Title

Bone Density in Adolescents and Young Adults with Autism Spectrum Disorders.

Journal

Journal of Autism and Developmental Disorders, 46(11)

Authors

Ekhlaspour, Laya
Baskaran, Charumathi
Campoverde, Karen
et al.

Publication Date

2016-11-01

DOI

10.1007/s10803-016-2871-9

Peer reviewed

HHS Public Access

Author manuscript

J Autism Dev Disord. Author manuscript; available in PMC 2017 November 01.

Published in final edited form as:

J Autism Dev Disord. 2016 November ; 46(11): 3387–3391. doi:10.1007/s10803-016-2871-9.

Bone Density in Adolescents and Young Adults with Autism Spectrum Disorders

Laya Ekhlaspour[1], **Charumathi Baskaran**[1], **Karen Joanie Campoverde**[2], **Natalia Cano Sokoloff**[2], **Ann M. Neumeyer**[3], and **Madhusmita Misra**[1]

Laya Ekhlaspour: lekhlaspour@mgh.harvard.edu; Charumathi Baskaran: cbaskaran@mgh.harvard.edu; Karen Joanie Campoverde: kcampoverdereyes@partners.org; Natalia Cano Sokoloff: natalia.cano@gmail.com; Ann M. Neumeyer: aneumeyer@mgh.harvard.edu; Madhusmita Misra: mmisra@partners.org

[1]Pediatric Endocrine Unit, Massachusetts General Hospital for Children and Harvard Medical School, 55 Fruit Street, Yawkey 6c, Boston, MA 02114, USA

[2]Neuroendocrine Unit, Massachusetts General Hospital, 101 Merrimac St, 6th Floor, Office 615, Boston, MA 02114, USA

[3]Lurie Center for Autism, Massachusetts General Hospital and Harvard Medical School, One Maguire Road, Lexington, MA 02421, USA

Abstract

Patients with autism spectrum disorder (ASD) are at increased risk for fracture, and peri-pubertal boys with ASD have lower bone mineral density (BMD) than controls. Data are lacking regarding BMD in older adolescents with ASD. We compared BMD using dual-energy X-ray absorptiometry in 9 adolescents/young adults with ASD against 9 typically developing matched controls. Patients with ASD and controls were excluded if they had other underlying conditions that may affect bone. Compared to controls, patients with ASD had (i) lower femoral neck and hip BMD Z-scores, and (ii) lower spine, femoral neck and hip height adjusted BMD Z-scores even after controlling for BMI. Understanding the underlying pathophysiology will be key to developing therapies to improve BMD and reduce fracture risk.

Keywords

Autism spectrum disorder; Bone mineral density; Adolescent; Dual energy X-ray absorptiometry; Body mass index

Correspondence to: Laya Ekhlaspour, lekhlaspour@mgh.harvard.edu.

Laya Ekhlaspour, Charumathi Baskaran have contributed equally to this work.

Electronic supplementary material The online version of this article (doi:10.1007/s10803-016-2871-9) contains supplementary material, which is available to authorized users.

Author Contributions MM and AMN conceived the study and interpreted the data. LE, CB, KJC and NCS collected the data and interpreted the data. LE and KJC performed the statistical analysis. LE and CB drafted the manuscript. All authors read and approved the final manuscript.

Introduction

Autism spectrum disorder (ASD) is defined by abnormalities in social communication and social interaction and restricted, repetitive patterns of behavior, interests, or activities (American Psychiatric Association 2013). Recent studies have reported decreased cortical thickness in children with ASD (Hediger et al. 2008) and low bone mineral density (BMD) in peripubertal boys with ASD 8–14 years old (Neumeyer et al. 2013). The childhood and adolescent years are a critical time for bone accrual towards attainment of peak bone mass, a key determinant of future fracture risk. More than 80 % of peak bone mass is achieved by the end of sexual and skeletal development (Wren et al. 2014), underscoring the importance of particularly the adolescent years for bone accrual. Low BMD during adolescence is associated with a higher risk of osteoporosis and fractures during adulthood (Kanis et al. 2004), and data are lacking regarding bone density in older adolescents with ASD.

