Review

Osteoporosis in paediatric patients with spina bifida

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The prevalence and morbidity associated with osteoporosis and fractures in patients with spina bifida (SB) highlight the importance of osteoporosis prevention and treatment in early childhood; however, the issue has received little attention. The method for the selection of appropriate patients for drug treatment has not been clarified.

Objective: To review the literature concerning fracture risks and low bone density in paediatric patients with SB. We looked for studies describing state-of-the-art treatments and for prevention of secondary osteoporosis.

Methods: Articles were identified through a search in the electronic database (PUBMED) supplemented with reviews of the reference lists of selected papers. The main outcome measures were incidence of fractures and risk factors for fracture, an association between bone mineral density (BMD) and occurrence of fracture, risk factors of low BMD, and effects of pharmacological and non-pharmacological treatments on BMD and on the incidence of fractures. We considered as a secondary outcome the occurrence of fractures in relation to the mechanism of injury.

Results: Results indicated that patients with SB are at increased risk for fractures and low BMD. Risk factors that may predispose patients to fractures include higher levels of neurological involvement, non-ambulatory status, physical inactivity, hypercalciuria, higher body fat levels, contractures, and a previous spontaneous fracture. Limitations were observed in the number and quality of studies concerning osteoporosis prevention and treatment in paediatric patients with SB. The safety and efficiency of drugs to treat osteoporosis in adults have not been evaluated satisfactorily in children with SB.

Keywords: Spina bifida, Spinal dysraphism, Myelomeningocele, Disability, Densitometry, Bisphosphonates, Bone mineral density, Fracture, Osteoporosis, Hypercalciuria, Paraplegia, Treatment, Prevention, Child, Adolescence

Introduction

In congenital paraplegia caused by myelomeningocele (MMC), the body lacks the usual axial load on the legs, which have decreased sensation and muscular activity.[1] These deficits can impair ambulation and lead to physical inactivity and osteoporosis,[2,3] which predisposes the patient to fragility fractures. In patients who are already disabled and subject to frequent surgical interventions, osteoporosis-related fractures result in a vicious cycle in which further immobilization heightens the risk of multiple fractures.[2–7] In childhood and adolescence, the formation of bone prevails;[8] consequently, childhood and adolescence constitute critical periods for the foundation of a lifetime of bone health. Failure to achieve peak bone mass has been linked to an increased risk of osteoporosis and fracture in adulthood. Therefore, preventing osteoporosis and identifying and treating children with established osteoporosis could be an important strategy for achieving peak bone mass in patients with spina bifida (SB).[9]

Because fractures are a widespread problem in this population, determining which risk factors will identify the individuals more likely to suffer fractures is an extremely important task that is critical for the subsequent determination for intervention.

We reviewed the literature regarding the prevention and treatment of osteoporosis in patients with SB and discuss which risk factors for fractures and low bone mineral density (BMD) are associated with SB in paediatric populations.

Study design and methods

To examine the current scientific recommendations regarding osteoporosis and the prevention of fractures in paediatric patients with SB, we performed a

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systematic electronic search of papers published from 1970 through 2011 in a major electronic database (MEDLINE/PUBMED) focusing on three domains: (1) the incidence and risk factors of fractures, (2) BMD, and (3) the prevention and treatment of osteoporosis. The last search was performed on 10 June 2011. Promising reports were identified through the evaluation of abstracts and MeSH terms.

Findings were supplemented by reviewing the reference lists of selected papers.

Only original studies in humans were selected. For BMD and treatment studies, selected studies included heterogeneous data and patients with SB. For incidence and risk factors of fractures excluded studies included patients without SB. To examine the incidence and risk factors of fractures and BMD studies, case reports were eliminated. For BMD studies, studies with medical interventions were excluded. Articles were excluded if the full article was not freely available in PUBMED or in Portuguese libraries or if studies only included adults.

There were three main outcomes of interest: (1) the incidence of fractures and risk factors for fractures, (2) an association among BMD and the occurrence of fractures and risk factors of low BMD, and (3) the effects of pharmacological and non-pharmacological treatments on BMD and the incidence of fractures. A secondary outcome was the occurrence of fractures in relation to the mechanism of injury. The searches were restricted to articles published in English. Keywords and search criteria used to identify studies on the incidence and risk of fractures were performed in the following format: 'Spinal Dysraphism,' OR 'Meningomyelocele,' AND 'Fracture'. We restricted our search to articles in which 'Fracture' was a MeSH Major Topic.

