Clinical Reviews in Bone and Mineral Metabolism (2019) 17:160–169
https://doi.org/10.1007/s12018-019-09268-w

REVIEW PAPER

Bone Health and BMD Research in Pediatric and Adolescent Individuals with ASD: Current Data, Evaluation, and Next Steps

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Published online: 26 November 2019

Abstract

Austin spectrum disorder (ASD) is a complex neurodevelopmental disorder that can include impairments in communication skills and social interaction as well as behavioral challenges. Recent research has evaluated bone health and bone mineral density (BMD) in cohorts of pediatric, adolescent, and young adult participants. Consistent findings across publications indicate that individuals with ASD have decreased BMD when compared to non-ASD age-matched peers. Factors raised in the literature for consideration of impact on BMD status include dietary intake, feeding behavior, nutrient status, gastrointestinal (GI) symptoms and diagnoses, physical activity, and prescription medication usage. This review aims to provide a comprehensive overview of published research evaluating BMD in those with ASD, analyze potential issues of correlation with lowered BMD in this population, offer perspective for future research consideration, and propose evaluation and intervention strategies to address and potentially ameliorate both the short-term and long-term impact of decreased BMD in children and adolescents.

Keywords BMD · Bone mineral density · Autism spectrum disorder · ASD

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by persistent deficits in social communication and social interaction as well as restricted, repetitive patterns of activities, behavior, and interests [1]. The most recent Centers for Disease Control (CDC) ASD prevalence rate is 1 in 59 based on 8–11 year old children in 11 diverse populations across the USA [2]. Prevalence rates for ASD continue to increase worldwide, with estimates of 1.5% or greater in developed countries. This increase reflects changes in prevalence for those primarily without intellectual disability comorbidity [3].

In the past decade, research publications have highlighted complex medical comorbidities that could impact behavioral diagnostic criteria for ASD such as self-injurious behavior (SIB), aggression, and stereotypy, which includes repetitive behaviors such as hand flapping, rocking, and vocal sounds [4–6]. The presence of specific medical comorbidities such as gastrointestinal and sleep concerns has been associated with an increase in self-injurious and aggressive behaviors [7, 8]. Anxiety and ADHD symptoms may aggravate certain ASD symptoms, such as social withdrawal and increased ritual/stereotypic behaviors, which may affect overall functioning [9]. Those with ASD also have an increased risk of feeding concerns, food selectivity, and food neophobia resulting in challenging behaviors over non-ASD peers [10–12]. Other specific comorbid medical diagnoses such as inflammatory bowel disease directly impact bone health [13, 14].

Within the field of bone health research, seminal work published in 2008 evaluated bone development for males with ASD aged 4–8 years, noting that participants with ASD had significantly lower bone cortical thickness than normative values [15]. Since that publication, several cohorts of pediatric, adolescent, and young adults with ASD have been evaluated for overall bone health markers in comparison with non-ASD peers. Evaluation included bone cortical thickness, bone mineral density (BMD), and bone microarchitecture, as well as nutritional status and dietary intake [16–18].

An increasing prevalence of ASD coupled with the long-term health implications of potentially decreased BMD and overall bone health speaks to the need for proactive identification and intervention for those diagnosed with ASD and at-

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risk for lowered BMD status. In this review, we will speak to the current body of research literature on the topic of pediatric and adolescent BMD in ASD, offer potential direction for research consideration in the future, and propose potential clinical identification and evaluation strategies in this population. We aim also to speak to ongoing challenges that remain in this endeavor.

Current Status in the Research Literature

It has been established across several cohorts of participants that pediatric, adolescent, and young adult males with ASD have lower BMD than non-ASD peers (Table 1) [15–20]. This represents consistent data across multiple research study cohorts and sites.

The 2008 work of Hediger and colleagues established decreased bone cortical thickness in males 4–8 years of age with ASD versus normative values. In this cohort, bone cortical thickness reflected a slowing of appositional bone development in participants, with older males showing greater deviations from normative values than those 4–5 years of age [15]. The authors suggested that this concern could be a function of a number of issues, including decreased calcium and vitamin D intake potentially associated with adherence to gluten and casein free dietary protocols (GFCF), gastrointestinal disorders, limited physical activity, and decreased access to sunlight.

Research on a second cohort followed by Neumeyer and colleagues expanded the work in bone health in males with ASD, finding that 18 males aged 8–14 years old had significantly lower BMD *z*-scores than 19 age-matched non-ASD peers [16]. The authors also documented decreased dietary intake of vitamin D and lower levels of physical activity. This work supported the earlier conclusions that decreased dietary intake of vitamin D3, decreased endogenous vitamin D synthesis, and reduced activity levels could contribute to decreased BMD in males with ASD.

