Bone protective agents in children

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Abstract

Evaluation of bone health in childhood is important to identify children who have inadequate bone mineralisation and who may benefit from interventions to decrease their risk of osteoporosis and subsequent fracture. There are no bone protective agents that are licensed specifically for the prevention and treatment of osteoporosis in children. In this review we discuss the mechanism of action and use of bisphosphonates and other new and established bone protective agents in children.

Introduction

Healthy bone is metabolically active and undergoes continuous modelling and remodelling during childhood to maintain the balance between bone formation and bone resorption. The size and shape of the skeleton changes rapidly during modelling in childhood and adolescence and approximately 90% of bone mass is accrued during the first 18 years of life[1]. If this finely tuned process is disturbed, then osteoporosis can result. Osteoporosis is

defined as a skeletal disorder characterised by compromised bone strength and predisposing a person to an increased risk of fracture[2] and the importance of correctly diagnosing osteoporosis in children has been highlighted by the International Society for Clinical Densitometry (ISCD) [3]. The finding of one or more vertebral fracture is indicative of osteoporosis in the absence of local disease or high energy trauma. In the absence of vertebral compression, a diagnosis of osteoporosis is indicated by the presence of both a clinically significant fracture history and bone mineral density (BMD) z-score ≤ 2.0[3]. Skeletal fragility in children may be primary, due to an intrinsic bone abnormality (usually genetic in origin) or secondary as a result of an underlying medical condition or its treatment. Examples of conditions that can result in primary skeletal fragility include osteogenesis imperfecta, idiopathic juvenile osteoporosis and osteoporosis pseudoglioma syndrome. In most but not all cases, this skeletal fragility is associated with reduced bone mineral density and will also satisfy the ISCD definition of osteoporosis. Secondary osteoporosis is more common and has been reported in several chronic conditions in children. It may arise due to a combination of factors including the inflammatory process itself, sub-optimal nutrition, reduced lean body mass, decreased physical activity, delayed puberty or due to treatment for the underlying condition, particularly glucocorticoids (GC)[4].

Although there are several bone-protective agents currently used in adults with osteoporosis, none are licensed specifically for the prevention or treatment of osteoporosis in childhood. For children with chronic illness, treatment of the underlying condition should be the mainstay of osteoporosis prevention and treatment.

Bisphosphonates

In children, bone protective therapy has often been delivered using anti-resorptive therapy, and in particular, bisphosphonates (BPs). Because a detailed review of the use of BPs in every chronic childhood condition is not possible within this article, we will focus on three examples:

1. Osteogenesis Imperfecta (OI) - an example of primary skeletal fragility

2. Cerebral palsy- secondary osteoporosis related to immobility

3. Duchenne Muscular Dystrophy- secondary osteoporosis associated with GC use.

Bisphosphonates were the first pharmacological agent to be used in children with fragility fractures[5]. Although BPs have now been widely used in adults with a range of conditions, their use in children has been more limited, in part because of concerns regarding the effects on the growing skeleton[6]. They are so called because they have two phosphonate groups, which enable them to bind to bone. They reduce osteoclast activity primarily by promoting osteoclast apoptosis and so inhibiting bone resorption. BPs also reduce overall bone turnover because bone resorption is coupled to bone formation. However, because osteoblast activity at the periosteal surface is unaffected, an overall increase in bone formation in the growing skeleton and potential re-shaping of existing vertebral fractures can still occur, despite the low turnover state[7]. The newer, nitrogen-containing BPs (e.g. alendronate, zoledronate, risedronate and pamidronate) work by inhibiting the enzymes within osteoclasts that are involved in the farnesyl pyrophosphate synthase and mevalonate pathways, which are important for varying aspects of osteoclast function and also inducing osteoclast apoptosis[7]. Although they have poor oral absorption, BPs have an extremely long half-life; a study of pamidronate in paediatric OI found that 2 years after cessation of treatment, bone mineral content (BMC) z-scores remained above pre-treatment levels[8] and urinary excretion of pamidronate has been detected up to 8 years later[9]. This has potential implications for females of reproductive age as rodent studies have shown that BPs can cross the placenta and accumulate in the fetal skeleton causing decreased bone growth and deaths in the offspring[10]. There is, however, no evidence to date that prior BP exposure or even BP exposure during pregnancy is associated with reproductive toxicity[11].

