Chapter 16
Adolescent and Young Adult Bone Health

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Introduction

Childhood, adolescence and early adulthood are critical developmental stages for skeletal mineralisation. Optimal bone mass is defined as "the maximum amount of bone mineral content present at the end of skeletal maturation [1]". As the vast majority of optimal bone mass is accrued in the first two decades of life, chronic diseases during this period can leave a lifelong legacy. The effect can be further exacerbated by overexposure to glucocorticoids, a common treatment for a range of RMD. Up to 50% of individuals affected by juvenile idiopathic arthritis (JIA) have a decreased BMD [2].

The International Society for Clinical Densitometry (ISCD**)** consensus was that osteoporosis is said to be present in the context of ">1 vertebral compression fracture in the absence of local disease or high-energy trauma". As such in AYA, the diagnosis of osteoporosis requires the presence of a "clinically significant fracture history (≥2 long bone fractures by the age of 10 or ≥3 long bone fractures at any age up to 19)" in addition to reduced BMD [3]. Suboptimal bone mass obviously increases risk of early-onset osteoporosis. With osteoporosis being a major cause of morbidity and mortality in adults [4], it is clear that prevention begins by optimising bone health at a young age.

Normal Bone Modelling

Bone structure is determined by bone modelling during childhood and remodelling throughout the life course. Modelling involves adaptation to mechanical loading, and bone remodelling refers to the constant replacement of bone during life. This involves coordinated interaction of osteoclast-mediated bone resorption with osteoblast-mediated bone (re)formation. Bone remodelling occurs most often in areas high in trabecular (cancellous) bone such as the vertebrae, whilst cortical bone comprises the majority of the skeleton. In early adult life, endosteal apposition and trabecular thickening are

crucial for optimum bone mass [5]. Trabecular bone is susceptible to deleterious effects of supraphysiological glucocorticoids, particularly during adolescence [6].

Furthermore, during puberty, there are significant differences between males and females with regard to bone growth, especially in terms of bone size and mass. The development of adequate bone strength and the ability to respond to skeletal stress requires optimisation of numerous biochemical and physical factors at a young age. Genetic polymorphisms in the vitamin D, IGF-1 and oestrogen receptor genes may influence bone phenotype [7]. Aside from these heritable influences, modifiable factors include diet, physical activity, lifestyle, BMI and hormonal status [8].

Assessment of Bone Health in Adolescence and Young Adulthood

Assessing areal BMD (aBMD) and fracture risk in clinical practice is a challenge in adolescence and young adulthood. In general, aBMD accelerates in puberty and peaks between the ages of 25 and 35 [9]. The acceleration is associated with the period of rapid growth velocity and increased stature. The "gold standard" technique involves using dual-energy X-ray absorptiometry (DXA) at skeletal sites including the lumbar spine, hip or occasionally the forearm [10]. For children and adolescents, "posterior-anterior" (PA) spine and "total body less head" (TBLH) are the preferred skeletal sites [11]. For children, adolescents, men under the age of 50 and premenopausal women, the *Z*-score is used to evaluate fracture risk, as expressed in the equation below. Manufacturer-specific reference data is available to calculate gender- and ethnicity-specific aBMD *Z*-scores.

$$Z\text{-score} = \frac{(\text{BMD}) - (\text{Age matched mean BMD})}{(\text{Standard deviation})}$$

*BMD values expressed as g/cm^2

Due to the technical limitation of DXA, which measures areal bone density (g/cm^2) rather than a true volumetric bone density (g/cm^3), anomalous results are seen when assessing children with reduced stature. This may be of particular relevance in the context of chronic rheumatic disease [12–14]. When assessing a BMD in AYA height, weight and pubertal stage should also be considered. The International Society for Clinical Densitometry (ISCD) [3] states that the term "low bone density or low bone mass" should be used "if the aBMD *Z*-score or BMC is ≤−2.0 S.D". A diagnosis of osteoporosis in younger men, premenopausal women and children should not be solely based on the bone density test result. However, BMD is a useful predictor of fracture risk in an adult; each one standard deviation (SD) decrease below the reference population correlates to approximately double the fracture risk.