Next, we searched using the keywords 'Spinal Dysraphism,' 'Meningomyelocele,' and 'Myelomeningocele,' using OR as the combination term, and we combined these terms with 'Bone density' using AND as the combination term. Finally, we used the following searches in our review to analyse pharmacological and non-pharmacological treatments:

- Spinal Dysraphism
- Meningomyelocele
- Myelomeningocele
- Bone density
- Prevention
  'Myelomeningocele'[All Fields] OR 'Spina bifida'[All Fields] OR 'Meningomyelocele'[All Fields] AND 'Bone density'[All Fields] AND 'Prevention'[All Fields]
- Walking
- Bone and Bones
- (('Spinal Dysraphism'[Mesh] OR 'Meningomyelocele'[Mesh]) AND 'Walking'[Mesh]) AND 'Bone and Bones'[Mesh]
- Bone
- Osteoporosis
- 'Myelomeningocele'[All Fields] OR 'Spina bifida'[All Fields] OR 'Meningomyelocele'[All Fields] AND ('Osteoporosis'[All Fields] OR ('Bone'[All Fields] AND 'Walking'[All Fields])) AND ('humans'[MeSH Terms] AND English[lang] AND ('1970/01/01'[PDAT]: '2011/06/10'[PDAT]))
- Vibration
- ('Spinal Dysraphism'[Mesh] OR 'Meningomyelocele'[Mesh]) AND 'Vibration'[Mesh]
- Standing
- Vibrating platform
- 'Myelomeningocele'[All Fields] OR 'Spina bifida'[All Fields] OR 'Meningomyelocele'[All Fields] AND ('Osteoporosis'[All Fields] OR 'Bone density'[All Fields]) AND ('Standing'[All Fields] OR 'Vibrating platform'[All Fields] OR 'Vibration'[All Fields])
- Calcium
- ('Spinal Dysraphism'[Mesh] OR 'Meningomyelocele'[Mesh]) AND 'Calcium'[Mesh]
- Vitamin D
- ('Spinal Dysraphism'[Mesh] OR 'Meningomyelocele'[Mesh]) AND 'Vitamin D'[Mesh]
- Diphosphonates
- (('Spinal Dysraphism'[Mesh]) OR 'Meningomyelocele'[Mesh]) AND 'Diphosphonates'[Mesh]
- Treatment
- 'Myelomeningocele'[All Fields] OR 'Spina bifida'[All Fields] OR 'Meningomyelocele'[All Fields] AND ('Bone density'[All Fields] OR Osteoporosis [All Fields]) AND 'Treatment'[All Fields]
- 'Spina bifida'[All Fields] OR 'Myelomeningocele'[All Fields] OR 'Meningomyelocele'[All Fields] AND ('Calcium'[All Fields] OR 'Vitamin D'[All Fields] OR 'Diphosphonates'[All Fields]) AND ('1970/01/01'[PDAT] : '2011/06/10'[PDAT]) AND ('humans'[MeSH Terms] AND English[lang])

In a secondary search, to identify studies with patients with SB, we extended our search to English language articles from the last 10 years including patients with disabilities who were up to 18 years old.

1. Osteoporosis/Subheading
2. ('Osteoporosis/drug therapy'[Majr] OR 'Osteoporosis/prevention and control'[Majr]) AND ('humans'[MeSH Terms] AND English[lang] AND ('infant'[MeSH Terms] OR 'child'[MeSH Terms] OR 'adolescent'[MeSH Terms]) AND '2001/06/07'[PDat] : '2011/06/04'[PDat])
3. Disabled children
4. Osteoporosis
5. Prevention

6. ((‘Disabled Children’[Mesh]) AND ‘Osteoporosis’ [Mesh]) AND ‘prevention and control’ [Subheading]

For abstracts meeting the goals of this review, we downloaded the full articles.

Results

In the first domain titled, ‘incidence and risk of fracture,’ the search provided 37 articles, but only 16 met the inclusion criteria (Akbar, 2010[10]; Marreiros, 2010[4]; Okurowska-Zawada, 2009[11]; Dosa, 2007[12]; Khoury, 2002[13]; Parsch, 1991[1]; Boytim, 1991[14]; Lock, 1989[15]; Drabu, 1985[16]; Kumar, 1984[17]; Anschuetz, 1984[3]; Reikerås O, 1981[18]; Drummond 1981[6]; Townsend, 1979[19]; Quilis, 1974[20]; Korhonen, 1971[21]). By reviewing the reference lists of selected papers, we selected two additional articles (Drennan, 1971[22]; James, 1970[23]) (Table 1).

A second search focusing on BMD yielded 25 articles, but 13 records failed to meet the inclusion criteria. Twelve articles met the inclusion criteria (Szalay, 2010[24]; Apkon, 2009[25]; Okurowska-Zawada, 2009[11]; Ausili, 2008[26]; Taskinen, 2007[27]; Boylu, 2006[28]; Pluskiewicz, 2004[29]; Tuckerman, 2002[30]; Mingin, 2002[31]; Quan, 1998[5]; Koch, 1992[32]; Rosenstein, 1987[7]) (Table 2). The articles Pluskiewicz, 2004[29] and Tucherman, 2002[30] were not freely available in Portuguese libraries; therefore, we considered only 10 articles.