A 4-year follow-up study on this population evaluating bone accrual rates concluded decreases in bone mineralization occur early in life for those with ASD, with no difference in pubertal bone accrual for ASD and non-ASD participants [21]. Additional findings included significantly lower physical activity levels for those with ASD, but no significant difference in serum 25(OH) vitamin D between ASD and non-ASD participants. Further published work on this cohort [22] concluded that ASD participants consumed less animal protein, calcium, and phosphorus than non-ASD participants, and these values were positively associated with BMD results.

Neumeyer and colleagues also evaluated bone microarchitecture in participants from this cohort, concluding that males with ASD have lower cortical and trabecular thickness at the ultradistal radius and lower strength estimates both the ultradistal radius and the distal tibia in 16 ASD and 18 non-ASD peers [19]. Findings in this population indicated that decreased physical activity levels contributed significantly to this difference [19]. Through this contribution to the literature, the authors also suggested the influence of insulin-like growth factor (IGF-1) was protective of bone accrual in puberty and adolescence, with early decreased bone mass the likely primary factor in overall decreased BMD in those participants with ASD.

It is of note that these papers [19, 21, 22] evaluated 25 males with ASD and 24 age-matched non-ASD peers, including 14 males with ASD and 13 non-ASD peers included in the original 2012 paper. An additional 13 participants (6 ASD, 7 non-ASD) were also included at the follow up time point in 2015.

A third cohort retrospectively assessed BMD status in adolescents and young adults with and without ASD. In this study, Ehklaspour and colleagues included evaluation of a case-control cohort offering data on an older population of 9 individuals (8 male/1 female) with ASD and 9 non-ASD peers (8 male/1 female) aged 14–21 years [17]. The study identified on chart review participants with DXA assessment, finding adolescents and young adults with ASD have lower BMD *z*-scores than non-ASD peers. The study did not evaluate dietary intake, nutritional status, and physical activity of participants and the majority (8 of 9) of ASD participants were on medications known to impact bone density.

Barnhill and colleagues provided BMD data in a cohort of 40 males aged 4–8 years with ASD and 40 age-matched non-ASD participants. BMD was significantly lower in boys with ASD as opposed to peers [18]. Contrary to prior findings, in this study, dietary intake of vitamin D as well as serum vitamin 25(OH) D was significantly higher in males with ASD than that of non-ASD peers. This finding was likely a function of professional care and appropriate supplementation of both calcium and vitamin D for many participants with ASD included in the study. When comparing those participants with ASD who were following a dietary protocol limiting casein to those who were on unrestricted diets indicated no difference in BMD status in this population. This finding suggests that vitamin D and calcium intake in children on a specialized diet is not a contributing factor to decreased BMD in this population.

In summary, this body of work suggests that prepubescent males with ASD have decreased bone accrual when compared to non-ASD peers, though bone accrual in puberty is consistent in both ASD and non-ASD populations [21]. Additionally, adolescents with ASD have weaker bones than age-matched non-ASD peers [19]. Finally, research also suggests that individuals with ASD have a higher risk of bone fracture than non-ASD individuals in both pediatric and adult populations [23, 24]. Taken together, these findings are concerning as they establish reduced BMD in pediatric males which tracks through adolescence and adulthood.

Table 1 2019 Summary prospective assessment of BMD in pediatric and adolescent males with autism spectrum disorder