ISCD consensus is that the term "osteoporosis" cannot be applied to AYAs without a clinically significant fracture history (see above), whilst the term "osteopenia" should not be used in paediatric DXA reports at all [3]. Additionally, due to the technical limitations of DXA, size adjustments should be made for young people with short stature or growth delay. Spine and TBLH BMC and aBMD should be adjusted. With regard to the spine, either the bone mineral apparent density BMAD or the height for age *Z*-score should be calculated. For the TBLH, the height for age *Z*-score should be used.

DXA reports should also include technical information on scanning hardware and software in addition to patient demographics, weight, height, medical history, bone age and Tanner stage. For AYA with an increased risk of clinically significant fractures, a DXA scan should be conducted as part of a comprehensive health assessment. This is especially the case if the young person may benefit from intervention to decrease their fracture risk or if the results of the scan may affect the management plan.

General Approaches to Optimise Management and Promote Bone Health

Screening

Routine screening of healthy young people for osteoporosis is not advised. However, those with RMD or any other condition associated with increased bone fragility should undergo baseline bone densitometry testing in addition to assessment of vitamin D status. BMD should be monitored at a minimum interval of 1 year [15]. Cimaz and Ward [16] outlined screening criteria for osteoporosis in children and adolescents with chronic rheumatic disorders. Screening criteria are outlined in Table 16.1 [17]. Vertebral fractures may be occult and represent a severe failure of bone strength. As many as 7% of children had vertebral fractures at baseline (within 30 days) on commencing glucocorticoids for rheumatic diseases, and 6% had incident fractures over 12 months follow-up in the Steroid-associated Osteoporosis in the Pediatric Population (STOPP) study [18, 19]. Thornton and colleagues [20] advocate measuring baseline BMD with surveillance every 2 years in adults with a background of JIA.

Glucocorticoid Therapy

Adults have increased fracture risk with doses as low as 2.5–7.5 mg of oral prednisolone per day [21]. Effects on BMD are correlated with the cumulative glucocorticoid dose. Alternate-day rotations have been found to maintain growth in adolescents; however, the effects of glucocorticoid therapy on bone may not be reduced [22, 23]. When long-term therapy is indicated or predicted, steroid-sparing medications such as azathioprine should be used where possible [24]. Exposure to glucocorticoids should be minimised with the use of lowest effective treatment dose and duration to prevent decreased bone accrual.

Table 16.1 Summary of Key Clinical Points

History	Underlying diagnoses Fractures (mechanism of injury, site, number, age; NB ≥2 long bone fractures by the age of 10; or ≥ 3 long bone fractures at any age up to 19 in presence of low BMD required for diagnosis of osteoporosis in young people) Glucocorticoid use (dose, duration) Bisphosphonate use
Investigations	DXA (low BMD indicated by size adjusted BMD or BMC ≤−2.0 S.D) Screening (suggested in the context of confirmed fractures, back pain; glucocorticoid therapy for more than 3 months, weight gain whilst on steroid treatment, active inflammation, and decreased *Z*-scores of the spine)
General advice and management	Glucocorticoids should be prescribed at the lowest effective treatment dose Steroid-sparing medications should be considered Physical activity – weight bearing where possible, low-force activities if disease is active Ensure optimal vitamin D status and calcium intake

Physical Activity

Physical activity during child and adolescent development is a determinant of peak bone mass via effects on mechanical loading and osteocyte function. Exercise is deemed an essential component of long-term management for young people with RMD. Weight-bearing physical activities such as walking, running, jumping and dancing are more effective at optimising bone health than swimming or cycling. However during periods of inflammation of their underlying disease, low-force activities are recommended [2]. Furthermore, resistance training may be introduced if tolerated [25]. Nichols and colleagues [26] found that resistance training in growing

subjects increased BMD at the femoral neck. High-impact activities that of short duration with multiple rests are most effective in promoting bone metabolism. These maximal force activities enhance bone integrity [27]. Conversely sedentary behaviour is associated with reduced BMD in the lower limbs as confirmed in a recent systematic review. The authors stated however that the review was limited by the quality of included studies with heterogeneous samples, study design, lack of longitudinal and clinical outcome data [28].

