Bone mineral density comparative pilot study in autistic children

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Background
Bone mineral studies of children with autism are scanty.
Aim of the study
This cross sectional selective study aimed to compare bone mineral density (BMD) of autistic children to healthy children.
Subject and method
39 autistic children were recruited from outpatient clinics of Special Needs Center of Postgraduate Childhood Studies, Ain-Shams University. Using DSM-IV all diagnosed autistic children were assessed for severity by Childhood Autism Rating Scale, examined for anthropometric data and was subjected for Serum Complete Blood Picture, Serum Calcium and Phosphorus levels. Laboratory investigations were investigated. All data compared to normal children.
Results
showed highly statistical significant difference in total BMD Z-score with *P*-value = 0.001 and no significant difference in spine BMD Z-score *P*-value = 0.255.
Conclusion
The present study conclude that there is no relation between autism and BMD, for further evaluation of effect of diet restriction and drugs effect on BMD of autistic children.

Keywords:
autism, bone mineral density, Childhood Autism Rating Scale

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Background

Bone mineral studies of children with autism are scanty. This cross-sectional selective study aimed to compare the bone mineral density (BMD) of autistic children with healthy children; 39 autistic children were recruited from outpatient clinics of the Special Needs Center of Postgraduate Childhood Studies, Ain-Shams University. Using *Diagnostic and Statistical Manual of Mental Disorders* 4th ed. (DSM-IV), all autistic children diagnosed were assessed for severity by Childhood Autism Rating Scale (CARS), examined for anthropometric data, and subjected to serum complete blood picture, and assessment of serum alanine aminotransferase (ALT), serum alkaline phosphatase (ALKP), serum calcium, and phosphorus levels. Laboratory investigations were carried out. All data were compared with those of normal children. The results showed a highly statistical significant difference in the total BMD *Z*-score, with a *P*-value equal to 0.001, and no significant difference in the spine BMD *Z*-score, *P*-value equal to 0.255. The present study confirms lack of decrease in BMD in autistic children in comparison to health children.

Introduction

During childhood and adolescence, BMD increases until the peak bone mass is attained (Ott, 1990). Peak bone mass and subsequent bone loss are important determinants of osteoporosis later in life (Hansen *et al*., 1991). It is essential to know the factors that influence BMD in childhood, with the goal of achieving optimal peak bone density. At present, dual-energy X-ray absorptiometry (DEXA) is the method of choice to measure BMD because of low radiation exposure, high precision, and accuracy (Mazess *et al*., 1990).

Autism spectrum disorders (ASD) are a class of neurodevelopmental disorders characterized by impairments in communication and social reciprocity, and by the presence of restricted and repetitive interests and behaviors (American Psychiatric Association, 2000). Children with ASD are reported to have decreased bone cortical thickness (BCT) (Molloy *et al*., 2010).

For children with chronic disorders, identification of ways to increase bone mineral accrual is particularly important because many have been found to have low bone mineral content and BMD (Hopp *et al*., 1995; Henderson *et al*., 2000; Hediger, 2008). Furthermore, medications such as anticonvulsants and corticosteroids have been found to decrease bone mineral accrual (Allen *et al*., 1994; Semeao *et al*., 1999; Farhat *et al*., 2002).

Previously (Hediger *et al*., 2008), it has been reported that boys with autism and ASD are at a risk for poor bone development for a number of reasons. These factors are a lack of exercise, a reluctance to eat a varied diet, lack of vitamin D, digestive problems, and diets that exclude casein, which is a protein found in milk and milk products. Dairy products provide a significant source of calcium and

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vitamin D. Casein-free diets are a controversial treatment that is believed by some to reduce the symptoms of autism. Vitamin D deficiency is common among this group of children than normally developed children. As evidence has accumulated that vitamin D receptors are present in a wide variety of tissues, vitamin D deficiency has been implicated in numerous disease states (Holick, 2003). It usually occurs secondary to dietary restrictions as children with ASD may limit their own diet because of sensory aversions or restricted interests. The diet may also be restricted by their parents to eliminate exposure to certain dietary proteins, such as the milk protein casein, in an attempt to treat the ASD symptoms (Marcason, 2009). Moreover, children with ASD are not exposed to sunlight as they do not commonly participate in organized outdoor sports, and their preferred leisure activities often involve video game, computer, or TV screens in an indoor setting (Molloy *et al*., 2010). In addition, it has been (Hediger *et al*., 2008) reported that children with ASD have decreased mean metacarpal BCT compared with a reference population. In addition, another study (Molloy *et al*., 2010) has reported that these children may be at risk of additional threats to calcium homeostasis and bone health as they grow up. It has been found (Molloy and Manning-Courtney, 2003) that at least a quarter of children with ASD will also have chronic gastrointestinal symptoms that could have an impact on calcium absorption.