1. Osteogenesis Imperfecta (OI)

BPs were first used in children to treat OI (the most common primary disorder of bone fragility) in 1987[12] and are now the mainstay of treatment in this condition. The main

effect of BPs in children with OI appears to be an increase in cortical bone width (a growth-dependent process that in turn improves mechanical strength) and trabecular number. The primary aim of BP treatment in OI is to reduce fracture frequency. Despite there being some evidence from a recent Cochrane review[13] that included 14 studies and 819 participants to show that either oral or cyclical intravenous (IV) BPs increase bone mineral density in children with OI, the authors were unable to demonstrate reliable evidence of improvements in overall clinical status (reduced pain, improved growth or functional mobility). Also, whilst several studies independently reported a decreased fracture risk, the review could not show a consistent reduction in fracture rate after use of either oral or IV BP. There is growing interest in the use of oral BPs in OI, particularly in those with milder phenotypes, as they may be more cost-effective and easier to use than IV alternatives[1415]. As yet, there does not appear to be sufficient evidence to favour oral agents above IV BPs in the acute treatment phase or in those with severe OI[16], although they may have a role during the maintenance phase.

2. Secondary osteoporosis

Although BPs are now used for bone protection in many other childhood conditions, much of the justification for their use in other chronic diseases has been extrapolated from evidence in OI. A systematic review has concluded that there is insufficient evidence to recommend BPs as standard therapy for secondary osteoporosis in children because the link between increasing BMD and reducing fracture risk remains unproven[17]. The efficacy of BP therapy on BMD appears to depend on the age at time of treatment and the amount of bone growth remaining. Generally, they appear to be a safe and effective therapy in cases of severe bone loss, although the long-term effect of inhibition of bone turnover remains unknown. BPs may also ameliorate pain in certain circumstances[18] but further work is needed to clarify this[5].

- **BPs in Cerebral Palsy (CP)**

CP is a heterogeneous group of non-progressive disorders of motor function and posture. Some patients with CP have a significant reduction in mobility and bone mass quickly diminishes without adequate bone loading. By 10 years of age, over 95% of those with non-ambulatory severe CP have osteopaenia[19] and fractures are 20% more likely in those who are non-ambulatory. First line measures should include optimising vitamin D and calcium levels and the encouragement of weight bearing activity. Vibration therapies have also been used, although there is only limited evidence of their effectiveness. A recent meta-analysis[20] assessing the effect of BPs on increasing BMD in children with CP found that the lumbar spine and femoral BMD z-scores were significantly higher after BP treatment compared with pre-treatment values, but only 1 randomised controlled trial (RCT) met the inclusion criteria. Furthermore, it remains unclear whether this translates to a reduction in fracture incidence, which is important when the annual fracture incidence in children with moderate to severe CP is 4%[21]. In addition, oromotor dysfunction and gastro-oesophageal reflux are often present in CP which may preclude the use of oral BPs.

- **BPs in Duchenne Muscular Dystrophy (DMD)**

Long term GC use has dramatically improved the disease course in DMD[22]. GC are normally commenced once muscle function begins to plateau, usually at about 5 years of age and are continued through to adulthood. Growth retardation[23] and fragility fractures are important problems in DMD; it is predicted that after 100 months of GC therapy, 75% of boys will sustain a vertebral fracture[24]. Although BPs are frequently used, there is no consensus regarding timing of initiation, drug regimen or cessation of treatment. Prophylactic BP in DMD in those receiving GC has been reported to be associated with increased survival[25]. Whilst BPs may be associated with an improvement in back pain and some vertebral re-shaping, provided that the child is still growing, they do not completely prevent the development of new vertebral fractures[26]. Recent data from trans-iliac biopsies in boys with DMD have also shown that whilst BPs appear to be effective early in GC-induced bone loss, long term use may further dampen remodeling[27]. A recent Cochrane review concluded that there was no strong evidence to guide the use of any

therapy to prevent or treat GC-induced osteoporosis in boys with DMD[28]. Therefore, before considering prophylactic BP use, the potential risks must be weighed up against the benefits including consideration of the potential adverse effects of BP therapy and a decision made regarding the most appropriate time to use them[29].

Adverse effects of bisphosphonate therapy

BPs are generally well tolerated in children[30], but as little is known of the long-term consequences of BP treatment, all patients should be regularly reviewed, looking in particular for evidence of adverse effects. An acute phase response to the initiation of IV BP therapy is very common, with short-lived fever and flu-like symptoms. Hypophosphataemia and hypocalcaemia can also occur[31]. Delayed bone healing after osteotomy in OI has also been described with BP use[32]. There are also three rare, but potentially serious adverse events that may be related to longer-term exposure to BPs:

a) Osteonecrosis of the jaw

BP-associated osteonecrosis of the jaw (ONJ) is defined as, "an area of exposed bone in the maxillofacial region that does not heal within 8 weeks, in a patient who is receiving or has been exposed to a BP and has not had radiation therapy to the craniofacial region[33]". ONJ appears to be more common in adults using IV BPs[34], and it has not yet been reported in a child[35]. Most cases have been documented in those receiving doses higher than prescribed for osteoporosis (e.g. for malignancy) and in patients on therapy for more than two years. Experts have suggested doing any invasive dental procedures before starting treatment or suspending therapy for three or more months before and after such procedures, where possible[36], although there is no evidence to support these recommendations.

