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Vitamin D Intake Is Inadequate in Spinal Muscular Atrophy Type I Cohort: Correlations With Bone Health

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Abstract

Children with type I spinal muscular atrophy commonly demonstrate reduced bone mineral density. Our objectives were to evaluate and assess adequacy of vitamin D intake, serum levels, and association with bone mineral density. Assessments were completed using 3-day food records and dual energy x-ray absorptiometry scans. The spinal muscular atrophy type I cohort included 22 males and 18 females (N = 40), with a mean age of 18.6 months. Data collection occurred from 2001 to 2011. Seventy-five percent of patients had inadequate intake of vitamin D at the initial visit. Using mixed-effects analyses, vitamin D and calcium intakes correlated positively with bone mineral density (r = 0.31 and r = 0.53, respectively). Increased vitamin D and calcium consumption were associated with an increase in bone mineral density (P = .04 and P = .01, respectively). Vitamin D intake correlated positively with serum levels (r = 0.65). Further study is needed to determine optimal intakes of vitamin D and calcium in the spinal muscular atrophy type I population.

Keywords

vitamin D; spinal muscular atrophy type I; bone mineral density; SMN1

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Author Contributions

JA prepared and analyzed data, prepared draft and final manuscript. RHD contributed equally to this work; analyzed data, provided draft revisions, and prepared final manuscript. KCJ served as a mentor and provided support and critique of all versions of manuscript. CBS conducted statistical analysis. KJS was principal investigator and provided key support, including: funding procurement, data collection, analysis, and manuscript editing.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

The study was approved by the Institutional Review Board at the University of Utah. Written informed parental consent (children <18 years) and assent (children >7 years) were obtained for all participants.

Spinal muscular atrophy is an autosomal recessive disease characterized by a homozygous mutation or deletion of the survival motor neuron 1 (*SMN1*) gene.[1,2] A corresponding deficiency of the survival motor neuron (SMN) protein causes a degeneration of anterior horn cells in the spinal cord and brainstem, resulting in progressive muscular atrophy and weakness.

Spinal muscular atrophy is a common neuromuscular disorder with an incidence of 1 in 10 000 live births.[3–7] Clinically, subtypes of spinal muscular atrophy are categorized by age of onset and maximum achieved gross motor function.[8–10] The severe infantile variant, spinal muscular atrophy type I, is the most common form of spinal muscular atrophy, accounting for more than 50% of all cases.[11] Infants with spinal muscular atrophy type I typically present with progressive weakness and bulbar dysfunction within the first 6 months of life, and never achieve the ability to sit or bear weight independently. Historically, these infants had a poor prognosis for survival beyond the first few years of life. However, because of advances in supportive medical care, children with spinal muscular atrophy type I are increasingly surviving well beyond 2 years of age.[12]

Children with spinal muscular atrophy type I are at a significantly increased risk for osteoporosis, fractures, and scoliosis.[13–16] Typically, children with spinal muscular atrophy type I exhibit severe hypotonia and generalized muscle weakness. They are unable to sit unassisted and often lack the head control and tone necessary to permit opportunities for weight bearing. Weight bearing, physical activity, and lean body mass, via mechanical loading, are key attributors to bone mineralization in healthy individuals.[17–20] Additionally, mouse models of neuromuscular diseases indicate that the disease itself may have a bigger role in skeletal development than the loss of function.[16,21,22] For example, in spinal muscular atrophy, the survival motor neuron protein may play an active role in bone remodeling.[16,22] Patients with spinal muscular atrophy often exhibit severe osteopenia and may contend with fractures resulting from minimal disturbance.[22] Khatri et al[15] found that spinal muscular atrophy patients had the lowest bone mineral density compared with other neuromuscular disorders and ambulatory patients with spinal muscular atrophy had significantly higher bone mineral density than nonambulatory patients. The onset and severity of scoliosis in children with spinal muscular atrophy is also associated with the type of spinal muscular atrophy and muscle weakness.[23]

Restrictive lung disease is the most common and life-threatening chronic complication in spinal muscular atrophy type I.[13,24] However, dysphagia, gastrointestinal dysmotility, and constipation are highly prevalent in this population. Early and progressive bulbar denervation in infancy typically results in dysphagia and fatigue with feeds,[24] placing this population at high risk for inadequate growth/weight gain. Enteral feeds are eventually required to meet appropriate intake needs for growth. Furthermore, once enteral feedings begin, these patients are at increased risk for obesity since they have a significantly decreased lean body mass in comparison to healthy peers and may have a resultant lower metabolic rate in addition to lack of physical movement.[25–27] Clinical experience indicates that the daily caloric requirements for children with spinal muscular atrophy may be significantly less than the recommendation for healthy children their age.

