ever walked			
Yes	42	-2.2 ± 1.0	-1.9 ± 1.0
No	7	-1.9 ± 1.2	-0.6 ± 1.5
Currently walks without assistance			
Yes	37	-2.2 ± 0.9	-1.9 ± 1.0
No	12	-2.2 ± 1.3	-1.2 ± 1.7
Occurrence of skeletal fractures			
Yes	13	-3.0 ± 0.9‡	-2.6 ± 1.0†
No	36	-1.8 ± 0.9	-1.4 ± 1.1

*Values expressed as mean ± SD

**P<0.05

†P<0.01

‡P<0.001