b) Atypical femoral fractures

Although atypical sub-trochanteric femur fractures (AFF) are very rare and account for less than 1% of all hip/ femoral fractures, they have been predominantly reported in patients taking BPs[37] and have recently been associated with BP use in a child[38]. Because BPs act by reducing bone turnover, it is possible that by preventing remodelling and effectively

‘freezing’ the skeleton, they allow tiny cracks to form and stress fractures to develop. AFFs occur at sites of high tensional stress, such as the lateral cortex of the proximal femoral shaft. It is also thought that those taking concomitant GCs in addition to BPs or with a genetic disposition to fracture may have a further increased risk. A large Swedish observational study of femoral fractures in post-menopausal women[39] showed that fracture rate decreased rapidly after drug withdrawal, therefore intermittent use may be favourable and a BP ‘holiday’ in children on long term BPs could be considered.

c) Iatrogenic osteopetrosis

In 2003, the first case of BP-induced osteopetrosis (or marble bone disease) was described in a 12-year-old boy who had received pamidronate infusions for the previous 3 years for idiopathic bone pain and osteopaenia[40]. Abnormal over-suppression of bone remodelling (with a histological absence of osteoclasts on bone surfaces) was still present when he was followed up 7 years after cessation of BP.

Vitamin D and calcium

Vitamin D is essential for skeletal health and regulates calcium absorption[41]. Vitamin D deficiency may be associated with decreased BMC and increased risk of rickets[42]. Children with chronic diseases are more prone to vitamin D deficiency for a variety of reasons including malabsorption, limited sunlight exposure, nutritional restrictions and the use of medications such as anti-convulsants and GCs, therefore prevention of vitamin D deficiency should be routinely considered in those with chronic illnesses. The mean dietary intake of vitamin D in children may only be about 100IU/day[43] and therefore in the UK, the Scientific Advisory Committee for Nutrition has recommended a reference nutrient intake (RNI) of 400IU per day for children.[43] This requirement may be even higher in those with chronic illnesses[44]. Adequate dietary calcium to meet the RNI should also be advised and supplementation considered if this is unlikely to be reached. There is no clear evidence that calcium supplementation in excess of the RNI has additional benefits on bone density whilst there are significant associated risks of excessive total calcium

intake. Vitamin D and calcium levels should be optimized prior to the initiation of BP therapy to prevent BP-induced hypocalcaemia and maximize efficacy.

Growth Hormone (GH) and Insulin-like growth factor (IGF-1)

Whilst there is ample evidence that the GH-IGF-1 pathway has direct effects on bone mass and strength in experimental models[45] the effect of recombinant human GH (rhGH) on bone health in children is debatable[46]. In addition to a direct effect on osteoblast activity, it is possible that the anabolic effects of rhGH may also be mediated through an effect on lean mass[47], alterations in PTH sensitivity[48] or even modulation of the 11 beta hydroxysteroid dehydrogenase shuttle, which is responsible for the inactivation of cortisol to cortisone[49]. Given that both rhGH and rhIGF-1 are licensed for use in children with growth disorders and in light of data from children and adults with chronic inflammation, there is potential for these anabolic agents to improve growth potential, muscle strength and bone mass in many cases of primary and secondary osteoporosis. However, before using these pharmacological agents for this purpose, an improved understanding of their effects on linear growth and bone mass, and the underlying mechanisms through which they exert their effects on bone, is imperative.

Recombinant parathyroid hormone (PTH)

Teriparatide is a form of recombinant human PTH and is unique because unlike BPs, it stimulates new bone formation. It is approved for use in adults with osteoporosis and over half a million adults with severe osteoporosis have received this drug[50]. Furthermore, its anabolic effect on bone has opened up the possibility of using it in combination or sequentially with anti-resorptive agents such BPs[51]. However experimental studies have shown that almost half of the rats exposed to the highest doses developed osteosarcoma[52]. Despite there being many differences which make humans less susceptible than rats[53], this risk is still of particular concern to the paediatric and adolescent population where osteosarcoma is most prevalent. However, over the last decade, there have been increasing

reports of the use of recombinant PTH for intractable hypocalcaemia associated with hypoparathyroidism in children[54].