Important determinants of pubertal skeletal development include rising levels of growth hormone, IGF1 and the gonadal steroids (Theintz et al. 1992). Other factors include genetics (Estrada et al. 2012), gender (Nishiyama et al. 2012), race and ethnicity (Warden et al. 2006), mechanical loading of bone (Deere et al. 2012; Ginty et al. 2005), calcium and vitamin D intake (Lehtonen-Veromaa et al. 2002), nutritional status (Davies et al. 2005), presence of concomitant chronic illnesses, and life style choices such as smoking and alcohol intake (Riggs and Melton 1986). Risk factors for low BMD in ASD include reduced mechanical loading of bone from decreased physical activity (Pan 2008), impaired calcium and vitamin D intake, particularly in those with food aversions and restricted diets (Hyman et al. 2012), higher rates of co-morbid neurologic, psychiatric and gastrointestinal illnesses, and use of medications that impact bone, such as antiepileptics that impair vitamin D metabolism (Sheth et al. 2008; Chou et al. 2007), antipsychotics (Calarge et al. 2015; Roke et al. 2012) and proton pump inhibitors (Freedberg et al. 2015).

Despite the increased predisposition to low BMD in children with ASD, data evaluating BMD in older adolescents and young adults with this condition are limited. In this study, we performed a review of BMD in adolescents with ASD 14–21 years old (late pubertal to post-pubertal), and compared them to age, sex and race matched controls. We hypothesized that BMD, as assessed by dual energy X-ray absorptiometry (DXA), would be lower in older adolescents and young adults with ASD compared with typically developing controls.

Methods

The study was approved by the Partners Health Care Institutional Review Board. All children with ASD were receiving ongoing care at the Lurie Center for Autism of Massachusetts General Hospital for Children, and met DSM IV criteria for diagnosis of Autistic Spectrum Disorders based on clinical interviews. We reviewed the electronic medical records of nine children with ASD 14–21 years old, who were identified on chart review to have received a BMD assessment using DXA (as a part of their clinical evaluation) between the years 2010–2015. Please note that not all children with ASD recommended for scans are able to get these given the requirement to stay still for at least 30 s while the scans

are being obtained. Further, only scans obtained within our institutional system were available for analysis.

Age (within 2 years), sex and race matched healthy controls were recruited from ongoing research studies. Subjects (ASD and controls) with other medical conditions known to affect BMD such as celiac disease, inflammatory bowel disease or mitochondrial disorders, and those receiving medications that could impact BMD such as oral corticosteroids and pamidronate infusions were eliminated. This resulted in exclusion of three children from the current analysis. Subjects using inhaled or intranasal corticosteroid were included given their minimal impact on BMD (Emin et al. 2011). Subjects on anti-epileptic medications were also included given that a large proportion of children with ASD have seizure disorder and excluding such patients may lead to a sample not representative of a clinic population of children with ASD. Although indications for obtaining a BMD evaluation were not clear from chart review in most instances, possible indications included concerns regarding vitamin D status (n = 8) (of which seven had concomittant use of antiepileptic drugs) and use of proton pump inhibitors (n = 1). Of the patients on antileptic drugs, one also had a history of limited activity and the other had hypotonia. This suggests a potential referral bias and an inclination on the part of providers to obtain DXA assessments on children with ASD in whom there are concerns of vitamin D status (from use of anti-epileptic medications), or other concerns for low BMD such as use of medications that potentially impact bone such as proton pump inhibitors, and in those with low physical activity. This would be consistent with possible risk factors for low BMD reported in our recent study (Neumeyer et al. 2013).

Reliable data for pubertal stage was not available for most subjects. We retrieved information on the history of previous fractures and whether children with ASD were on a special diet, in addition to obtaining demographic information, and information regarding height, weight and Body Mass Index (BMI). In patients whose height and weight were not available at the time of scan, measurements within 2 months of the date of the scan were utilized.