Although nutrition is clearly important for this population, there is little published research to guide recommendations for specific nutrient supplementation. Recently published dietary intake data indicate that calorie intakes are less than healthy peers and intakes of several nutrients are less than dietary reference intakes.[27] Thus, ideal dietary management requires that intake of both calories and essential nutrients be balanced to prevent excess weight gain while avoiding nutritional deficiencies.

Micronutrient requirements of children with spinal muscular atrophy are currently considered to be the same as their age-matched peers.[13,25] However, their reduced calorie needs can lead to inadequate micronutrient consumption. Spinal muscular atrophy type I patients are particularly susceptible to vitamin D deficiency, not only because of poor intake, but limited exposure to sunshine due to heat intolerance, limited absorption, and drug-nutrient interactions.

Metabolic abnormalities consistent with fatty acid oxidation defects have been noted in weaker children with spinal muscular atrophy.[28] Gastrointestinal reflux and dysmotility can be exacerbated by a high-fat diet.[13] Thus, for children with spinal muscular atrophy on subsequent low-fat diets, absorption of dietary vitamin D, a fat-soluble vitamin, may also be limited.

Certain medications, such as valproic acid, which are being investigated for potential benefit in spinal muscular atrophy,[29] can interfere with the absorption of specific micronutrients including vitamin D.[30] A recent study among school-age children indicated that vitamin D intake and status played a key role in bone mineral density.[31] Inadequate intake of vitamin D could place children with spinal muscular atrophy at even greater risk for osteoporosis and fractures; therefore, close monitoring of intake of micronutrients associated with bone health is essential.[13,24,27] Specifically, a biochemical evaluation of vitamin D status is a key consideration to confirm a deficiency in at-risk patients.

The purpose of this observational study was to determine whether vitamin D intake in this population met current recommendations from the American Academy of Pediatrics, 400 IU/d.[32] To achieve this goal, we evaluated the dietary intake of vitamin D and calcium and compared it to total body bone mineral density and serum 25-hydroxy vitamin D levels. We hypothesized that (1) vitamin D intake of spinal muscular atrophy type I patients would be lower than the recommended intake for children of the same age as a result of their reduced caloric intake and (2) a suboptimal vitamin D intake would be associated with potential worsening of indicators of bone health. To evaluate these hypotheses, we reviewed dietary intake and bone density in a cohort of spinal muscular atrophy type I subjects.

Methods

Participants

In this observational study of vitamin D intake in spinal muscular atrophy type I patients, subjects were selected from all type I patients involved in an ongoing natural history study conducted by the Pediatric Motor Disorders Research Program at the University of Utah.

Inclusion criteria for this study included those children who had never achieved the ability to sit unsupported, thus meeting clinical criteria for spinal muscular atrophy type I, and a confirmed homozygous deletion and/or mutation in the survival motor neuron 1 (*SMN1*) gene. Specifically, this cohort represents those type I participants for whom we had dietary record data, obtained in association with clinical visits.

The mean age of subjects was 18.6 months with a median of 10 months. Participants ranged between 0 and 165 months in age. Recruitment and data collection occurred between June 1, 2001, and February 1, 2011. Written informed parental permission (children <18 years) and assent (children >7 years) were obtained for all participants. The study protocol was approved by the Institutional Review Board at the University of Utah.

Data Collection Methods

Dietary Record

A 3-day validated food record tool[33] was used to collect dietary and supplement intake information. At study initiation, parents were asked to complete a 3-day food record for their child in association with each clinical evaluation. Parents were given written materials and verbal explanation of how to fill out a record of dietary, fluid, and supplement intake for 2 weekdays and 1 weekend day. Growth parameters, including body weight and length, were assessed; this information was included with each diet record submission. The 3-day food records were submitted either as a handwritten document during clinic visits, by a parent via the SMA and Nutrition website (www.smaandnutrition.org), or via fax or email to the Pediatric Motor Disorders Research office.