Sex steroids

Growth and pubertal development are often impaired in chronic disease and the pubertal process and associated GH surge are vital to increase bone size and bone mineral accrual. Androgen deficiency is a recognised risk factor for osteoporosis and fracture and evidence suggests that early initiation of androgen therapy is associated with improved BMD in adults[55]. However, precocious puberty or treatment with high doses of either oestrogen or testosterone can paradoxically cause premature fusion of the epiphyses and a subsequent reduction in final height[56]. Oxandrolone, an anabolic steroid that is only weakly androgenic and does not aromatise, has been studied in children with severe burns. It has been reported to increase bone mass[57] but is often not readily available.. Physiological oestrogen replacement given transdermally, (so not to inhibit IGF-1 production) alongside cyclical progesterone has also been shown to increase bone mineral accrual in teenagers with anorexia[58] and the American College of Sports Medicine recommends that oral contraceptives be considered in amenorrheic athletes over 16 years of age if BMD is declining despite sufficient weight gain[59].

Alternative agents for consideration

- **RANKL inhibitors**

Denosumab is a monoclonal antibody to the receptor activator of nuclear factor-kB ligand (RANKL), a key mediator of osteoclast activity. It is given subcutaneously and targets the RANKL, (Figure 1), thus inhibiting osteoclast-mediated bone resorption and increasing BMD. There is extensive data to show its efficacy in postmenopausal osteoporosis[60] and it has also been used in a group of children with OI[61]. However, its efficacy and side-effect profile is not clearly understood in children and there may be an increased risk of calcium dysregulation, so further studies are warranted[62].

- **Sclerostin antibody**

Sclerostin is produced by osteocytes (Figure 1) and probably acts as antagonist of the Wnt signaling pathway to inhibit bone formation, although the exact mechanism remains unclear[63]. Neutralisation of sclerostin using monoclonal antibodies in a mouse model of OI, resulted in improved bone mass and reduced long bone fragility[64] and early clinical studies in adults have shown similar results[65]. Sclerostin antibodies have also been used to prevent GC-induced trabecular and cortical bone loss in mouse models of GC-induced osteoporosis[66].

- **Cathepsin K inhibitors**

Cathepsin K is a cysteine protease that is highly expressed by osteoclasts and degrades type 1 collagen[67], (Figure 1). Cathepsin K inhibitors are thought to reduce bone resorption whilst also increasing the number of cells of osteoclast lineage and therefore not suppressing bone formation to the same degree as BPs. Cathepsin K inhibitors such as odanacatib have shown promising efficacy data[68], but an increased risk of atrial fibrillation and stroke in adult phase 3 trials has meant that marketing of these agents has now been halted.

Conclusion

Alongside consideration of pharmacological approaches to maximise bone accrual, optimising nutritional factors and encouraging activity, within the constraints of the disease process are also important. Timely pubertal assessment should be performed in those with chronic disease and where appropriate, puberty induced. Optimal management includes regular screening to identify those at risk of fracture and then aiming to treat earlier, rather than waiting for fragility fractures to occur, particularly in those who have little potential for spontaneous recovery.

There is still limited evidence for the use of bone protective agents in most childhood

conditions and although BPs are commonly used, evidence for their efficacy remains limited. Most studies are small and only have limited follow up and there is no consensus on the length of BP treatment regimens and dosage in children. Long term safety needs to be assessed by large scale trials with extended follow-up; the rarity of many the conditions under study may necessitate international collaborative efforts. Many studies also use change in BMD as primary outcome but the extent of correlation with this and subsequent fracture rate remain unclear and age-appropriate reference ranges are not commonly available for very young children. As anti-resorptives result in a low bone-turnover state with an associated reduction in bone formation and hence reduced overall bone remodeling it would clearly be advantageous to find safe and effective anabolic agents to use in the paediatric population, either alone or in combination and this must remain a research priority.