All BMD evaluations for children with ASD and typically developing controls were performed on the Hologic 4500 DXA instrument (Waltham, MA). Z-scores for BMD measurements obtained from DXA reports were standardized using the longitudinal Bone Mineral Density in Childhood data base, available online at: http://www.bmdcspublic.com/zscore.htm. This database allows for calculation of a standardized Z-score for a given bone mineral density with reference to the subject's age, sex and race in addition to providing height adjusted Z-scores.

Statistical Analysis

Stata 13.1 was used for all statistical analysis. Based on the mean and standard deviation for lumbar spine and femoral neck BMD Z-scores from our previous study (Neumeyer et al. 2013), a sample size of 9 in each group has >90 % power to detect a significant difference across groups at an alpha level of 0.05 at these sites. The Wilcoxon rank sum test was used to compare groups for continuous variables, and the Chi square test was to compare categorical variables. In order to control for BMI (a known determinant of BMD), multivariate analysis was performed with lumbar, total hip and femoral neck Z scores as the

dependent variable and BMI and subject group (ASD vs. typically developing controls) as the independent variables. A p value of <0.05 was considered statistically significant.

Results

Participant characteristics are depicted in Table 1. Eighty-nine percent of participants were male (consistent with the higher prevalence of males amongst patients with ASD), and all were Caucasian. Of the nine children with ASD, one was on a gluten free, casein free and soy free diet, another was on a lactose free diet, and one had multiple food allergies. Information regarding dietary restrictions for the typically developing controls was unavailable. Review of the medication list showed that seven ASD patients were being treated with antiepileptic medications and one with an anticoagulant. Six patients were on proton pump inhibitors and four on SSRIs as well as antipsychotics. Two ASD patients were on inhaled glucocorticoids. Two ASD patients and three typically developing controls had a previous history of fractures. Both ASD patients had had fractures within the past five years. One ASD patient had a fracture in his right tibia and the other had three ankle fractures (the first followed a fall, the second was incidentally noted when his mother noticed that the patient was limping, and the history for the third was unclear).

Participants with ASD had lower unadjusted BMD and BMD Z-scores at the hip and femoral neck than controls ($p < 0.03$) (data not shown). BMD Z-scores for all the sites continued to be lower in ASD compared to controls after controlling for BMI Z-Score. Height adjusted BMD Z-scores (using the Bone Mineral Density in Childhood database) at the lumbar spine, femoral neck and hip were lower in children with ASD than controls ($p < 0.05$) before and after adjustment for BMI Z-scores (Table 2). Our data did not change when we removed the subject with ASD who was on an anticoagulant and the corresponding matched control from data analysis (Supplemental Table).

Future studies are necessary that account for other comorbidities associated with ASD on BMD.

Conclusion

Post pubertal children with ASD have lower BMD Z-scores at the lumbar spine, femoral neck and hip compared to their healthy counterparts. In this limited report we did not examine the association of low BMD with diet, physical activity, or calcium and vitamin D intake. However, children with ASD who received a DXA scan were on medications such an anti-epileptics and proton pump inhibitors (n = 7 and 1 respectively), one had a history of limited physical activity, and another had hypotonia. These factors may have contributed to low bone density in this cohort. Our data in older adolescents with ASD 14–21 years old follow those in (i) boys with ASD 4–8 years old that demonstrated decreased cortical bone thickness in radiographs compared to reference medians, leading the authors to propose bone health evaluation as part of routine care for patients with autism (Hediger et al. 2008), and (ii) peripubertal boys with ASD 8–14 years old that reported lower BMD at the spine, femoral neck and total hip compared to typically developing controls (Neumeyer et al. 2013). Impaired bone health in older adolescents with ASD raises concerns for peak bone