Three-day dietary records were analyzed by a dietitian or a research assistant for a variety of nutrients, including vitamin D and calcium intake, using ESHA Food Processor (versions 9.1.0 and 10.5.2, 2003 and 2009 ESHA Research, Salem, Oregon). Calcium and vitamin D contributions to dietary intake from vitamin and mineral supplements were included in the analysis. Formula variations that were not in the database were manually entered based on nutrient information from the formula manufacturer. Vitamin D intake less than 400 IU/d was considered to be deficient based on American Academy of Pediatrics guidelines. Dietary Reference Intakes were not used for comparison because, during the data collection period, they were lower than American Academy of Pediatrics standards. Dietary Reference Intakes for vitamin D and calcium were not increased until the end of data collection in 2011.[34] Vitamin D intake between 400 and 2000 IU was considered optimal; greater than 2000 IU was considered a possible toxicity based on 1997 Dietary Reference Intakes: Tolerable upper intake levels.

The type of diet and formula consumed by patients was chosen by the parent and/or primary care provider, no nutritional interventions were instituted by this study unless dietary analysis indicated obvious nutrient deficiencies. Three-day food records were collected for the initial visit from all participants (n = 40). Fifty-eight subsequent 3-day food record data from any follow-up visit were also collected from participants (n = 24) and compared to corresponding biochemical measures and dual-energy x-ray absorptiometry scans.

Biochemical Measures

A subset of 14 participants had a blood test for serum 25-OH vitamin D and serum calcium taken in conjunction with their visit in 2009–2011. This subset consisted of all subjects for whom laboratory data were available. Serum 25-OH vitamin D levels were stratified into the following categories: less than 20 ng/mL (50 nmol/L) (deficient), 20–29.9 ng/mL (50–74 nmol/L) (inadequate), 30–39.9 ng/mL (75–99 nmol/L) (low normal), 40–80 ng/mL (100–200 nmol/L) (optimal), and greater than 80 ng/mL (200 nmol/L) (high), with deficient and high categories defined by laboratory reference values and low normal and optimal categories defined by the authors for reasons of comparison.

Dual-Energy X-Ray Absorptiometry Scan

Thirty-seven participants underwent a dual-energy x-ray absorptiometry scan at each visit, as frequently as every 3 to 6 months at the beginning of the study and closer to every 6 months to a year near the end of the data collection period, to evaluate bone mineral density and bone mineral content. This subset consisted of all patients for which a dual-energy x-ray absorptiometry scan and dietary data were available. Norland DEXA (XR-36 software version 3.3.1, Fort Atkinson, Wisconsin) for small subjects was used. Dual-energy x-ray absorptiometry has been validated as an appropriate measure of bone mineral density in the target population.[35,36]

Clinical Variables

Demographic data were provided on the parental consent form. Details regarding each patient's medical history and physical examination were collected on clinical research forms at initial contact and at each visit. Types of data included family medical history, presence of allergies, medication use, laboratory results, and physical exam information including growth parameters.

Statistical Methods, Data Analysis, and Interpretation

The Statistical Analysis Software (version 9.1.2, 2010, SAS Institute Inc, Cary, North Carolina) was used to conduct data analyses.[37] A power analysis for the study dependent variable, vitamin D intake, revealed that a sample size of 14 participants was required to detect a 10% difference from the American Academy of Pediatrics recommendation. Vitamin D intake and serum levels were stratified into categories and the associations were analyzed with Pearson correlation. The correlation between vitamin D intake over time was conducted with regression analysis. Mixed-effects analysis was employed to compare vitamin D intake to bone mineral density and calcium intake to bone mineral density. The association between vitamin D and calcium intake and bone health measures was assessed for all participants (n = 40). For all analyses, the level of significance was set at $P < .05$.

Results

Demographic data for the study population are presented in Table 1. The subject population age was slightly skewed to the right due to a patient who was 165 months at the time of initial visit. Inclusion of this outlier in the analysis did not significantly affect the results. Data were collected for 98 visits. These included 40 initial 3-day diet records, 14 25-OH

vitamin D tests, 80 total body bone mineral density dual-energy x-ray absorptiometry scans, and 63 serum calcium levels. There were data from follow-up visits for 24 patients. The age of patients at follow-up visits ranged from 3.4 to 81.5 months (mean = 23.5 months).