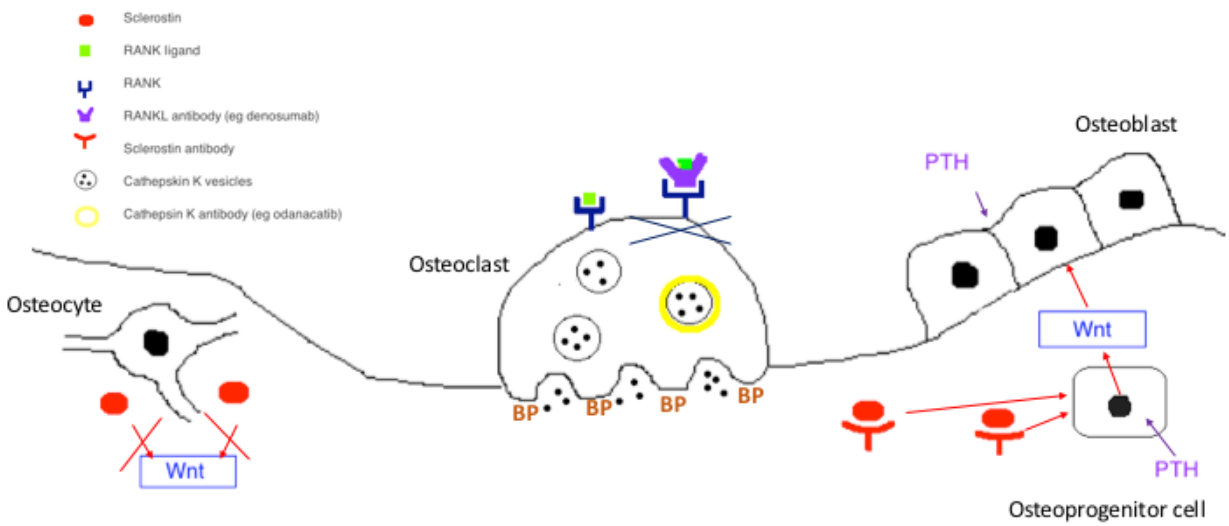

Figure 1 Schematic diagram to show the mechanism of action of bone protective agents. Bisphosphonates (BP) act at the osteoclast to reduce bone resorption. Recombinant parathyroid hormone (PTH) eg teriparatide promotes bone formation. Sclerostin is secreted by osteocytes; sclerostin antibody binds to circulating sclerostin and so enables Wnt signaling of osteoprogenitors and osteoblasts. RANKL antibodies (eg denosumab) target the RANK ligand and prevent bone resorption at the osteoclast. Cathepsin K inhibitors (eg odanacatib) prevent release of enzymes that degrade collagen at the osteoclast.

Table 1. Examples of conditions associated with skeletal fragility and/or osteoporosis in children

Primary: the result of a specific condition (usually genetic in origin) causing increased skeletal fragility	**Secondary:** the result of a medical condition or medication used to treat it (children with chronic illness often have multiple risk factors)
• Osteogenesis Imperfecta • Idiopathic juvenile osteoporosis • Osteoporosis pseudoglioma syndrome	• Medications e.g. glucocorticoids used in asthma, arthritis, Duchenne Muscular Dystrophy • Nutritional problems e.g. Crohns, Anorexia nervosa • Reduced mobility e.g. Cerebral palsy and neuromuscular conditions • Conditions causing delayed puberty or insufficient production of sex hormones • Chronic illness such as thyroid disease, leukaemia

1 **Table 2. Drugs that are used in children and their mechanism of action**

Agents that have been used in clinical practice in children and may have a beneficial effect on bone health:	**Main Mechanism of action**
Vitamin D and calcium	Vitamin D regulates calcium absorption which is main mineral component of bone
Bisphosphonates	Reduce osteoclast activity so inhibiting bone resorption. Also reduce overall bone turnover as resorption is coupled to formation
Sex steroids	Oestrogen decreases osteoclast number and activity so reducing resorption. Also increases GH levels, which is anabolic to bone
GH	Stimulates osteoblast and pre-osteoblast proliferation directly and also indirectly through IGF-1 to increase bone formation. Also stimulates osteoclast differentiation, so overall increases bone remodeling
IGF-1	Enhances Wnt-dependent activity and increases both osteoblast proliferation and osteoblast differentiation
New therapies that are not in clinical practice in children but may have a beneficial effect on bone health	
Cathepsin K inhibitors	Prevents type 1 collagen degradation and reduces bone resorption
RANKL inhibitors	Inhibits osteoclast mediated bone resorption
Sclerostin antibodies	Prevents antagonism of Wnt signalling pathway so promotes bone formation
Teriparatide (Recombinant parathyroid hormone)	Stimulates new bone formation when given intermittently, but is associated with increased risk of sarcoma in growing skeleton

References

1 Bachrach LK. Acquisition of optimal bone mass in childhood and adolescence. *Trends Endocrinol Metab*;**12**:22–8.

2 NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. Osteoporosis prevention, diagnosis, and therapy. *JAMA* 2001;**285**:785–95.

3 Crabtree NJ, Arabi A, Bachrach LK, *et al.* Dual-Energy X-Ray Absorptiometry Interpretation and Reporting in Children and Adolescents: The Revised 2013 ISCD Pediatric Official Positions. *J Clin Densitom* 2014;**17**:225–42.

4 Joseph S, McCarrison S, Wong SC. Skeletal Fragility in Children with Chronic Disease. *Horm Res Paediatr* 2016;**86**:71–82.