Vitamin D and Calcium Supplementation

Vitamin D deficiency is highly prevalent worldwide. Severe deficiency results in rickets and osteomalacia. Risk factors relate to reduced exposure to UVB light, low dietary intake and medication use (including glucocorticoids) [29]. There are also associations with chronic disease states. There is general agreement that calcium and vitamin D supplementation can improve skeletal outcomes as evidenced by epidemiological and a number of RCTs [29]. There is some controversy as to the optimum thresholds of vitamin D for the general population. The Institute of Medicine and UK National Osteoporosis Society advise deficiency as serum 25OHD <30 nmol/L, insufficiency between 30 and 50 nmol/L and sufficiency as >50 nmol/L. The Endocrine Society set higher thresholds of 50 nmol/L for deficiency and up to 72.5 nmol/L for insufficiency [30–32]. The latter advocate an induction dose of a vitamin D supplement (e.g. 300,000 IU total over 6–10 weeks) followed by maintenance dosing (e.g. 800 IU/day). The Institute of Medicine (IOM) endorses routine screening for vitamin D deficiency and higher recommended dietary allowances (RDA) for vitamin D supplements in AYAs with chronic rheumatic diseases treated with glucocorticoids. Others have suggested an RDA for adolescents with chronic inflammatory diseases should be at least twice the RDA of healthy controls [33]. It is clear that there is a need for high-quality vitamin D supplementation studies in adolescent and young adults to refine clinical protocols.

Diet and Nutrition

Clinicians are encouraged to promote healthy nutrition and enquire about the diet of their AYA patients with RMD. During health maintenance visits, specifically ask about the use of calcium and vitamin D supplements, dairy intake, non-dairy sources of calcium or vitamin D and fizzy drinks consumption. Increased intake of foods and drinks that contain calcium and vitamin D should be encouraged. Dairy products are the major source of calcium in the diet, whilst cereals and beverages may be fortified [29]. A recent cross-sectional study in healthy children reported positive correlations between dairy intake and BMD [34]. Randomised controlled trial evidence indicates that intake equivalent to two glasses of milk is sufficient for normal bone development between the ages of 8 and 16 years [35], with no additional benefit with increased intake. Reduced fat alternatives of dairy products such as reduced-fat milk and yoghurt also provide a good source of calcium. Misconceptions as to the caloric content of dairy products should be addressed and rectified in health maintenance visits. There is growing recognition that nutritional factors can act synergistically with exercise to impact on bone health [36].

Bisphosphonates

Bisphosphonates are widely used in osteoporosis in older adults. Their mechanism of action involves inhibition of osteoclast-mediated bone resorption. They are used to impact on BMD and fracture risk in children and adolescents with osteogenesis imperfecta (OI) [37]. A Cochrane review in this area confirmed that both oral and intravenous bisphosphonates increase BMD in such patients. The authors stated that further study to establish effects on quality of life and long-term safety and fracture reduction outcomes. As a rare disease, optimal outcomes would be expected if the patient is managed in a dedicated clinical service. Outside of this context, the use of bisphosphonates in children and AYAs remains controversial due to safety concerns.

These agents are not licensed in premenopausal women and are contraindicated in pregnancy. Many specialists advocate that bisphosphonates should be limited to men with low-trauma fractures and postmenopausal women [14]. However, there is recent evidence that young people receiving steroids for RMD may benefit from prophylactic treatment with bisphosphonates to increase lumbar spine BMD, although the effect on fracture risk is uncertain [38]. At present their role is limited to use in OI and other diseases associated with frequent fractures, vertebral collapse or critical pain.

Conclusions

Careful consideration of bone health in AYA with RMD is critical to ensure optimal long-term outcomes. Young people with RMD may be exposed to a number of risk factors for low BMD including active inflammation, glucocorticoid use and reduced activity. Osteoporosis in young people is defined by clinically significant fracture history and confirmed low BMD. Young people with RMD should undergo baseline assessment of BMD by DXA. Principles of management as outlined in Table 16.1 include minimising glucocorticoid exposure to that which is required for disease control, encouraging weight-bearing physical activity where appropriate and ensuring optimal vitamin D and calcium status.

Key Management Points

1. RMD is associated with a number of factors which result in reduced bone accrual. This may result in an increased fracture risk throughout life.
2. Bone health screening is recommended for AYA diagnosed with RMD. This should include assessment of BMD and vitamin D status.
3. Weight-bearing exercise and ensuring adequate vitamin D and calcium intake and use of steroid-sparing agents are useful preventative measures.

4. The use of bisphosphonates in AYA with RMD remains controversial. At present, there is evidence for their use in AYA diagnosed with OI or other conditions associated with fragility fractures.