Aim of the study

This study aimed to investigate bone mineral density, serum calcium, phosphorus, ALT, and ALKP in children newly diagnosed with autistic disorder in comparison with healthy children.

Participants and methods

This is a cross-sectional study; the sample was a selective one. Thirty-nine patients were recruited from the out-patient clinics of Special Needs Center of Postgraduate Childhood Studies, Ain-Shams University. All patients were newly diagnosed with pervasive developmental disorder according to DSM-IV TR (American Psychiatric Association, 2000). Both male and female patients were included. Children with comorbid medical or psychiatric conditions or those receiving any medical or psychotropic medications were excluded. Thirty healthy age-matched and sex-matched children were enrolled as controls.

The study protocol was approved by the ethical committee of the Postgraduate Study Institute, Ain-Shams University. An informed consent was obtained from the parents of the patients and the control group before their participation in the study.

Procedures

All recruited patients were subjected to the following:

(1) Clinical interview: Structured Clinical Interview for DSM-IV, Childhood Diagnoses (Williams *et al*., 1992).

(2) CARS (Schopler *et al*., 1980): The severity of autistic symptoms was measured by the CARS using the Arabic version that was translated by El-Shemry and Al-Saratawy (2002). It consists of 15 categories, each rated on a four-point scale. The individual is considered nonautistic when his/her total score is in the range of 15–29, mild to moderately autistic when his/her total score is in the range of 30–36, and severely autistic when his/her score is in the range of 37–60.

(3) Socioeconomic level scale for the family (Al shakhs, 2006): an assessment of the socioeconomic level of the family was applied by collecting data on occupation, education of the father, occupation and education of the mother, and the mean monthly family income divided by the number of family members.

(4) Anthropometric measure of patients. Full clinical examination, followed by anthropometric measures including:
   (a) Weight assessment (kg): this was assessed using a kilogram weighing balance ranging from 1 to 140 kg while the patient stood in light clothes and bare footed; weight was recorded to the nearest 0.5 kg.
   (b) Standing height assessment (cm): all patients were assessed without shoes; the measurement was taken while the patient was standing against a firm wall with a fixed stadiometer, the heels together stretched upward to a full extent, with the back straight as possible, and the head in a horizontal Frankfurt position (imaginary line passing by the middle of the ear tragus and the lower edge of the eye globe). Measurements were taken to the nearest 0.5 cm.
   (c) BMI calculation: BMI was calculated from the previous weight and height measurements using the equation body weight (kg)/standing height (m^2).
   (d) According to the Official Center for Disease Control growth charts (Kuczmarski *et al*., 2000) created by the National Center for Health Statistics, the BMI values of cases and controls were plotted against the standard Egyptian percentile curves for BMI of patients.

(5) DEXA: BMD (g/cm^2) of the lumbar spine and total body were measured by DEXA (DXA, Lunar DPXL/PED; Lunar Radiation Corp., Madison, Wisconsin, USA). Pediatric software was used for children with a weight below 30 kg. During measurement of the lumbar spine, the child was supine, and the physiological lumbar lordosis was flattened by elevation of the knees. All measurements were performed and analyzed by the same individual. Quality assurance was performed weekly. The coefficient of variation has been reported to be 1.04% for spine BMD and 0.64% for total-body BMD. The coefficient of variation was not determined because it was considered unethical to subject a child to several measurements. For 39 children, only the BMD of the lumbar spine was measured. The BMD (g/cm^2) from this measurement is an areal density that varies with

bone size. Ancillary DXA-derived data were used to calculate the apparent BMAD of the lumbar spine using the model BMAD 5 BMD 3. BMD scores were compared with reference data for the same sex and age by calculating the *Z*-score (Johnson and Dawson-Hughes, 1991). The validity of this model was tested using in-vivo volumetric data obtained from MRI of lumbar vertebrae (Kröger *et al*., 1995).

(6) Laboratory investigations including complete blood picture, and assessment of serum ALT, ALKP, serum calcium, and phosphorus levels were carried out. Laboratory investigations were also carried out for the control group.

Statistical analysis

Data analysis was carried out using the statistical package for social sciences version-15 (SPSS Inc., Chicago, Illinois, USA). Student's *t*-test was used for comparison of the means of the different groups. The Pearson χ^2-test was used for comparison between qualitative variables. *P*-value was used to indicate the level of significance, where *P* less than or equal to 0.05 was considered significant, *P* less than or equal to 0.01 as highly significant, and *P* less than or equal to 0.001 as very highly significant.