Finally, for the ‘Prevention and nonpharmacological and pharmacological treatment of osteoporosis’ review, we initiated our search by focusing on randomized, quasi-randomized, and non-randomized controlled trials and cohort and case-control studies. Because of the low number of studies identified, we considered case studies and case series. We inspected 50 articles from the searches conducted, but only four met the inclusion criteria (Mazur, 1989[33]; Quan, 2003[34]; Sholas, 2005[35]; Ausili, 2008[26]) (Table 3).

Because all of the studies were retrospective and because only a limited number of controlled studies in this clinical research area have been performed, to increase the number of child patients in the review, the search was extended to other paediatric diseases commonly seen in non-ambulatory patients to identify studies with heterogeneous data including patients with SB. This search provided one additional article that met the requirements (Steelman, 2003[36]) (Table 4).

An article that met our inclusion criteria, but was not obtained using the search strategy was selected (Liptak, 1992[37]). Thus, in the section review titled, ‘prevention and treatment of osteoporosis,’ six articles met the eligibility criteria.

Likewise, we selected some general articles not focusing on SB to introduce different topics and to identify fields in which more research is needed in SB. A total of 89 articles were selected for analysis.

Frequency of fractures in SB

Prior studies have demonstrated an 11–30% frequency of fractures in paediatric patients with SB.[4,10,15,20,22,23] In SB, fractures occur more frequently below the level of neurological involvement in the paralysed lower extremities, which can be caused by a lack of vertical load.[1,10] The most common fracture site is the distal femur.[4]

Occurrence of fractures in relation to the mechanism of injury

Many fractures result from minor stress or are spontaneous.[1,4,10,15,18,19,21] Thus, the true incidence of fractures is probably higher than presently recorded because not all fractures are recognized.[17] Akbar *et al.* analysed the records of 862 patients with MMC (retrospective cross-sectional study) and detected 170 fractures ($n = 92$). The aetiologies of the fractures

Table 1 Search strategy used

Incidence and risk factors of fractures	Articles	
(‘Spinal Dysraphism’[Mesh] OR ‘Meningomyelocele’[Mesh]) AND ‘Fractures, Bone’[Majr] AND (‘humans’[MeSH Terms] AND English[lang] AND (‘1970/01/01’[PDAT] : ‘2011/06/10’[PDAT]))	37 records identified on PUBMED 21 reports excluded 8, Case reports (Kiymaz, 2005; Asirdizer, 2005; Blanco, 1999; Johnson, 1998; Hes, 1997; Dirschl, 1992; Montgomery, 1984; Sachdev, 1981) 1, Review articles (Westcott, 1992) 11, Other subject (Szalay, 2010; Akbar, 2009; Laidlaw, 1998; Saleh, 1995; Blanda, 1993; Pomeranz, 1991; Feiwell, 1980; Rodgers, 1997; Wolverson, 1981; Wenger, 1980; Repasky, 1976) 1, Fractures not associated to SB (Hyre, 1989) Total: 37 records	18 record identified that met all eligibility requirements 16, reports selected through PUBMED (Akbar, 2010; Marreiros, 2010; Okurowska-Zawada, 2009; Dosa, 2007; Khoury, 2002; Parsch, 1991; Boytim, 1991; Lock, 1989; Drabu, 1985; Anschuetz, 1984; Kumar, 1984; Reikerås, 1981; Drummond 1981; Townsend, 1979; Quilis, 1974; Korhonen, 1971) 2, selected through the reference lists of selected papers (Drennan, 1971; James, 1970) 18 records identified that met all eligibility requirements