5 Glorieux FH, Bishop NJ, Plotkin H, *et al.* Cyclic administration of pamidronate in children with severe osteogenesis imperfecta. *N Engl J Med* 1998;**339**:947–52.

6 Brumsen C, Hamdy NA, Papapoulos SE. Long-term effects of bisphosphonates on the growing skeleton. Studies of young patients with severe osteoporosis. *Med* 1997;**76**:266–83.

7 Russell RG, Watts NB, Ebetino FH, *et al.* Mechanisms of action of bisphosphonates: similarities and differences and their potential influence on clinical efficacy. *Osteoporos Int* 2008;**19**:733–59.

8 Rauch F, Munns C, Land C, *et al.* Pamidronate in children and adolescents with osteogenesis imperfecta: effect of treatment discontinuation. *J Clin Endocrinol Metab* 2006;**91**:1268–74.

9 Papapoulos SE, Cremers SC. Prolonged bisphosphonate release after treatment in children. *N Engl J Med* 2007;**356**:1075–6.

10 Graepel P, Bentley P, Fritz H, *et al.* Reproduction toxicity studies with pamidronate. *Arzneimittelforschung* 1992;**42**:654–67.

11 Green SB, Pappas AL. Effects of maternal bisphosphonate use on fetal and neonatal

outcomes. *Am J Heal Pharm* 2014;**71**:2029–36.

12 Devogelaer JP, Malghem J, Maldague B, *et al.* Radiological manifestations of bisphosphonate treatment with APD in a child suffering from osteogenesis imperfecta. *Skeletal Radiol* 1987;**16**:360–3.

13 Dwan K, Phillipi CA, Steiner RD, *et al.* Bisphosphonate therapy for osteogenesis imperfecta. *Cochrane Database Syst Rev* 2014;**7**:Cd005088.

14 Unal E, Abaci A, Bober E, *et al.* Efficacy and safety of oral alendronate treatment in children and adolescents with osteoporosis. *J Pediatr Endocrinol Metab* 2006;**19**:523–8.

15 Bishop N, Adami S, Ahmed SF, *et al.* Risedronate in children with osteogenesis imperfecta: a randomised, double-blind, placebo-controlled trial. *Lancet* 2013;**382**:1424–32.

16 Ward LM, Rauch F, Whyte MP, *et al.* Alendronate for the Treatment of Pediatric Osteogenesis Imperfecta: A Randomized Placebo-Controlled Study. *J Clin Endocrinol Metab* 2011;**96**:355–64.

17 Ward L, Tricco AC, Phuong P, *et al.* Bisphosphonate therapy for children and adolescents with secondary osteoporosis. *Cochrane Database Syst Rev* 2007;:Cd005324.

18 Aström E, Söderhäll S. Beneficial effect of long term intravenous bisphosphonate treatment of osteogenesis imperfecta. *Arch Dis Child* 2002;**86**:356–64.

19 Henderson RC, Lark RK, Kecskemethy HH, *et al.* Bisphosphonates to treat osteopenia in children with quadriplegic cerebral palsy: a randomized, placebo-controlled clinical trial. *J Pediatr* 2002;**141**:644–51.

20 Kim MJ, Kim S-N, Lee I-S, *et al.* Effects of bisphosphonates to treat osteoporosis in children with cerebral palsy: a meta-analysis. *J Pediatr Endocrinol Metab* 2015;**28**:1343–50.

21 Mergler S, Evenhuis HM, Boot AM, *et al.* Epidemiology of low bone mineral density and fractures in children with severe cerebral palsy: a systematic review. *Dev Med*

Child Neurol 2009;**51**:773–8.

22 Moxley 3rd RT, Pandya S, Ciafaloni E, *et al.* Change in natural history of Duchenne muscular dystrophy with long-term corticosteroid treatment: implications for management. *J Child Neurol* 2010;**25**:1116–29.

23 Wood CL, Straub V, Guglieri M, *et al.* Short stature and pubertal delay in Duchenne muscular dystrophy. *Arch Dis Child* 2015;**101**:101–6.

24 Bothwell JE, Gordon KE, Dooley JM, *et al.* Vertebral fractures in boys with Duchenne muscular dystrophy. *Clin Pediatr* 2003;**42**:353–6.

25 Gordon KE, Dooley JM, Sheppard KM, *et al.* Impact of bisphosphonates on survival for patients with Duchenne muscular dystrophy. *Pediatrics* 2011;**127**:e353-8.

26 Srinivasan R, Rawlings D, Wood CL, *et al.* Prophylactic oral bisphosphonate therapy in duchenne muscular dystrophy. *Muscle Nerve* 2016;**54**:79–85.