Results

The studied sample included 39 patients, mean age 6.15 ± 2.75 years, 29 (75%) female and 10 (25%) male patients; in contrast, 30 children were included as control participants matched in terms of age and sex to the patient group, mean age 5.9 ± 2.57 years, 22 female patients and eight male patients. No statistically significant relationship was observed between the patient group and the control group in terms of socioedemographic variables, weight, and height (Table 1).

Using the *t*-test to compare the total BMD *Z*-score in the patient and the control group, a highly significant relation was found (−0.96 ± 0.93, −0.17 ± 0.9), respectively, with *P*-value equal to 0.001, whereas the spine BMD *Z*-score showed no significant difference (*P* = 0.255).

Comparison of the biochemical profile of the patient and the control group in terms of ALT showed highly significantly higher values in patients compared with controls (18.46 ± 6.48, 14.47 ± 2.78), respectively, with *P*-value of at least 0.001, as well as phosphorus (5.26 ± 0.76, 3.63 ± 0.44), *P*-value of at least 0.000, respectively, in contrast to ALKP and calcium, which showed no significant difference (Table 1).

Assessment of the severity of autism using CARS indicated that the majority of patients (64%) had mild autism, four patients (10%) had moderate autism, and 10 patients (26%) had severe autism.

A confidence interval test to assess the possible relation between the severity of autism and BMD indicated no significant relation in either the total BMD *Z*-score (*P* = 0.06) or the BMD spine *Z*-score (0.49). The biochemical profile of patients such as ALT (*P* = 0.89), ALKP (*P* = 0.44), calcium (*P* = 0.56), and phosphorus (*P* = 0.45), when correlated with the severity of autism using the CARS score, showed no significant relation (Table 2).

Table 1 Comparison of the patient and the control group

	Mean ± SD			
	Patient group (*N*=39)	Control group (*N*=30)	*t*-value	*P*-value
Mean age (years)	6.15 ± 2.758	5.9 ± 2.578	0.39	0.698 (NS)
Weight	23.44 ± 10.169	23.07 ± 8.598	0.16	0.874 (NS)
Height	122.59 ± 22.74	118.5 ± 17.76	0.812	0.42 (NS)
BMI	15.4 ± 3.44	16.11 ± 2.65	−0.93	0.356 (NS)
Total BMD	0.64 ± 0.89	0.68 ± 0.1	−1.589	0.47 (NS)
Z-score	−0.96 ± 0.93	−0.17 ± 0.9	−3.522	0.001 (HS)
Spine BMD	0.46 ± 0.068	0.47 ± 0.07	−0.48	0.633 (NS)
Z-score Spine	−1.05 ± −0.83	−0.83 ± 0.78	−1.149	0.255 (NS)
Alanine aminotransferase	18.46 ± 6.48	14.47 ± 2.78	3.155	0.001 (HS)
Alkaline phosphatase	748.5 ± 1174.51	388.47 ± 109.947	1.67	0.064 (NS)
Calcium	8.41 ± 0.90	8.36 ± 0.81	0.251	0.802 (NS)
Phosphorus	5.26 ± 0.76	3.63 ± 0.44	10.43	0.000 (VHS)
Hemoglobin	11.08 ± 1.96	10.9 ± 2.18	0.344	0.732 (NS)
	N (%)		χ^2-test	*P*-value
Sex			*df*=1 χ^2=1	0.569 (NS)
Male	10 (25.6%)	8 (26.7%)		
Female	29 (74.4%)	22 (73.3%)		
Social class			*df*=3 χ^2=0.057	0.069 (NS)
1	6 (15.4%)	12 (40%)		
2	26 (66.7%)	12 (40%)		
3	6 (15.4%)	6 (20%)		
4	1 (2.6%)	0 (0%)		

BMD, bone mineral density; HS, highly significant; VHS, very highly significant.

Table 2 Correlation of severity of Childhood Autism Rating Scale with bone mineral density and blood chemistry