Nutrition received by this subject population ranged from exclusive breast milk, exclusive infant/pediatric formula, to combinations of breast milk, formula and/or supplemental vitamins, minerals, and foods. Vitamin D intake from the initial visit was compared to the recommended value from the American Academy of Pediatrics (400 IU). Thirty of 40 patients (75%) had an inadequate vitamin D intake at the first visit. Baseline vitamin D intake data for 40 initial visits are presented in Table 2. Vitamin D intake was plotted over 3 years for those patients with follow-up visits. There was not a clear pattern of vitamin D intake over time between patients. Vitamin D intake did improve over time; however, this relationship was not strongly correlated ($r = 0.23$, $P = .0021$).

Fourteen participants had a serum 25-OH vitamin D level taken during the same visit that a diet record was available. There was 1 participant with multiple serum levels. In this case, only the initial level was used for analysis. For this subset, only 1 participant had an inadequate serum level (<29.9 ng/mL) (74 nmol/L). Ten of the 14 patients (71%) in the subgroup had a serum vitamin D level within the optimal or high range (>40 ng/mL) (100 nmol/L). The rest were in the low normal range. Increased vitamin D intakes correlated positively with an elevated serum level ($r = 0.65$). However, when these 2 sets of values were stratified into categories, the 2 measures did not correlate.

The result of each dual-energy absorptiometry scan was compared with vitamin D intake and a calcium intake from the same visit. Data from 80 visits were analyzed for vitamin D intake and 76 visits for calcium intake. The correlation between vitamin D intake and bone mineral density was significant ($r = 0.31$, $P = .04$). The same was true for calcium intake and bone mineral density ($r = 0.53$, $P = .01$) (Figures 1 and 2).

There were only 5 serum vitamin D levels that corresponded with a bonemineral density value; therefore, the sample size was too small to conduct a reliable analysis. Calcium serum levels were too tightly ranged (9–10.7 mg/dL) (2.3–2.7 mmol/L), with limited variation, to show a correlation with bone mineral density.

Discussion

Overall, the results from this observational study support the hypothesis that spinal muscular atrophy type I patients are at risk for micronutrient deficiencies relevant to bone health. Children with spinal muscular atrophy type I require fewer calories per day than their healthy age-matched peers.[25,27] With decreased caloric intake, achieving adequate micronutrient intake can be difficult. The majority of subjects in this study (75%) had inadequate intakes of vitamin D at baseline. Dietary management of spinal muscular atrophy in this time period has not changed drastically. However, the importance of vitamin D intake has received increasing attention in popular media over the past few years. Despite the media focus, the improvement in vitamin D intake over the period of this study was modest. Some parents increased their child's vitamin D intake in the 3 years following their initial

visit; others decreased or maintained their child's intake of vitamin D. Barriers to obtaining an adequate amount of vitamin D, aside from inadequate intake, include lack of sun exposure due to geographic location, limited time outside, or increased use of sunscreen.[38] Because many children with spinal muscular atrophy have heat intolerance and more limited opportunities for sun exposure, this may put them additionally at risk for vitamin D deficiency in the setting of inadequate dietary intake.

Vitamin D dietary reference intake guidelines were increased toward the very end of data collection for this study from 200 to 400 IU per day.[34] Until this time, American Academy of Pediatrics guidelines (400 IU) were used as a reference for vitamin D intake for many children because they were considered more appropriate than the previous vitamin D dietary reference intakes and, thus, were used in this comparison.

Serum vitamin D levels and vitamin D intake were strongly correlated. However, when serum and intake levels were stratified into categories, the 2 measures did not correlate. This lack of significance was likely due to a small sample size. Six participants within the subset had inadequate vitamin D intake, but half of them had optimal blood levels. Seasonality may also have affected the results.[39] Ten of 14 serum levels were collected between April and October, a time of potentially greater sun exposure.

Calcium and vitamin D intakes from 80 visits were individually compared to corresponding bone mineral density scores. Dual-energy x-ray absorptiometry scans and 3-day food records were matched as closely as possible by date. Most dual-energy x-ray absorptiometry scans and 3-day food records were recorded at the same visit. In 3 instances, a dual-energy x-ray absorptiometry scan was not conducted at the same visit that a 3-day food record was received. Bone mineral density is a long-term measure of calcium and vitamin D intake. Therefore, we assumed that a dual-energy x-ray absorptiometry scan would reflect micronutrient intake.