27 Misof BM, Roschger P, Mcmillan HJ, *et al.* Histomorphometry and Bone Matrix Mineralization Before and After Bisphosphonate Treatment in Boys With Duchenne Muscular Dystrophy : A Paired Transiliac Biopsy Study. *J Bone Min Res* 2016;**31**:1–10.

28 Bell JM, Shields MD, Watters J, *et al.* Interventions to prevent and treat corticosteroid-induced osteoporosis and prevent osteoporotic fractures in Duchenne muscular dystrophy. *Cochrane database Syst Rev* 2017;**1**:CD010899.

29 Wood CL, Marini Bettolo C, Bushby K, *et al.* Bisphosphonate use in Duchenne Muscular Dystrophy – why, when to start and when to stop? *Expert Opin Orphan Drugs* 2016;**4**:407–16.

30 Batch JA, Couper JJ, Rodda C, *et al.* Use of bisphosphonate therapy for osteoporosis in childhood and adolescence. *J Paediatr Child Health* 2003;**39**:88–92.

31 George S, Weber DR, Kaplan P, *et al.* Short-Term Safety of Zoledronic Acid in Young Patients With Bone Disorders: An Extensive Institutional Experience. *J Clin Endocrinol Metab* 2015;**100**:4163–71.

32 Munns CF, Rauch F, Zeitlin L, *et al.* Delayed Osteotomy but Not Fracture Healing in

Pediatric Osteogenesis Imperfecta Patients Receiving Pamidronate. *J Bone Miner Res* 2004;**19**:1779–86.

33 Khosla S, Burr D, Cauley J, *et al.* Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. *J Bone Min Res* 2007;**22**:1479–91.

34 Silverman SL, Landesberg R. Osteonecrosis of the jaw and the role of bisphosphonates: a critical review. *Am J Med* 2009;**122**:S33-45.

35 Hennedige AA, Jayasinghe J, Khajeh J, *et al.* Systematic Review on the Incidence of Bisphosphonate Related Osteonecrosis of the Jaw in Children Diagnosed with Osteogenesis Imperfecta. *J Oral Maxillofac Res* 2013;**4**:e1.

36 Malden N, Beltes C, Lopes V. Dental extractions and bisphosphonates: the assessment, consent and management, a proposed algorithm. *Br Dent J* 2009;**206**:93–8.

37 Girgis CM, Sher D, Seibel MJ. Atypical femoral fractures and bisphosphonate use. *N Engl J Med* 2010;**362**:1848–9.

38 van de Laarschot DM, Zillikens MC. Atypical femur fracture in an adolescent boy treated with bisphosphonates for X-linked osteoporosis based on PLS3 mutation. *Bone* 2016;**91**:148–51.

39 Schilcher J, Koeppen V, Aspenberg P, *et al.* Risk of atypical femoral fracture during and after bisphosphonate use. *N Engl J Med* 2014;**371**:974–6.

40 Whyte MP, Wenkert D, Clements KL, *et al.* Bisphosphonate-Induced Osteopetrosis. *N Engl J Med* 2003;**349**:457–63.

41 Tomlinson PB, Joseph C, Angioi M. Effects of vitamin D supplementation on upper and lower body muscle strength levels in healthy individuals. A systematic review with meta-analysis. *J Sci Med Sport* Published Online First: 2014.

42 Pearce SHS, Cheetham TD. Diagnosis and management of vitamin D deficiency. *BMJ* 2010;**340**:b5664.

43 SACN. Vitamin D and Health report. 2016.

44 Wood CL, Cheetham TD. Vitamin D: increasing supplement use among at-risk groups (NICE guideline PH56). *Arch Dis Child - Educ Pract Ed* 2016;**101**:43–5.

45 Ahmed SF, Farquharson C. The effect of GH and IGF1 on linear growth and skeletal development and their modulation by SOCS proteins. *J Endocrinol* 2010;**206**:249–59.

46 Hogler W, Shaw N. Childhood growth hormone deficiency, bone density, structures and fractures: scrutinizing the evidence. *Clin Endocrinol (Oxf)* 2010;**72**:281–9.

47 Schweizer R, Martin DD, Schönau E, *et al.* Muscle Function Improves during Growth Hormone Therapy in Short Children Born Small for Gestational Age: Results of a Peripheral Quantitative Computed Tomography Study on Body Composition. *J Clin Endocrinol Metab* 2008;**93**:2978–83.

48 White HD, Ahmad AM, Durham BH, *et al.* PTH Circadian Rhythm and PTH Target-Organ Sensitivity Is Altered in Patients With Adult Growth Hormone Deficiency With Low BMD. *J Bone Miner Res* 2007;**22**:1798–807.