Citations	ASD Subjects (*n*)	Non-ASD Subjects (*n*)	Age range (years)	Summary
Neumeyer AM, Cano Sokoloff N, McDonnell El, et al. Nutrition and bone density in boys with autism spectrum disorder JADD[1]; 2018;118(5):865–877	19	19	8–17	BMD *z*-scores for boys aged 8–17 years with ASD (25 boys with ASD, 24 non-ASD controls) were lower than age-matched peers. Boys with ASD also had lower protein, calcium, and phosphorus intake.
Barnhill K, Ramirez L, Gutierrez A, et al. BMD in boys diagnosed with autism spectrum disorder: a case-control study JADD[1]; 2017;47(11):3608–3619	40	40	4–8	BMD for boys aged 4–8 years with ASD (−) was lower than boys without ASD, and not correlated with any biochemical markers, dietary intake of calcium and vitamin D, elimination diet status, or GI symptomology
Neumeyer AM, Cano Sokoloff N, McDonnell E, Macklin EA, McDougle CJ, Misra M Bone microarchitecture in adolescent boys with autism spectrum disorder Bone; 2017;97:139–146	16	18	9–18	Bone strength estimates (failure load and stiffness) in a study of 16 boys with ASD were reduced when compared to 18 boys without ASD aged (−). The study also concluded that boys with ASD had lower physical activity and calcium intake.
Neumeyer AM, Cano Sokoloff N, McDonnell E, Macklin EA, McDougle CJ, Misra M Bone accrual in males with autism spectrum disorder JPEDS[2]; 2017;181:195–201	25	24	8–17	BMD *z*-scores for 25 boys with ASD remained lower than 24 boys without ASD on 4-year follow-up assessment, though bone accrual rates did not differ between the 2 groups.
Ekhlaspour L, Baskaran C, Campoverde KJ, Sokoloff NC, Neumeyer AM, Misra M Bone density in adolescents and young adults with autism spectrum disorders JADD[1]; 2016;46(11):3387–3391	9	9	14–21	BMD *z*-scores for 9 adolescent and young adults (8 male/1 female) with ASD were lower than those of 9 age-matched controls without ASD. 8 of 9 participants with ASD were on medications known to decrease BMD.
Neumeyer AM, Gates A, Ferrone C, Lee H, Misra M Bone density in peripubertal boys with autism spectrum disorders JADD[1]; 2013;43(7):1623–1629	18	19	8–14	BMD *z*-scores were lower for 18 boys aged 8–14 years than 19 age-matched boys without ASD. Vitamin D intake, Vitamin D serum levels, and exercise were lower in boys with ASD than boys without ASD.
Roke Y, Van Harten PN, Buitelaar JK et al. BMD in male adolescents with autism spectrum disorders and disruptive behavior disorder with or without antipsychotic treatment EJE[3]; 2012;167(6):855–863	108		10–20	BMD *z*-scores for 56 boys with ASD aged 10–20 years receiving antipsychotic treatment compared to 47 age-matched boys with ASD not receiving treatment were similar. 49% of boys receiving treatment developed hyperprolactinemia. 11% of these boys had lowered BMD.
Soden SE, Garrison CB, Egan AM, Beckwith AM Nutrition, physical activity, and BMD in youth with autism spectrum disorders JDBP[4]; 2012;33(8):618–624	26		10–18	27 individuals (21 male/6 female) aged 10–18 years with ASD with low body mass index, low caloric, and low calcium intake were at risk for low BMD. Additionally, 50% of participants had insufficient vitamin D(OH) 25 levels.
Goodarzi M, Hemayattalab R BMD accrual in students with autism spectrum disorders: Effects of calcium intake and physical training RASD[5]; 2011;6(2):690–695	60		8–10	Evaluation of 60 males aged 8–10 years with ASD concluded that calcium intake and physical exercise had a synergistic effect on bone health, with a 22.68% increase in BMD status than control cohort.
Hedinger ML, England LJ, Molloy CA, Yu KF, Manning-Courtney P, Mills JL Reduced bone cortical thickness in boys with autism or autism spectrum disorder JADD[1]; 2008;38(5):848–856	75		4–8	Decreased bone cortical thickness in males aged 4–8 years with ASD. Potential suggested variables included decreased calcium and vitamin D intake, gastrointestinal concerns, decreased physical activity, and decreased access to sunlight.

[1] Journal of Autism and Developmental Disorders

[2] Journal of Pediatrics

[3] European Journal of Endocrinology

[4] Journal of Developmental and Behavioral Pediatrics

[5] Research in Autism Spectrum Disorders

Additional original research in this body of literature includes work from Roke et al. evaluating the use of antipsychotic medications in males with ASD aged 10–20 years [25]. The authors conclude that BMD in the study population was similar for participants with and without antipsychotic treatment. An important finding here was decreased volumetric

BMD for those experiencing hyperprolactinemia with antipsychotic treatment versus those without hyperprolactinemia. This result suggests that antipsychotic-induced hyperprolactinemia may be an influence on bone health in this population.

An evaluation of bone health in 21 male and 6 female ASD participants aged 10–18 years indicated that those with ASD coupled with low body mass index, low caloric, and low calcium intake were at risk for low BMD [20]. Serum vitamin D (OH)25 was insufficient in more than 50% of participants. The findings also indicated a high screen time to physical activity ratio, supporting the influence of exercise upon BMD in this population.