A stronger correlation exists between calcium intake and bone mineral density than vitamin D intake and bone mineral density. This result was expected because calcium has a direct effect on bone mineralization, whereas vitamin D has an indirect effect.[38] As expected, improvements in vitamin D and calcium intake were associated with an increase in bone mineral density. The same results were reflected in studies conducted with healthy individuals.[40–42] Decreased bone mineral density increases the risk of osteoporosis, scoliosis, and fracture.

Serum calcium is not a good measure of calcium status because the body is very efficient in regulating levels to a tight range. Serum calcium does not reflect calcium intake or bone health.[38] This statement was evidenced by the limited variance observed in serum calcium levels (9–10.7 mg/dL) (2.3–2.7 mmol/L). For this reason, statistical analysis was not performed to compare serum calcium and bone mineral density or serum calcium and calcium intake. Of note, other studies have demonstrated increased serum calcium values in spinal muscular atrophy patients[43] and previously published data examining this same cohort of subjects showed a correlation between increased serum calcium and increased bone mineral density.[27]

The sample of vitamin D serum levels was too small to make a reliable comparison to bone mineral density. We chose to include this subset of patients to observe preliminary vitamin D status in this population. In future studies, obtaining a 25-OH vitamin D level for each patient would be beneficial for determining if vitamin D intake is optimal. Bone mineral density is one functional measure of vitamin D intake, although the test is neither specific nor sensitive. Some studies have established a relationship between 25-OH vitamin D serum levels and bone mineral density in school-age children[31] and adolescent women.[40,44] Vitamin D serum levels are reflective of vitamin D intake as the majority of biological vitamin D is pooled in the blood.[38] Because there are additional factors affecting bone health in the spinal muscular atrophy population, the authors believe that bone mineral density measured by dual-energy x-ray absorptiometry is more reflective of overall bone health than serum vitamin D levels.

The methodology for data collection was a strength of this study. A 3-day dietary record is a validated measure for assessing intake,[33] particularly for this population. Spinal muscular atrophy type I patients require 24-hour care; consequently, a parent or caregiver can record intake for the child at regular intervals throughout the day as this is likely to increase accuracy. In general, a blood test is an accurate method of assessing status of vitamin D, but reflects sun exposure as well as dietary intake.[38] A dual-energy x-ray absorptiometry scan is used clinically to diagnose poor bone mineral density, and is the most valid and reliable measure available for this purpose.[35,36]

This was an observational design; therefore, the study lacked power compared to an experimental study. The objective of this study was not to impose a dietary intervention but rather to observe current dietary practices, specifically calcium and vitamin D intake among the spinal muscular atrophy population. A significant limitation of this study was the lack of vitamin D serum data for all subjects with a 3-day food record. We chose to include a subset of subjects who did receive a blood test because this measure is a practical application for assessing vitamin D adequacy in the diet. A limitation of this study was that medication usage fluctuated during the study. Therefore, we were unable to cleanly compare medications used against vitamin D intake and status.

Conclusion

Nutrition plays a vital role in the quality of life and outcome of patients with spinal muscular atrophy.[12] Despite its importance, there is very little evidence-based research to support specific recommendations for dietary management in this population. Currently, most spinal muscular atrophy patients do not have access to a registered dietitian, placing the burden on parents and physicians to make decisions without clear evidence to guide them.

This study aimed to observe dietary practices of spinal muscular atrophy type I children. These results support the hypothesis that type I patients are at increased risk for vitamin D deficiency. Risk for nutrient deficiency is likely due to decreased caloric intake. Inadequate intakes of vitamin D were not reflected in corresponding serum levels in our small subset of subjects; thus, further studies are needed to help determine appropriate intakes for vitamin D and other nutrients in this population. When making a recommendation for this population,

caloric and micronutrient intake are equally important. Nutrient supplementation may be necessary if appropriate nutrient intake cannot be met while adhering to restricted calories. Further prospective studies will be necessary to determine optimal intakes of vitamin D and calcium in the spinal muscular atrophy type I population.