mass acquisition and future fracture risk, and is consistent with our previous report of an increased risk for hip fractures in children and adults with ASD (Neumeyer et al. 2015). It is important to develop recommendations regarding indications to obtain a DXA scan in children with ASD, and in addition to known indications (coexisting inflammatory bowel disorders, celiac disease, use of chronic high dose steroids, prolonged immobilization), additional indications to consider include those with seizure disorder and on anti-seizure medications, as well as those with marked hypotonia. Data regarding the impact of antiseizure medications on vitamin D status and BMD are mixed (Serin et al. 2015; Yaghini et al. 2015); (Beniczky et al. 2012; Babayigit et al. 2006; Tekgul et al. 2006; Rieger-Wettengl et al. 2001) and the use of these medications is not an indication for DXA assessments. However, children with ASD and seizure may be at particular risk for low BMD. Lower physical activity is a risk factor for low BMD, particularly in younger children (Ginty et al. 2005; Tan et al. 2014). Of note, low BMD in children with ASD who may not be that physically active might be physiologically “appropriate” (Schoenau 2005), and studies are necessary to determine whether or not physically inactive chldren with ASD are also at a higher risk of fracture. Future interventional studies targeted at improving BMD in children with ASD are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

American Psychiatric Association. Diagnostic and statistical manual disorders. 5th. VA: American Psychiatric Association; 2013.

Babayigit A, Dirik E, Bober E, Cakmakci H. Adverse effects of antiepileptic drugs on bone mineral density. Pediatric Neurology. 2006; 35(3):177–181. DOI: 10.1016/j.pediatrneurol.2006.03.004 [PubMed: 16939856]

Beniczky SA, Viken J, Jensen LT, Andersen NB. Bone mineral density in adult patients treated with various antiepileptic drugs. Seizure. 2012; 21(6):471–472. DOI: 10.1016/j.seizure.2012.04.002 [PubMed: 22541979]

Calarge CA, Burns TL, Schlechte JA, Zemel BS. Longitudinal examination of the skeletal effects of selective serotonin reuptake inhibitors and risperidone in boys. Journal of Clinical Psychiatry. 2015; 76(5):607–613. DOI: 10.4088/JCP.14m09195 [PubMed: 26035190]

Chou IJ, Lin KL, Wang HS, Wang CJ. Evaluation of bone mineral density in children receiving carbamazepine or valproate monotherapy. Acta Paediatrica Taiwanica. 2007; 48(6):317–322. [PubMed: 18437965]

Davies JH, Evans BA, Gregory JW. Bone mass acquisition in healthy children. Archives of Disease in Childhood. 2005; 90(4):373–378. DOI: 10.1136/adc.2004.053553 [PubMed: 15781927]

Deere K, Sayers A, Rittweger J, Tobias JH. A crosssectional study of the relationship between cortical bone and high-impact activity in young adult males and females. Journal of Clinical Endocrinology and Metabolism. 2012; 97(10):3734–3743. DOI: 10.1210/jc.2012-1752 [PubMed: 22802090]

Emin O, Fatih M, Emre D, Nedim S. Lack of bone metabolism side effects after 3 years of nasal topical steroids in children with allergic rhinitis. Journal of Bone and Mineral Metabolism. 2011; 29(5):582–587. DOI: 10.1007/s00774-010-0255-3 [PubMed: 21327885]

Estrada K, Styrkarsdottir U, Evangelou E, Hsu YH, Duncan EL, Ntzani EE, et al. Genome-wide meta-analysis identifies 56 bone mineral density loci and reveals 14 loci associated with risk of fracture. Nature Genetics. 2012; 44(5):491–501. DOI: 10.1038/ng.2249 [PubMed: 22504420]

Freedberg DE, Haynes K, Denburg MR, Zemel BS, Leonard MB, Abrams JA, et al. Use of proton pump inhibitors is associated with fractures in young adults: A population-based study. Osteoporosis International. 2015; 26(10):2501–2507. DOI: 10.1007/s00198-015-3168-0 [PubMed: 25986385]

Ginty F, Rennie KL, Mills L, Stear S, Jones S, Prentice A. Positive, site-specific associations between bone mineral status, fitness, and time spent at high-impact activities in 16- to 18-year-old boys. Bone. 2005; 36(1):101–110. DOI: 10.1016/j.bone.2004.10.001 [PubMed: 15664008]