References

1. Matkovic V, Heaney RP. Calcium balance during human growth: evidence for threshold behavior. Am J Clin Nutr. 1992;55:992–6.
2. Roth J, Bechtold S, Borte G, et al. Osteoporosis in juvenile idiopathic arthritis- a practical approach to diagnosis and therapy. Eur J Pediatr. 2007;166:775–84. https://doi.org/10.1007/s00431-007-0484-1.
3. Bishop N, Arundel P, Clark E, et al. Fracture prediction and the definition of osteoporosis in children and adolescents: the ISCD 2013 pediatric official positions. J Clin Densitom. 2014;17:275–80. https://doi.org/10.1016/j.jocd.2014.01.004.
4. Javaid MK, Cooper C. Prenatal and childhood influences on osteoporosis. Best Pract Res Clin Endocrinol Metab. 2002;16:349–67. https://doi.org/10.1053/beem.2002.0199.
5. Levine MA. Assessing bone health in children and adolescents. Indian J Endocrinol Metab. 2012;16:S205–12. https://doi.org/10.4103/2230-8210.104040.
6. Rousseau-Nepton I, Lang B, Rodd C. Long-term bone health in glucocorticoid-treated children with rheumatic diseases. Curr Rheumatol Rep. 2013;15:315. https://doi.org/10.1007/s11926-012-0315-x.
7. Mitchell JA, Cousminer DL, Zemel BS, et al. Genetics of pediatric bone strength. Bonekey Rep. 2016;5:823. https://doi.org/10.1038/bonekey.2016.50.
8. Kambas A, Leontsini D, Avloniti A, et al. Physical activity may be a potent regulator of bone turnover biomarkers in healthy girls during preadolescence. J Bone Miner Metab. 2017;35:598–607. https://doi.org/10.1007/s00774-016-0794-3.
9. Davies JH, Evans BAJ, Gregory JW. Bone mass acquisition in healthy children. Arch Dis Child. 2005;90:373–8. https://doi.org/10.1136/adc.2004.053553.

10. Lewiecki EM, Borges JLC. Bone density testing in clinical practice. Arq Bras Endocrinol Metabol. 2006;50:586–95. https://doi.org/10.1590/S0004-27302006000400004.
11. Gordon C, Leonard M, Zemel B. 2013 pediatric position development conference: executive summary and reflections. J Clin Densitom. 2014;17:219–24. https://doi.org/10.1016/j.jocd.2014.01.007.
12. Rauch F, Schoenau E. Changes in bone density during childhood and adolescence: an approach based on bone's biological organization. J Bone Miner Res. 2001;16:597–604. https://doi.org/10.1359/jbmr.2001.16.4.597.
13. Schoenau E, Saggese G, Peter F, et al. From bone biology to bone analysis. Horm Res. 2004;61:257–69. https://doi.org/10.1159/000076635.
14. Coulson EJ, Hanson HJM, Foster HE. What does an adult rheumatologist need to know about juvenile idiopathic arthritis? Rheumatology (Oxford). 2014;53:2155–66. https://doi.org/10.1093/rheumatology/keu257.
15. Golden NH, Abrams SA, Committee on Nutrition. Optimizing bone health in children and adolescents. Pediatrics. 2014;134:e1229–43. https://doi.org/10.1542/peds.2014-2173.
16. Cimaz R, Ward L. In: Petty RE, Laxer RM, Lindsley CB, Wedderburn L, editors. Textbook of pediatric rheumatology. 7th ed. Elsevier Health Sciences; 2016. p. 693–705.
17. Shiff NJ, Brant R, Guzman J, et al. Glucocorticoid-related changes in body mass index among children and adolescents with rheumatic diseases. Arthritis Care Res (Hoboken). 2013;65:113–21. https://doi.org/10.1002/acr.21785.
18. Huber AM, Gaboury I, Cabral DA, et al. Prevalent vertebral fractures among children initiating glucocorticoid therapy for the treatment of rheumatic disorders. Arthritis Care Res (Hoboken). 2010;62:516–26. https://doi.org/10.1002/acr.20171.
19. Rodd C, Lang B, Ramsay T, et al. Incident vertebral fractures among children with rheumatic disorders 12 months after glucocorticoid initiation: a national observational study. Arthritis Care Res (Hoboken). 2012;64:122–31. https://doi.org/10.1002/acr.20589.
20. Thornton J, Pye SR, O'Neill TW, et al. Bone health in adult men and women with a history of juvenile idiopathic arthritis. J Rheumatol. 2011;38:1689–93. https://doi.org/10.3899/jrheum.101232.