Finally, a 2012 study assessed the impact of weight-bearing exercise and calcium supplementation on BMD in 60 males with ASD aged 8–10 years old [26]. Study participants were randomly assigned to research groups with or without calcium supplementation and then also those with or without an exercise regime, resulting in possible enrollment in 1 of 4 cohorts. Results of this work indicated that weight-bearing exercise and calcium supplementation had a synergistic effect on bone health, with a 22.68% greater increase in BMD than in the control population.

Potential Factors Influencing BMD in Individuals with ASD

Multiple factors are known to play a role in BMD and bone health. A number of specific variables have been identified to influence BMD in children with ASD, including physical activity levels [21], gastrointestinal disorders [27], medications [28], food selectivity and restrictive eating behavior [29], and dietary intake and nutritional status, with particular focus on calcium and vitamin D [30, 31].

Bone accrual and bone mineral status in childhood, puberty, and adolescence plays a critical role in long-term bone health. Peak bone mass is a determinant of future bone health as 90% of peak bone mass is gained in the first 20 years of life, with 40% of lifetime bone mass accrued in puberty [32]. Low BMD affects 1 in 4 females and 1 in 20 males over the age of 65 [33] presenting a significant health challenge as bone tissue is altered with age and the risk of bone fractures increases over time.

Physical Activity and Exercise

Exercise and physical activity are established important determinants of BMD. Exercise is associated with increases in skeletal mass in children, and physical activity is particularly important in the pediatric and prepubertal population, as weight-bearing activity is noted to make a significant difference in bone accrual in this population [34–36]. Weight-bearing activity leads to an increase in overall bone formation rate through the stimulation of osteoblasts in the tissue [37, 38]. Decreased physical activity (including weight bearing activity) is established for pediatric males with ASD vs non-ASD peers in multiple research publications [21]. This decreased activity is a risk factor for compromised BMD in those with ASD [16, 19, 20, 22, 39]. Finally, lean muscle mass is positively correlated with BMD in the pediatric population; thus, children with greater muscle mass have greater BMD [40]. Decreased muscle mass associated with decreased physical activity in children with ASD is therefore a concern.

Hypotonia

With regard to decreased muscle mass and tone, children with ASD can also experience comorbid hypotonia [41], a disorder defined by low or abnormal muscle tone [42]. Mechanical loading of the skeleton is a key factor in bone mineral accrual in peripubertal and adolescent children [43]. Many children with ASD present with idiopathic toe-walking in which they walk on the balls of their feet and their heels do not touch the ground [44]. Idiopathic toe-walking is a diagnosis of exclusion, and while there are several potential comorbid diagnoses which could lead to toe-walking, in the majority of those with ASD, this is likely a function of decreased core and lower body tone or sensory processing disorder [41, 45, 46]. This hypotonia contributes to this decreased mechanical loading of muscle/bone interaction, leading to diminished overall bone health [47, 48].

Gastrointestinal Concerns

Gastrointestinal (GI) symptoms have been very well documented in the literature for children with ASD [49]. These can include constipation, diarrhea, gastroesophageal reflux disease (GERD), bloating, flatulence, and pain [50], but noted symptoms vary widely across multiple studies [51]. Symptoms can be difficult to recognize in children with ASD and often go undiagnosed and untreated [52]. One recent BMD study evaluated GI symptoms for all participants through a standardized questionnaire across 5 separate domains. Males with ASD reported significantly greater GI concerns across all domains [18].

Individuals with ASD are also noted to be at greater risk for comorbid inflammatory bowel disease (IBD) [53, 54]. It has been established in the literature that pediatric patients with IBD have decreased BMD [55]. The GI tract is responsible for digestion and absorption of key bone nutrients including calcium, vitamin D, and magnesium, and phosphorus [56]. If the GI tract is compromised in some fashion, there is ongoing

concern for digestion, absorption, and assimilation of key bone building nutrients. Of note, several dietary micronutrient deficiencies reported for those with IBD, such as vitamins B1, B6, B12, D and iron are also found as serum deficiencies in studies of those with ASD [18, 57].

A body of literature now points to the role of the microbiota in bone health and mineral metabolism. A number of studies have identified changes to the gut microbiome in children with ASD (reviewed by [58] leading to an imbalance in intestinal flora [59, 60]. This imbalance can be addressed through the use of both prebiotic and probiotic foods and nutritional supplementation [61–66].