Table 2 Search strategy used

Bone mineral density	Articles	
('Spinal Dysraphism'[Mesh] OR 'Meningomyelocele'[Mesh]) AND 'Bone Density'[Mesh]	14 records identified 6 studies excluded 2, BMD focusing, but not available (Pluskiewicz, 2004; Tuckerman, 2002) 1, Adult study (Valtonen, 2006) 1, Case reports (Asirdizer, 2005) 1, Review articles (Mingin, 2004) 1, Medical intervention (Quan, 2003)	8 records identified that met all eligibility requirements: (Szalay, 2010; Okurowska-Zawada, 2009; Apkon, 2009; Ausili, 2008; Boylu, 2006; Mingin, 2002; Quan, 1998; Koch, 1992)
Spina bifida OR Myelomeningocele AND Bone density ('spinal dysraphism'[MeSH Terms] OR ('spinal'[All Fields] AND 'dysraphism'[All Fields]) OR 'spinal dysraphism'[All Fields] OR ('spina'[All Fields] AND 'bifida'[All Fields]) OR 'spina bifida'[All Fields]) OR ('meningomyelocele'[MeSH Terms] OR 'meningomyelocele'[All Fields] OR 'myelomeningocele'[All Fields]) AND ('bone density'[MeSH Terms] OR ('bone'[All Fields] AND 'density'[All Fields]) OR 'bone density'[All Fields])	25 records identified 15 records excluded 2, BMD focusing, but not available (Pluskiewicz, 2004; Tuckerman, 2002) 3, Non-English articles (Funk, 2011; Bellotti, 2009; Torbus, 2002) 2, Case reports (Miyano, 2009; Asirdizer, 2005) 1, Low BMD not associated with SB (Hafez, 2003) 1, Adult study (Valtonen, 2006) 1, Review articles (Mingin, 2004) 1, Medical intervention (Quan, 2003) 4, Other subject (Hermann-Kleiter, 2009; Semler, 2007; Patel, 1987; Fulford, 1975)	10 records identified that met all eligibility requirements: (Taskinen, 2007; Rosenstein, 1987) and 8 were duplicate: (Szalay, 2010; Okurowska-Zawada, 2009; Apkon, 2009; Ausili, 2008; Boylu, 2006; Mingin, 2002; Quan, 1998; Koch, 1992)
	Total: 25 records identified	10 records identified that met all eligibility requirements

were the following: fall (35%), transfer (28%), cast immobilization (37%), and unknown (21%).[10] In our previous study, we showed that spontaneous fractures were the principal mechanism of injury (64.4%).[4] Parsch *et al.* have detected 261 fractures in 173 patients from a sample of 1414 patients followed over a 15-year period (1975–1989). In 35% of the cases, the fractures occurred spontaneously. Only 5% of all the fractures were associated with adequate trauma.[1] Lock *et al.* detected 66 fractures in 37 of 186 patients. Only seven (9%) were associated with a history of known trauma.[15]

The results of all these studies suggest the importance of fragility fracture in this population and that these fractures are amenable to measures of prevention.

Fracture risk assessment in SB patients

SB is a complex disease that involves several organ systems; thus, it requires an individualized approach for the clinical assessment of fracture risk. Evidence has shown that multiple risk factors may act independently or in combination to increase the fracture risk. The importance of each of these risks is still undefined.

Neurological level of involvement and ambulatory status

There is considerable evidence linking neurological involvement and ambulatory status with fracture risk. Fractures occur more frequently with a higher level of neurological involvement[1,4,10,14,15] and in non-ambulatory patients.[4,10] James verified that in asymmetrically affected patients with SB, the paralytic limb was more likely to be fractured than the active limb.[23]

Boytim *et al.* retrospectively reviewed neonatal fractures in a group of 80 newborn patients with SB over a 4-year period. Of the six patients with fractures in the neonatal period, three had high-level neurological involvement (thoracic or L1), three had an intermediate level (L3), and all had significant contractures.[14]

Environmental factors

Okurowska-Zawada *et al.* showed that body fat levels were higher in MMC patients with fractures than in those without fractures.[11] Body mass index (BMI) can be difficult to evaluate in patients with MMC because of the scoliosis, the presence of contracture in the lower extremities and their altered dimensions and growth delay.[38,39] Previous studies from general paediatric populations have reported that maternal dietary folate intake during pregnancy positively correlates with BMD of the child.[40]

Association between fractures and prolonged inactivity

In paediatric patients with SB, there is an association between fractures and prolonged inactivity secondary