	CARS	Number of cases	Mean ± SD	Confidence interval	*F*-value	*P*-value
BMD total	Mild	25	0.625 ± 0.08	0.58; 0.66	2.32	0.113
	Moderate	4	0.72 ± 0.16	0.55; 0.89		NS
	Severe	10	0.66 ± 0.07	0.60; 0.71		
Z-score total	Mild	25	−1.04 ± 1.02	−1.46; −0.61	3.05	0.06
	Moderate	4	0.05 ± 0.70	−1.07; 1.17		NS
	Severe	10	−1.18 ± 0.39	−1.45; −0.9		
BMD spine	Mild	25	0.45 ± 0.06	0.42; 0.48	0.79	0.45
	Moderate	4	0.48 ± 0.06	0.38; 0.58		NS
	Severe	10	0.48 ± 0.08	0.42; 0.54		
Z-score spine	Mild	25	−1.15 ± 0.77	−1.47; −0.83	0.7	0.49
	Moderate	4	−0.8 ± 0.43	−1.48; −0.11		NS
	Severe	10	−0.89 ± 0.74	−1.42; −0.35		
GPT	Mild	25	18.6 ± 5,72	16.24; 20.96	0.1	0.89
	Moderate	4	17 ± 3.36	11.64; 22.36		NS
	Severe	10	18.7 ± 9.22	12.1; 25.3		
Alkaline phosphatase	Mild	25	667.4 ± 806.11	334.69; 1000.19	0.84	0.44
	Moderate	4	314 ± 106.17	145.05; 483.95		NS
	Severe	10	1125 ± 1956.58	−274.66; 2524.66		
Calcium	Mild	25	8.5 ± 0.79	8.175; 8.83	0.42	0.65
	Moderate	4	8.1 ± 0.74	6.9; 9.2		NS
	Severe	10	8.3 ± 1.2	7.44; 9.17		
Phosphorus	Mild	25	5.38 ± 0.81	5.05; 5.72	1.06	0.35
	Moderate	4	5.23 ± 0.6	4.26; 6.19		NS
	Severe	10	4.97 ± 0.63	4.52; 5.42		

BMD, bone mineral density; GPT, glutamic-pyruvic transaminase.

Discussion

Children with ASD are reported to have decreased BCT (Rao *et al*., 2009) and an abnormal metabolic profile (Mills *et al*., 2007). Previous studies (Rao *et al*., 2009) have shown that growth-related hormones are higher in patients with autism, leading to an increase in their height, weight, and head circumference. Still, this could not be replicated in the current study as no statistical significance was found between the patient and the control group in their heights or weights, although it was found that the mean height and weight of the patient group was slightly higher than that of the control group, in contrast to BMI, which was found to be greater in autistic children compared with the controls.

Reduced BMD in children has been receiving increased attention. The etiology of osteopenia in healthy children is multifactorial and incompletely understood, but poor calcium intake during the adolescent growth spurt may be an important (and potentially reversible) factor. Other clinically relevant causes of reduced BMD in children include osteogenesis imperfecta, rickets, juvenile rheumatoid and other chronic arthritides, osteopenia associated with neuromuscular disorders, and idiopathic osteoporosis (Tortolani *et al*., 2002).

BMD studies of autistic children are scarce and, from preliminary results, studies have reported decreased mean metacarpal BCT in patients with ASD compared with a reference population, suggesting that children with ASD are at a risk of decreased BMD compared with typically developing children (Hediger *et al*., 2008). Another study has reported that BMD, bone mineral content, and spine (bone) mineral density were found to be significantly reduced in patients with Rett syndrome (Haas *et al*., 1997), which was not evident in the current study. This can be attributed to the difference in the age group of the studied sample and diet restriction, which was not applied in our study.

A previous study (Molloy *et al*., 2010) had suggested a reduction in the plasma level of hydroxy cholecalcifererol in children with ASD. However, they did not prove it in their studied sample, which included three groups of children: those with autism with diet restriction and those without diet restriction, and healthy children as controls. They observed a decrease in the level of OH-cholecalciferol in the entire sample because of many factors such as use of sun block creams and indoor activities have limited sun exposure for children in western society, which cannot not be applicable in our society since children in our sample are more exposed to sun and activities. In addition, our sample was not subjected to medical advice for dietary restrictions as they were newly diagnosed cases.

Moreover, ALT, formerly called serum glutamic-pyruvic transaminase, was also found to be higher in the patient group than the control group, with a highly significant difference, which is in agreement with a previously carried out study on intellectually disabled children and adolescents (Lin *et al*., 2010).

Serum levels of calcium and phosphorus were assessed in both groups. No differences were found in the calcium level, although a very high statistical significance was found in the phosphorus level, being much more elevated in the patient group. Previous research (Kuntziger and Altman, 1989) has shown that hyperphosphatemia *per se* does not have any clinical effects, except for ectopic calcifications. These results must draw clinician attention to the importance of follow-up of serum calcium and phosphorus levels; thus, monitoring is necessary for early detection of any abnormalities in calcium level. Moreover, increased phosphorus may be a normal finding in growing children;

however, the significant difference found between the studied groups should be taken into consideration.

Conclusion

No abnormal BMD was detected in newly diagnosed, drug-free autistic children compared with normal children; still, ALT and phosphorus showed a significant difference that require further studies on larger sample to identify possible relation of ALT and phosphorus to BMD in autistic children.

Limitations

The small number of previous studies on this topic, the small sample size, and difficulties in the implementation of DEXA in autistic children are the major limitations of this study.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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