Of note, prebiotics were first fully described in the literature in 1995 as non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, thus improving host health [67]. As knowledge in this area expanded, the definition has been widened to "a non-digestible compound that, through its metabolization by microorganisms in the gut, modulates composition and/or activity of the gut microbiota, thus conferring a beneficial physiologic effect on the host" [68]. A growing body of research has established that prebiotics are essential for improving the digestion and absorption of calcium and other minerals and enhancing skeletal health [69, 70]. It has also been suggested that the use of prebiotics to maximize mineral accretion and facilitate bone accrual in childhood, puberty, and adolescence will contribute to greater bone mass later in life [71].

Hormones: Insulin-Like Growth Factor-1 and Serotonin

There are many factors that regulate bone growth and turnover including hormones, neurotransmitters, growth factors, and cytokines [72]. Disruption of this process and the resulting imbalance between bone resorption and formation can lead to osteoporosis [73].

Insulin-Like Growth Factor-1 (IGF-1)

Important determinants of pubertal skeletal development include rising levels of growth hormone, IGF-1, and the gonadal steroids [74]. IGF-1 crosses the blood brain barrier where it stimulates DNA synthesis, cell production, and neurite outgrowth, and enhances secretion of several neurotransmitters [75]. Low levels of serum IGF-1 in both newborns and young children point to a disruption of the normal neurobiological mechanisms in this period, and are associated with an increased risk for ASD [76]. Both animal and human cell culture studies suggest a beneficial effect of IGF-1 on synaptic development by promoting neuronal cell survival, synaptic maturation, and synaptic plasticity [77, 78]. In recent years, IGF-1 has been explored as a potential treatment for the core symptoms of ASD. One pilot study investigating the effects of IGF-1 on behavior in children with Phelan-McDermid syndrome (PMS), a monogenic disorder closely associated with ASD, reported improvements in social impairment and restrictive behaviors establishing preliminary evidence of benefit of IGF-1 on ASD symptomatology [79]. However, the precise mechanisms by which IGF-1 exerts its effects on the CNS in ASD remain an active area of study.

Serotonin

Serotonin, a neurotransmitter that is known to influence the balance between bone formation and resorption [80], is frequently elevated in ASD [81]. Selective serotonin reuptake inhibitors (SSRIs) are a class of antidepressants that are sometimes given to reduce anxiety or obsessive-compulsive behaviors in children with ASD, although there is limited evidence as to their effectiveness [82]. Clinical studies have reported an association of SSRIs with increase in fracture and decrease in bone mineral density (reviewed by [80] raising concerns regarding the effect of blocking serotonin reuptake on bone metabolism.

Medication

Use of anticonvulsants, such as diphenylhydantoin, phenobarbital, topiramate carbamazepine, and valproic acid, is reported to reduce bone density [83]. Furthermore, lower bone turnover has been reported in those receiving lithium [84]. Stimulant medications, frequently used to treat attention-deficit/hyperactivity disorder and ASD, increase sympathetic tone and may affect bone remodeling [85]. Additionally, antidepressants which are used to address anxiety and obsessive-compulsive behaviors are suggested to affect BMD, though the research is mixed [86, 87].

Feeding Behavior

Research indicates that children with ASD and GI concerns are at a higher risk of developing problem feeding behaviors than children with ASD who do not have these symptoms [88–90], although a clear understanding of etiology for children with ASD has yet to be clearly established [91]. Children with ASD often have restrictive eating habits, such as picky or problem eating and they are more likely to have food selectivity and feeding issues resulting in challenging behaviors surrounding food intake than their typically developing peers [10, 12, 92]. Those with ASD are 5 times as likely to experience feeding problems than non-ASD peers [93]. This food selectivity, defined as consumption of an abnormally limited

variety of food, leaves children with ASD at elevated risk for altered nutritional status and growth [94–99], and is likely to have detrimental effects on bone health.

Diet and Nutritional Status

Various micronutrient deficiencies for those with ASD have been identified in the research literature with conflicting results [93, 100]. Several studies have shown that children with ASD are more likely to have inadequate intake of protein, vitamin D, pantothenic acid, vitamin B6, folic acid, vitamin K, and calcium compared to children without ASD, but that data is not always consistent across the literature [29, 97, 101–103]. Of particular interest in bone health are calcium, magnesium, phosphorus, and vitamin D.

One consistent finding across multiple publications is a deficiency in both calcium and vitamin D intake [15, 18, 22, 96, 102–105]. The research literature establishes that lower calcium and vitamin D intake affects bone accrual in the pediatric population [106]. Further, decreased vitamin D intake is one of the most consistent findings in the literature where not only a large majority of ASD participants had inadequate intake of vitamin D, but non-ASD participants also presented with inadequate intake as well [12, 18, 29, 107].