Table 3 Search strategy used

Prevention and treatment of osteoporosis	Articles	
'Myelomeningocele'[All Fields] OR 'Spina bifida'[All Fields] OR 'Meningomyelocele' [All Fields] AND 'Bone density'[All Fields] AND 'Prevention'[All Fields]	3 records identified 2 reports excluded 2, No intervention (Taskinen, 2007; Mingin, 2002)	1 record identified that met all eligibility requirements (Quan, 2003)
(('Spinal Dysraphism'[Mesh] OR 'Meningomyelocele'[Mesh]) AND 'Walking'[Mesh]) AND 'Bone and Bones'[Mesh]	8 records identified 8 records excluded 1, Non-English studies (Jóźwiak, 2007) 1, Review articles (Wright, 2011) 6, Other subject (Geertzen, 2009; Nguyen, 2004; Bartonek, 2002; Guille, 2002; Fraser,1992; Fraser, 1991)	—
('Spinal Dysraphism'[Mesh] OR 'Meningomyelocele'[Mesh]) AND 'Vibration'[Mesh]	2 records identified 2 reports excluded 2, Other subject (Semler, 2007; VanSickle, 2001)	—
'Myelomeningocele'[All Fields] OR 'Spina bifida'[All Fields] OR 'Meningomyelocele'[All Fields] AND ('Osteoporosis'[All Fields] OR ('Bone'[All Fields] AND 'Walking'[All Fields])) AND ('humans'[MeSH Terms] AND English[lang] AND ('1970/01/01'[PDAT] : '2011/06/10'[PDAT]))	19 records identified 17 records excluded: 6, Other subject (Mountain, 2010; Geertzen, 2009; Semler, 2007; Brasili, 1997; Fraser, 1993; Dickel, 1989) 7, No intervention (Marreiros, 2010; Okurowska-Zawada, 2009; Apkon, 2009; Taskinen, 2007; Quan, 1998; Anschuetz, 1984; Osebold, 1982) 1, Adult patients (Valtonen, 2006) 3, Review articles (Webb, 2010; Lubicky, 2005; Roussos, 2001)	2 records identified that met all eligibility requirements (Ausili, 2008; Mazur, 1981)
'Myelomeningocele'[All Fields] OR 'Spina bifida'[All Fields] OR 'Meningomyelocele'[All Fields] AND ('Osteoporosis'[All Fields] OR 'Bone density'[All Fields]) AND ('Standing'[All Fields] OR 'Vibrating platform'[All Fields] OR 'Vibration'[All Fields])	2 record identified 2 records excluded 2, Other subject (Mountain, 2010; Semler, 2007)	—
('Spinal Dysraphism'[Mesh] OR 'Meningomyelocele'[Mesh]) AND 'Calcium'[Mesh]	11 records identified 11 records excluded 9, No intervention (Kinoshita, 2010; Okurowska-Zawada, 2009; Ozard, 2008; Mingin, 2002; Quan, 1998; Pettit, 1980; Lowe, 1971; Wit, 1970; Fedrick, 1970) 2, Other subject (Quan, 2003; Elwood, 1977)	—
('Spinal Dysraphism'[Mesh] OR 'Meningomyelocele'[Mesh]) AND 'Vitamin D'[Mesh]	1 record identified 1 record excluded 1, No intervention (Quan, 1998)	—
(('Spinal Dysraphism'[Mesh]) OR 'Meningomyelocele'[Mesh]) AND 'Diphosphonates'[Mesh]	3 records identified 3 records excluded 1, Other subject (Semler, 2007) 1, No intervention (Duprez, 1996) 1, Review articles (Oakley, 1984)	—
'Myelomeningocele'[All Fields] OR 'Spina bifida'[All Fields] OR 'Meningomyelocele'[All Fields] AND ('Bone density'[All Fields] OR Osteoporosis [All Fields]) AND 'Treatment'[All Fields]	7 records identified 6 records excluded 2, No intervention (Marreiros, 2010; Anschuetz, 1984) 3, Other subject (Funk, 2011; Semler, 2007; Osebold, 1982) 1, Review articles (Lubicky, 2005)	1 duplicate record identified that met all eligibility requirements (Quan, 2003)
'Spina bifida'[All Fields] OR 'Myelomeningocele'[All Fields] OR 'Meningomyelocele'[All Fields] AND ('Calcium'[All Fields] OR 'Vitamin D'[All Fields] OR 'Diphosphonates'[All Fields]) AND ('1970/01/01'[PDAT] : '2011/06/10'[PDAT]) AND ('humans'[MeSH Terms] AND English[lang])	23 records identified 22 articles excluded 14, Other subject (Kinoshita, 2010; Semler, 2007; Matlaga, 2006; Rueffert, 2004; Quan, 2003; Patwardhan, 2002; Bound, 1997; Litman, 1996; Osborn, 1989; Petersen, 1987; Pettit, 1980; Griffiths, 1980; Pettit, 1979; Elwood, 1977) 1, Review articles (Oakley, 1984) 6, No intervention (Okurowska-Zawada, 2009; Apkon, 2009; Ozard, 2008; Taskinen, 2007; Mingin, 2002; Quan, 1998) 1, Low BMD not associated with SB (Hafez, 2003)	1 record identified that met all eligibility requirements (Sholas, 2005)
	Total: 50 records identified	4 records identified that met all eligibility requirements

Table 4 Search strategy used

Prevention and treatment of osteoporosis	Articles	
('Osteoporosis/drug therapy'[Majr] OR 'Osteoporosis/prevention and control'[Majr]) AND ('humans'[MeSH Terms] AND English[lang] AND ('infant'[MeSH Terms] OR 'child'[MeSH Terms] OR 'adolescent'[MeSH Terms]) AND '2001/06/07' [PDat] : '2011/06/04'[PDat])	209 records identified	1 record identified that met all eligibility requirement 1 article included (Steelman, 2003)
(('Disabled Children'[Mesh]) AND 'Osteoporosis' [Mesh]) AND 'prevention and control' [Subheading]	3 records identified	— 1 record identified that met all eligibility requirements

to cast immobilization and operative orthopaedic procedures, a relationship that highlights the need for careful preoperative selection of patients whose clinical backgrounds may increase their fracture risk.[1,3,4,6,10,13,15,16,18,20–22]