Hediger ML, England LJ, Molloy CA, Yu KF, Manning-Courtney P, Mills JL. Reduced bone cortical thickness in boys with autism or autism spectrum disorder. Journal of Autism and Developmental Disorders. 2008; 38(5):848–856. DOI: 10.1007/s10803-007-0453-6 [PubMed: 17879151]

Hyman SL, Stewart PA, Schmidt B, Cain U, Lemcke N, Foley JT, et al. Nutrient intake from food in children with autism. Pediatrics. 2012; 130(Suppl 2):S145–S153. DOI: 10.1542/peds.2012-0900L [PubMed: 23118245]

Kanis JA, Johnell O, De Laet C, Johansson H, Oden A, Delmas P, et al. A meta-analysis of previous fracture and subsequent fracture risk. Bone. 2004; 35(2):375–382. DOI: 10.1016/j.bone.2004.03.024 [PubMed: 15268886]

Lehtonen-Veromaa MK, Mottonen TT, Nuotio IO, Irjala KM, Leino AE, Viikari JS. Vitamin D and attainment of peak bone mass among peripubertal Finnish girls: A 3-y prospective study. American Journal of Clinical Nutrition. 2002; 76(6):1446–1453. [PubMed: 12450915]

Neumeyer AM, Gates A, Ferrone C, Lee H, Misra M. Bone density in peripubertal boys with autism spectrum disorders. Journal of Autism and Developmental Disorders. 2013; 43(7):1623–1629. DOI: 10.1007/s10803-012-1709-3 [PubMed: 23124396]

Neumeyer AM, O'Rourke JA, Massa A, Lee H, Lawson EA, McDougle CJ, et al. Brief report: Bone fractures in children and adults with autism spectrum disorders. Journal of Autism and Developmental Disorders. 2015; 45(3):881–887. DOI: 10.1007/s10803-014-2228-1 [PubMed: 25193141]

Nishiyama KK, Macdonald HM, Moore SA, Fung T, Boyd SK, McKay HA. Cortical porosity is higher in boys compared with girls at the distal radius and distal tibia during pubertal growth: An HR-pQCT study. Journal of Bone and Mineral Research. 2012; 27(2):273–282. DOI: 10.1002/jbmr.552 [PubMed: 22028110]

Pan CY. Objectively measured physical activity between children with autism spectrum disorders and children without disabilities during inclusive recess settings in Taiwan. Journal of Autism and Developmental Disorders. 2008; 38(7):1292–1301. DOI: 10.1007/s10803-007-0518-6 [PubMed: 18157623]

Rieger-Wettengl G, Tutlewski B, Stabrey A, Rauch F, Herkenrath P, Schauseil-Zipf U, et al. Analysis of the musculoskeletal system in children and adolescents receiving anticonvulsant monotherapy with valproic acid or carbamazepine. Pediatrics. 2001; 108(6):E107. [PubMed: 11731634]

Riggs BL, Melton LJ 3rd. Involutional osteoporosis. New England Journal of Medicine. 1986; 314(26):1676–1686. DOI: 10.1056/NEJM198606263142605 [PubMed: 3520321]

Roke Y, van Harten PN, Buitelaar JK, Tenback DE, Quekel LG, de Rijke YB, et al. Bone mineral density in male adolescents with autism spectrum disorders and disruptive behavior disorder with or without antipsychotic treatment. European Journal of Endocrinology. 2012; 167(6):855–863. DOI: 10.1530/EJE-12-0521 [PubMed: 23011870]

Schoenau E. From mechanostat theory to development of the "functional muscle-bone-unit". Journal of Musculoskeletal and Neuronal Interactions. 2005; 5(3):232–238. [PubMed: 16172514]

Serin HM, Koc ZP, Temelli B, Esen I. The bone mineral content alterations in pediatric patients medicated with levetiracetam, valproic acid, and carbamazepine. Epilepsy & Behavior. 2015; 51:221–224. DOI: 10.1016/j.yebeh.2015.06.025 [PubMed: 26298867]