With regard to calcium, more recent studies examining dietary status in ASD demonstrated no significant differences in calcium intake when comparing children who were on a well-supported gluten free and casein free (GFCF) diet versus those that did not report any dietary intervention [18, 108, 109]. Therefore, dietary intervention in ASD, such as a GFCF diet, does not necessarily result in deficiencies in calcium and vitamin D [105, 110] or decreased bone density, as long as it is implemented and well supported by a clinician [18]. For example, a child on a nutrient-dense, casein-free diet may receive more than adequate levels of calcium and vitamin D compared to a child receiving the standard American diet [96]. It is also worth noting here that children on a supported GFCF diet are more likely to be taking a vitamin D supplement [111] and meet their vitamin D intake requirements [112].

The most recent work on the Neumeyer cohort [22] suggests that higher calcium, phosphorus, and animal protein intake is positively associated with greater BMD. Further, calcium and phosphorus intake were both consistent predictors of all BMD measures in those with ASD.

Sleep Status

Sleep disruption is correlated with gastrointestinal symptoms, anxiety, sensory sensitivity, and ASD severity per a 2013 evaluation of Autism Treatment Network participants [113]. Further disrupted sleep in children with ASD is associated with daytime behavioral dysregulation, and night waking has the strongest correlation with daytime behavioral concerns in this population [8]. While previous clinical studies have failed to reach a consensus on the association between sleep duration and BMD due to the many variables in conducting such studies, sleep disruption in a rat model was found to markedly affect bone mass and bone metabolism by lowering BMD, deteriorating bone microarchitecture, and decreasing bone formation and resorption markers [114].

Limitations of Current Data

There are several limitations of the current bone density literature in children with ASD that should be considered. These include the study design (some studies were retrospective or cross-sectional and did not include a control group; the study size was likely underpowered in some datasets; several papers did not include a control group; and the age of cohorts included children as young as 4, as well as prepubescent and pubescent participants, which represent quite distinct periods of bone development). Some studies did not confirm an ASD diagnosis and relied on parental report. Similarly, nutrient intake and use of medication and supplements could not always be verified. This is particularly important in studies looking at the effects of diet on bone health as a GFCF diet was not shown to be deleterious to bone density when it was well-supported with the appropriate clinical oversight. Finally, several of the papers included in this review are based on the same cohorts, or additional subjects were added to the original cohorts in subsequent papers to expand the analyses, which complicated the interpretation of the data. Larger prospective studies would be very helpful in assessing the many variables that can impact bone metabolism in children with ASD.

Direction on Future Research and Current Clinical Assessment

The literature is clear that physical activity and weight-bearing exercise specifically are positively correlated with bone health and BMD. Researchers have demonstrated that those with ASD are less active than age-matched non-ASD peers. Future research can be directed toward investigation of the impact of hypotonia early in life on BMD and establishing a better understanding of appropriate exercise opportunities for those with ASD.

Research has recently demonstrated the safety and efficacy of IGF-1 treatment in children with Phelan-McDermid syndrome, particularly in the treatment of the core symptoms of ASD. Therefore, these studies should be expanded to include the idiopathic autism population. Further, there is no work published to-date on the impact of serotonin levels and bone

health in this population. Finally, given the presence of significant sleep disturbance in children and adolescents with autism and the known impact of sleep on bone health, research evaluating sleep and bone health status in this population may be warranted.

It is known that diets higher in calcium, vitamin D, and amino acids appear important in overall bone health of those with ASD, and that these nutrients coupled with physical activity appear to have a synergistic effect on bone health. For primary care practitioners, this translates to early assessment for dietary intake and nutritional status. This would include the recommendation of a comprehensive anthropometric, dietetic, and physical assessment for all children with ASD in a primary care setting as a baseline measurement to evaluate the need for referral for more specialized evaluation and potential intervention on a case-by-case basis. Additionally, it is recommended that PCPs follow current guidelines for serum vitamin D assessment in at-risk populations [30] for all patients with ASD.

Author Contribution KB designed and organized this review. MD completed literature searches, the first draft of the manuscript was written by KB, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants performed by any of the authors.

Abbreviations ASD, autism spectrum disorder; BMC, bone mineral content; BMD, BMD; DEXA, dual-energy X-ray absorptiometry; GFCF, gluten free casein free; IBD, inflammatory bowel disease; PCP, primary care practitioner

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