Laboratory parameters

Okurowska-Zawada *et al.* identified an association between the incidence of fractures in children with MMC and increased levels of calcium in a 24-hour urine sample.[11]

Genetic predisposition to low BMD

Occurrence of fractures varies even among children with SB with similar levels of neurological involvement and ambulatory status. Among wheelchair users with higher levels of paralysis with a significant number of orthopaedic interventions and postoperative inactivity, some suffer multiple pathological fractures, while others do not. The propensity for fractures could reflect skeletal weakness or lower BMD associated with environmental factors, body mass, hormonal imbalance, or genetic factors.[9,41]

We did not find any studies evaluating the relationship between genetic factors and low BMD in paediatric patients with SB. Steer *et al.* observed an allele-dose association between the C677T MTHFR genotype and spinal BMD in children.[42] The C677T homozygosity has been associated with a moderately increased risk of SB[43] and early, recurrent paediatric strokes.[44]

To our knowledge, no study has investigated the influence of the C677T MTHFR polymorphism on fracture frequency in paediatric patients with SB.

Risk factors associated with a second fracture

According to our recently published results, patients with SB who were partially ambulatory and had lower lumbar motor involvement have a 5% risk of a second fracture, whereas non-ambulatory wheelchair users, who were totally dependent on their wheelchair with thoracic motor involvement, had a 74% risk.[4] The lesion level and ambulatory status are useful for identifying the high-risk group but are not precise enough because multiple variables confound these factors. It has been documented that paediatric patients with SB who sustain a spontaneous fracture are at high risk of having future fractures.[4] It is therefore crucial to identify the propensity for multiple fractures early in a child's life.

Factors not associated with fractures

Factors that were not related to the occurrence of fractures in SB included sex,[4,10–12] syringomyelia,[4] and neurosurgical interventions.[1,4]

Dosa *et al.* found that while neither shunted hydrocephalus nor cognitive subscores on the Functional Independence Measure were associated with fractures.[12]

Okurowska-Zawada *et al.* did not detect a correlation between parathyroid hormone (PTH) and bone formation markers (bone-specific alkaline phosphatase) and the occurrence of fractures.[11]

Risk factors of fractures not yet evaluated

To date, no studies have examined this population's fracture risk in relation to the following factors: family history of fractures, mother's folic acid intake and tobacco use during pregnancy, history of breastfeeding, calcium, vitamin D and milk intake, vitamin D stores, soft drink and fruit juice consumption, chronic use of medications known to interfere with bone mineral deposition (glucocorticoids and anticonvulsants), lean body mass, exercise habits, smoking habits, susceptibility to falls, chronic kidney insufficiency with metabolic acidosis, hormonal status, and genetics. To our knowledge, there are no studies assessing the bone resorption by urinary markers, such as pyridinoline/deoxypyridinoline or n- and c-telopeptides, or bone formation markers, such as osteocalcin.

Of the many independent variables that have been tested, those reported to influence fracture risk are listed in Table 5.

BMD assessment

The most widely validated technique for assessing BMD is dual-energy X-ray absorptiometry (DXA).[45] The *Z*-score, which is defined as the number of standard deviations above or below the average BMD for age- and sex-matched controls, is often used to determine how a child's BMD compares with other children.[46]

Few studies testing BMD have been conducted in paediatric SB patients. Ausili *et al.* investigated 60 patients with MMC aged 5–14 years old (22 ambulatory and 38 non-ambulatory) and detected that BMD was lower in the non-ambulatory group than in the ambulatory group.[26]

Apkon and colleagues have done a cross-sectional observational study, analysed BMD of the femoral neck and whole body using DXA in children with MMC (age range: 4–18 years) and detected low BMD at the femoral neck in nine of 21 children (42.9%). A significant relationship was found between low femoral neck BMD in children who are wheelchair users, and a trend towards improved femoral neck BMD was found in children with lower neurological levels of involvement. No relationship between a history of fractures and low BMD was described. The authors hypothesized that this finding may have been due to the mean age of the studied children (9 years, 8 months).[25] Rosenstein *et al.* also evaluated BMD using single-photon absorptiometry in 80 patients with MMC aged 1.3–21.7 years and found that both patients with higher-level neurological involvement and non-ambulatory patients had lower BMDs than ambulatory patients and those with lower-level neurological involvement. In this cohort, no correlation between BMD and the presence of single or multiple fractures was identified. The mean age of patients (9.1 years) was similar the patients in the study by Apkon *et al.*[7] Consistent with these findings, Okurowska-Zawada *et al.* did not identify significant differences in BMD *Z*-scores between the fracture and non-fracture groups.[11] Szalay *et al.* have analysed 37 patients with SB using DXA scans and were unable to identify an association between *Z*-score and fracture due to small sample size.[24]