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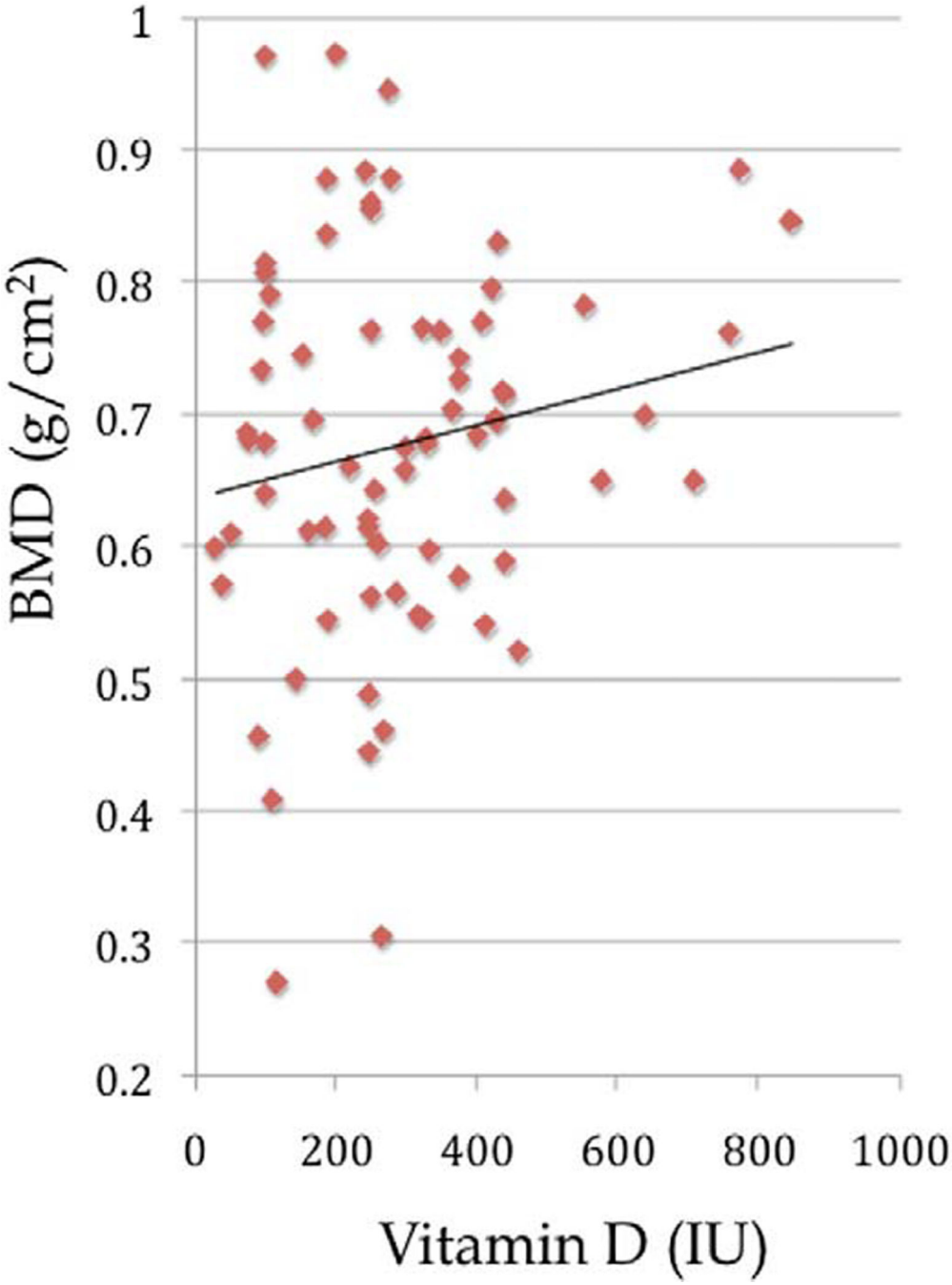

Figure 1.
Correlation between vitamin D intake (IU) and bone mineral density (g/cm^2).