49 Stewart PM, Toogood AA, Tomlinson JW. Growth hormone, insulin-like growth factor-I and the cortisol-cortisone shuttle. *Horm Res* 2001;**56 Suppl 1**:1–6.

50 Hodsman AB, Bauer DC, Dempster DW, *et al.* Parathyroid Hormone and Teriparatide for the Treatment of Osteoporosis: A Review of the Evidence and Suggested Guidelines for Its Use. *Endocr Rev* 2005;**26**:688–703.

51 Whitmarsh T, Treece GM, Gee AH, *et al.* Mapping Bone Changes at the Proximal Femoral Cortex of Postmenopausal Women in Response to Alendronate and Teriparatide Alone, Combined or Sequentially. *J Bone Miner Res* 2015;**30**:1309–18.

52 Vahle JL, Sato M, Long GG, *et al.* Skeletal Changes in Rats Given Daily Subcutaneous Injections of Recombinant Human Parathyroid Hormone (1-34) for 2 Years and Relevance to Human Safety. *Toxicol Pathol* 2002;**30**:312–21.

53 Subbiah V, Madsen VS, Raymond AK, *et al.* Of mice and men: divergent risks of teriparatide-induced osteosarcoma. *Osteoporos Int* 2010;**21**:1041–5.

54 Winer KK, Zhang B, Shrader JA, *et al.* Synthetic human parathyroid hormone 1-34 replacement therapy: a randomized crossover trial comparing pump versus injections

in the treatment of chronic hypoparathyroidism. *J Clin Endocrinol Metab* 2012;**97**:391–9.

55 Katznelson L, Finkelstein JS, Schoenfeld DA, *et al.* Increase in bone density and lean body mass during testosterone administration in men with acquired hypogonadism. *J Clin Endocrinol Metab* 1996;**81**:4358–65.

56 Crawford JD. Treatment of Tall Girls With Estrogen. *Pediatrics* 1978;**62**.

57 Reeves PT, Herndon DN, Tanksley JD, *et al.* Five-year outcomes after long-term oxandrolone adminstration in severely burned children: a randomized clinical trial. *Shock* 2016;**45**:367–74.

58 Misra M, Katzman D, Miller KK, *et al.* Physiologic estrogen replacement increases bone density in adolescent girls with anorexia nervosa. *J Bone Miner Res* 2011;**26**:2430–8.

59 Nattiv A, Loucks AB, Manore MM, *et al.* The Female Athlete Triad. *Med Sci Sport Exerc* 2007;**39**:1867–82.

60 Cummings SR, Martin JS, McClung MR, *et al.* Denosumab for Prevention of Fractures in Postmenopausal Women with Osteoporosis. *N Engl J Med* 2009;**361**:756–65.

61 Hoyer-Kuhn H, Netzer C, Koerber F, *et al.* Two years' experience with denosumab for children with Osteogenesis imperfecta type VI. *Orphanet J Rare Dis* 2014;**9**:145.

62 Setsu N, Kobayashi E, Asano N, *et al.* Severe hypercalcemia following denosumab treatment in a juvenile patient. *J Bone Miner Metab* 2016;**34**:118–22.

63 MacNabb C, Patton D, Hayes JS. Sclerostin Antibody Therapy for the Treatment of Osteoporosis: Clinical Prospects and Challenges. *J Osteoporos* 2016;:6217286.

64 Sinder BP, Eddy MM, Ominsky MS, *et al.* Sclerostin antibody improves skeletal parameters in a Brtl/+ mouse model of osteogenesis imperfecta. *J Bone Miner Res* 2013;**28**:73–80.

65 Recker RR, Benson CT, Matsumoto T, *et al.* A Randomized, Double-Blind Phase 2 Clinical Trial of Blosozumab, a Sclerostin Antibody, in Postmenopausal Women with Low Bone Mineral Density. *J Bone Miner Res* 2015;**30**:216–24.

66 Yao W, Dai W, Jiang L, *et al.* Sclerostin-antibody treatment of glucocorticoid-induced osteoporosis maintained bone mass and strength. *Osteoporos Int* 2016;**27**:283–94.

67 Duong LT, Leung AT, Langdahl B. Cathepsin K Inhibition: A New Mechanism for the Treatment of Osteoporosis. *Calcif Tissue Int* 2016;**98**:381–97.

68 Bone HG, Dempster DW, Eisman JA, *et al.* Odanacatib for the treatment of postmenopausal osteoporosis: development history and design and participant characteristics of LOFT, the Long-Term Odanacatib Fracture Trial. *Osteoporos Int* 2015;**26**:699–712.