Table 5 Etiological factors contributing to fracture risk in paediatric patients with spina bifida

1.	Personal history of spontaneous fracture[4]
2.	Non-ambulatory status[4,10]
3.	Higher level of neurological involvement[1,4,10,14,15]
4.	Physical inactivity (e.g. postoperative inactivity)[1,3,4,6,10,13,15,16,18,20–22]
5.	Contractures[14]
6.	Hypercalciuria[11]
7.	Higher body fat levels[11]

In a study that included 35 patients with MMC aged 6–19 years, randomly chosen, Quan *et al.* used single-photon absorptiometry and detected low BMD in the radius, a bone that is often used extensively in full-time wheelchair users. The authors hypothesized that overall physical inactivity may have a systemic effect on total body bone mineralization and influence the mineralization of bones not affected directly by the neurological lesions. The urinary calcium excretion of non-ambulators was higher compared to ambulators and likely contributed to their decreased BMD. In disagreement with the previous studies, the authors documented that patients with fractures had greatly diminished BMD compared to those without fractures; however, enrolled patients were slightly older (average age was 11.1).[5] A limitation of this study is its evaluation of BMD in the radius, which is less often fractured in this population.

Most of the studies analysed did not support an association between a history of fractures and low BMD in young children. This finding can have important clinical implications, since treating low BMD may not improve the incidence of fractures in young children with SB.[25]

Total body BMC increases nearly three-fold in females and more than triples in males between 8 and 17 years of age.[8] Rosenstein and colleagues documented that the effect of neurological level in BMD in the lower-extremity change with age. Tibial and metatarsal density was greater in those with more distal neurological levels at all ages, but the difference was proportionally larger in older patients.[7] Thus, it is possible that the differences in the lower age group could be related to bone strength without repercussions in BMD analysis by DXA. In older children, the differences in BMD might be detectable with DXA. The ideal age for BMD evaluation to predict the occurrence of fractures is not yet known.

The low number, the limited sample size, and the retrospective and retrospective/cross-sectional nature of the available studies preclude definitive conclusions about the relationship between low BMD and fracture risk in this population.

Patients who require bladder augmentation are prone to the development of metabolic acidosis.[32] Comparisons between MMC children who underwent conduit urinary diversion (ileal or colonic) or were managed with intermittent catheterization showed no significant difference in BMD.[32] In a comparison of BMD in MMC children with or without bladder augmentation, age- and sex-matched MMC children did not show any significant differences.[31]

Boylu *et al.* evaluated BMD after ileal augmentation cystoplasty in children with and without MMC and

identified a significant difference between the two groups even though their mean creatinine, pH, and bicarbonate levels were similar. The data suggested that lower BMD depends more on the underlying neurologic pathology and its locomotor consequences than enterocystoplasty.[28] This conclusion was supported by a second study, which described skeletal health after intestinal bladder augmentation.[27]

Indication and timing of BMD assessment

BMD evaluation may be an essential clinical tool to identify patients with SB who are at risk for fracture and may benefit from a direct bone health program;[24] however, there is no standard approach to measuring BMD in this population. An expert panel consensus from the International Society for Clinical Densitometry (ISCD) in 2007 reported that in children with chronic immobilization, spine and total body less head (TBLH) BMC and areal BMD should be measured at fracture presentation.[47] Conventional radiographic findings compatible with osteopenia may also prompt performing a DXA scan.[45,48] Other indications for DXA evaluation include chronic disease with possible secondary effects on skeletal maturity, chronic use of a medication known to interfere with bone mineral accrual, and prolonged immobilization.[48] The British Pediatric and Adolescent Bone Group has recommended that a DXA assessment should be considered for children with conditions that put them at risk of low BMD if they have a history of low trauma or recurrent fractures, back pain, spinal deformity, loss of height, change in mobility status, or malnutrition.[49] The ideal time to evaluate children with chronic, bone-impacting disease is unknown. Scans should not be performed more than once every 12 months, except for research to determine new drug therapies, for monitoring the response to a pharmacological intervention or evaluating worsening disease.[45,49,50] The minimal time interval between bone density measurements to monitor treatment with a bone-active agent or disease processes is 6 months, and assessments should be performed using the same machine and software.[47]

DXA limitations in SB

Despite the wide use of DXA, the technique does have several limitations. First, DXA does not discriminate between cortical bone and trabecular or cancellous bone.[41,46,48,50,51] It has a limited ability to assess certain structural characteristics of bone that affect strength (e.g., material properties, protein content, geometry and bone size).[51] DXA scans in only two directions (length and width) yield only an areal BMD value. This areal density provides an incomplete correction for size because it does not provide information about bone depth. Areal bone density is inherently related to the size of the individual; thus, lower BMDs are expected in shorter children compared to taller ones, who are expected to have more bone mineralization because they have larger bones.[41,45,46,51] In children with SB, the delay in growth is important because individuals with SB are often short for their age.[38] Small children may have low BMDs either because they have smaller bones or they have less bone mineralization than the size of their bones would predict.[52–54]