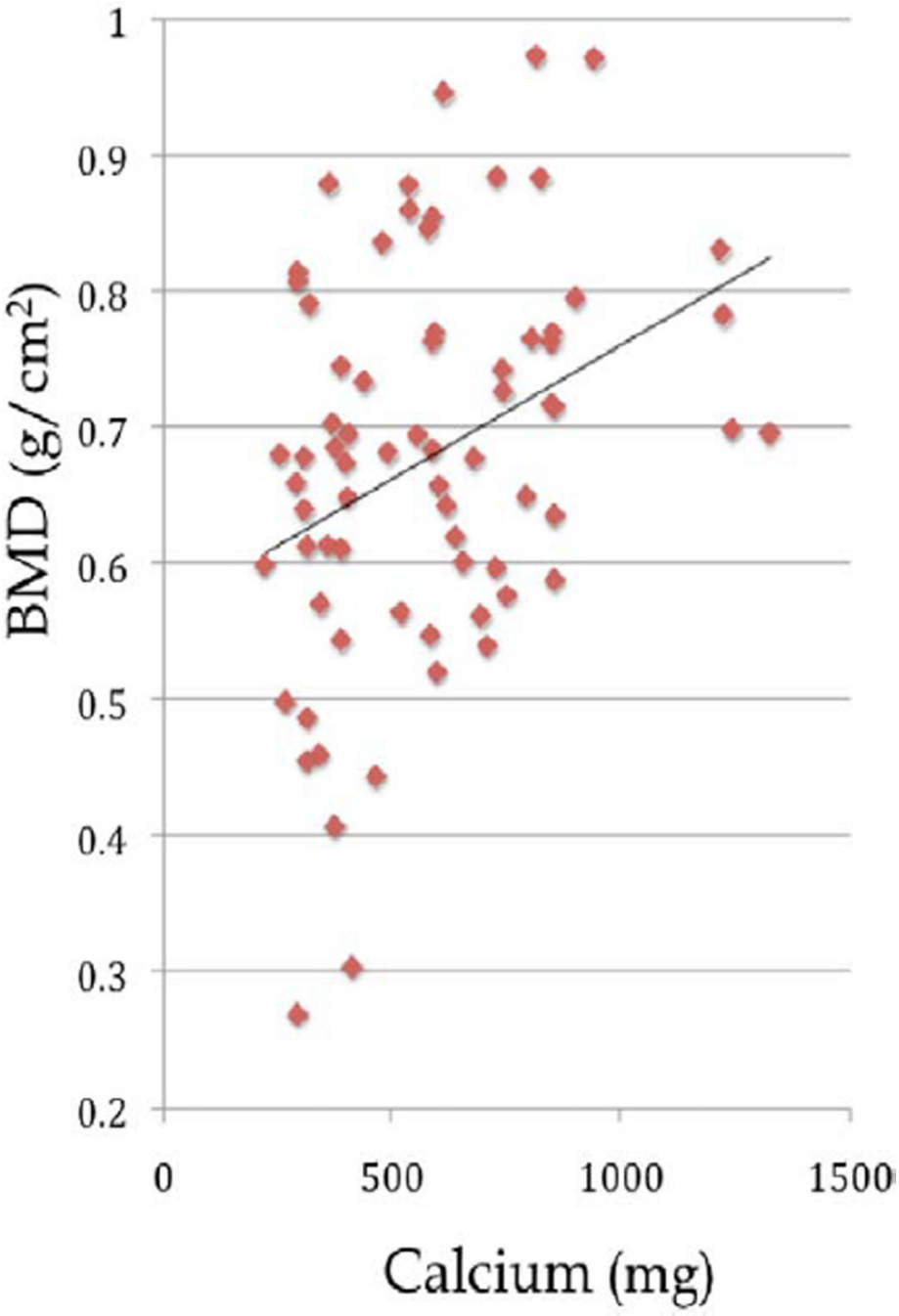

Figure 2.
Correlation between calcium intake (mg) and bone mineral density (g/cm^2).

Table 1

Subject Demographic Data

Subject profile	
Age	**Months**
Range	0.0–165.0
Mean	18.6
Median	10.0
Gender	(%)
Male	55.0 (n = 22)
Female	45.0 (n = 18)
Ethnicity	(%)
White/non-Hispanic	90.0 (n = 36)
Other	10.0 (n = 4)

Table 2

Vitamin D Intake at Baseline

Category	Participants (%)	(n = 40)
Inadequate[a]	75.0	(n = 30)
Optimal[b]	22.5	(n = 9)
Possible toxicity[c]	2.5	(n = 1)

[a] <400 IU/d.

[b] 400–2000 IU/d.

[c] >2000 IU/d.