Sheth RD, Binkley N, Hermann BP. Progressive bone deficit in epilepsy. Neurology. 2008; 70(3):170–176. DOI: 10.1212/01.wnl.0000284595.45880.93 [PubMed: 18057319]

Tan VP, Macdonald HM, Kim S, Nettlefold L, Gabel L, Ashe MC, et al. Influence of physical activity on bone strength in children and adolescents: A systematic review and narrative synthesis. Journal of Bone and Mineral Research. 2014; 29(10):2161–2181. DOI: 10.1002/jbmr.2254 [PubMed: 24737388]

Tekgul H, Serdaroglu G, Huseyinov A, Gokben S. Bone mineral status in pediatric outpatients on antiepileptic drug monotherapy. Journal of Child Neurology. 2006; 21(5):411–414. [PubMed: 16901447]

Theintz G, Buchs B, Rizzoli R, Slosman D, Clavien H, Sizonenko PC, et al. Longitudinal monitoring of bone mass accumulation in healthy adolescents: Evidence for a marked reduction after 16 years of age at the levels of lumbar spine and femoral neck in female subjects. Journal of Clinical Endocrinology and Metabolism. 1992; 75(4):1060–1065. DOI: 10.1210/jcem.75.4.1400871 [PubMed: 1400871]

Warden SJ, Burr DB, Brukner PD. Stress fractures: Pathophysiology, epidemiology, and risk factors. Curr Osteoporos Rep. 2006; 4(3):103–109. [PubMed: 16907999]

Wren TA, Kalkwarf HJ, Zemel BS, Lappe JM, Oberfield S, Shepherd JA. Longitudinal tracking of dual-energy X-ray absorptiometry bone measures over 6 years in children and adolescents: Persistence of low bone mass to maturity. The Journal of Pediatrics. 2014; 164(6):1280–1285. DOI: 10.1016/j.jpeds.2013.12.040 [PubMed: 24485819]

Yaghini O, Tonekaboni SH, Amir Shahkarami SM, Ahmad Abadi F, Shariat F, Abdollah Gorji F. Bone mineral density in ambulatory children with epilepsy. Indian Journal of Pediatrics. 2015; 82(3): 225–229. DOI: 10.1007/s12098-014-1518-0 [PubMed: 25106841]

Table 1

Demographic and clinical characteristics of participants with ASD and typically developing controls

	ASD n = 9	Controls n = 9	*P* value
Sex (M/F)	8/1 (88.9/11.1 %)	8/1 (88.9/11.1 %)	1.00
Race (white)	9 (100 %)	9 (100 %)	1.00
Age (years)	17.6 (1.87)	16.6 (2.62)	0.23
Height (cm)	171.5 (8.26)	173.4 (7.5)	0.38
Height Z-score	−0.02 (1.11)	0.15 (1.20)	0.35
Weight (kg)	70.5 (24.8)	62.2 (4.2)	0.12
Weight Z-score	0.93 (2.36)	0.30 (1.13)	0.27
BMI	25.30 (7.20)	20.71 (2.50)	0.04
BMI Z-score	0.81 (1.50)	0.18 (0.93)	0.03

Values are presented as median and interquartile range or n (%). Wilcoxon rank sum test was used for comparing continuous variables and the Chi square test for categorical variables

Table 2

Bone mineral density in ASD versus typically developing control groups

Age, sex, height, race/ethnicity adjusted BMD Z-score	ASD n = 9	Control n = 9	*P* value	BMI Z-score adjusted *p* value
Lumbar Spine	−0.79 (0.31)	0.05 (1.20)	**0.047**	**0.020**
Femoral neck	−1.57 (0.93)	−0.01 (0.95)	**0.014**	**0.002**
Total hip	−2.2 (1.03)	0.01 (1.68)	**0.006**	**0.002**

Bold values are statistically significant ($p < 0.05$)

Values are presented as median and inter quartile range IQR or n (%). Wilcoxon rank sum test was used for comparing continuous variables