21. van Staa TP, Leufkens HG, Abenhaim L, et al. Oral corticosteroids and fracture risk: relationship to daily and cumulative doses. Rheumatology (Oxford). 2000;39:1383–9.
22. De Vries F, Bracke M, Leufkens HGM, et al. Fracture risk with intermittent high-dose oral glucocorticoid therapy. Arthritis Rheum. 2007;56:208–14. https://doi.org/10.1002/art.22294.
23. Rüegsegger P, Medici TC, Anliker M. Corticosteroid-induced bone loss. A longitudinal study of alternate day therapy in patients with bronchial asthma using quantitative computed tomography. Eur J Clin Pharmacol. 1983;25:615–20. https://doi.org/10.1007/BF00542348.
24. Devogelaer J-P. Glucocorticoid-induced osteoporosis: mechanisms and therapeutic approach. Rheum Dis Clin. 2017;32:733–57. https://doi.org/10.1016/j.rdc.2006.09.001.
25. Layne JE, Nelson ME. The effects of progressive resistance training on bone density: a review. Med Sci Sports Exerc. 1999;31:25–30.
26. Nichols DL, Sanborn CF, Love AM. Resistance training and bone mineral density in adolescent females. J Pediatr. 2017;139:494–500. https://doi.org/10.1067/mpd.2001.116698.
27. Boreham CAG, McKay HA. Physical activity in childhood and bone health. Br J Sports Med. 2011;45:877–9.
28. Koedijk JB, van Rijswijk J, Oranje WA, et al. Sedentary behaviour and bone health in children, adolescents and young adults: a systematic review. Osteoporos Int. 2017;28:2507–19. https://doi.org/10.1007/s00198-017-4076-2.
29. Hassan-Smith ZK, Hewison M, Gittoes NJ. Effect of Vitamin D deficiency in developed countries. Br Med Bull. 2017;122. https://doi.org/10.1093/bmb/ldx005.
30. Aspray TJ, Bowring C, Fraser W, et al. National osteoporosis society vitamin D guideline summary. Age Ageing. 2014;43:592–5. https://doi.org/10.1093/ageing/afu093.
31. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96:1911–30. https://doi.org/10.1210/jc.2011-0385.
32. Ross AC, Manson JE, Abrams SA, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab. 2011;96:53–8. https://doi.org/10.1210/jc.2010-2704.

33. Vojinovic J, Cimaz R. Vitamin D—update for the pediatric rheumatologists. Pediatr Rheumatol Online J. 2015;13:18. https://doi.org/10.1186/s12969-015-0017-9.
34. Sioen I, Michels N, Polfliet C, et al. The influence of dairy consumption, sedentary behaviour and physical activity on bone mass in Flemish children: a cross-sectional study. BMC Public Health. 2015;15:717. https://doi.org/10.1186/s12889-015-2077-7.
35. Vogel KA, Martin BR, McCabe LD, et al. The effect of dairy intake on bone mass and body composition in early pubertal girls and boys: a randomized controlled trial. Am J Clin Nutr. 2017;105:1214–29. https://doi.org/10.3945/ajcn.116.140418.
36. Willems HME, van den Heuvel EGHM, Schoemaker RJW, et al. Diet and exercise: a match made in bone. Curr Osteoporos Rep. 2017;15:555–63. https://doi.org/10.1007/s11914-017-0406-8.
37. Dwan K, Phillipi CA, Steiner RD, Basel D. Bisphosphonate therapy for osteogenesis imperfecta. Cochrane Database Syst Rev. 2016. https://doi.org/10.1002/14651858.CD005088.pub4.
38. Rooney M, Bishop N, Pilkington C, Beresford M, Clinch J, Satyapal R, Foster H, Gardner-Medwin J, McDonagh J, Wyatt S, on behalf of BSPAR. Prevention and treatment of steroid induced osteopenia in children and adolescents with rheumatic diseases: the pops study. PRES. 2016;15(Suppl 1):37.