Another specific issue in children with MMC and hydrocephalus is precocious puberty,[55,56] which may interfere with BMD.[24] Thus, the results of DXA in paediatric patients with SB should be interpreted with care by physicians who understand the influence of bone size, skeletal and sexual maturation, and body composition on BMC and BMD.[41]

For clinical use, scans of multiple regions of interest are preferred over whole-body scans.[57] In fact, whole-body scans are difficult to interpret and are often subject to artefacts. BMD may be difficult to assess because of heterotopic ossification, sequelae of surgical procedures,[9,58] and the presence of metallic or other radiodense implants, which can produce artefacts that skew the result of the scan. Patients with SB are likely to have contractures that preclude positioning of the spine or hip scans.[24,54,57] The absence of posterior elements in the vertebrae of SB patients artificially lowers the BMD of the lumbar spine, which must be taken into account when interpreting the DXA scan.[53] Sites that are fractured should be excluded from evaluation because disuse osteopenia and increased density from exuberant fracture calluses will not give an accurate picture of overall bone health.[57]

Low femoral neck BMD in children with sacral-level MMC and minimal gait impairments may be due to generalized hip-area weakness from poor innervation of the sacral-level gluteal muscles[25] and would not be useful for identifying patients who are more likely to suffer a fracture.

The distal lateral femoral scan is of unequivocal importance in paediatric patients with SB because this area is the most common fracture site.[4,24] Because it can be evaluated in children with significant contractures, the distal lateral femoral scan is likely to replace femoral neck measurement in children with disabilities.[24,25,54,57] Reference Z-scores for the distal lateral femur are available for children aged 3 years and older.[54]

Probability-based assessment of fracture in SB patients

The striking question is how to identify children with SB with a high fracture risk through their clinical characteristics to prevent fractures. A defined protocol could alert the physician to the risk of new fractures following prolonged immobilization and could reduce the subsequent risk of the fracture–plaster–fracture cycle. The manner in which clinical risk factors have been used to identify high-risk individuals has not yet been validated. Currently, there is no tool to predict BMD in paediatric patients. Because it would not be cost effective to universally screen for BMD in children with SB, the guidance should be based on an opportunistic case-finding strategy in which physicians are alerted to the possibility of osteoporosis and high fracture risk by the presence of clinical risk factors associated with fracture.[59] Although several studies have been conducted to assess BMD in paediatric populations, there is no consensus for predicting fracture risk,[41,47,57,60] particularly in those with chronic conditions[45] such as SB.[7,11,25]

The misunderstood concept of paediatric osteoporosis and its limitations

The ISCD proposed that the diagnosis of osteoporosis in children and adolescents should require a clinically significant fracture history and a decreased BMD. A clinically significant fracture history includes one or more of the following: a long-bone fracture of a lower-extremity, vertebral compression fracture, or two or more long-bone fractures of the upper extremities. Low BMD is defined as a Z-score less than or equal to -2.0, adjusted for age, gender, and body size.[47] According to some authors, osteoporosis can be suspected clinically in patients who suffer a low-impact fracture.[61,62] Both the emphasis on the presence of fracture by the definition of osteoporosis used by the ISCD[47,63] and the importance of clinical bone fragility to some authors in diagnosing osteoporosis is appropriate given the challenges of interpreting densitometry in children.[57,61] Thus, unlike in adults, the diagnosis of osteoporosis in children depends on a history of fracture.[47,62,63] In patients with SB, waiting for the first fracture is counterproductive in maintaining bone health, and efforts should be directed at earlier prevention.

Prevention and non-pharmacological and pharmacological treatment of osteoporosis

Initial treatment for low bone mass and fractures in children is directed towards reducing or eliminating modifiable skeletal risk factors.[47,61] To prevent fractures secondary to postoperative inactivity,[4] surgeons recommend several interventions combined in one surgical procedure or at least within a certain period during which the patient needs to be immobilized.[6] The period of immobilization after a surgical intervention should be reduced, if possible,[6,15] and weight-bearing should be allowed as soon as possible,[1,10] depending on X-rays signs of consolidation.[10] There is limited evidence that passive weight-bearing in children with SB improves BMD,[25] although standing with the use of a standing frame appears to increase BMD in children with cerebral palsy.[64] In a double-blinded, prospective, randomized, placebo-controlled study including 20 ambulant children with disabilities but no mention of the diagnosis of each child, Ward and colleagues observed that low-magnitude, high-frequency mechanical stimuli increase tibial and spinal volumetric trabecular BMD.[65]

Data from physical therapy research,[66] including investigations of standing on vibrating platforms[65] in children with disabilities, suggest that gains in bone mass may occur with even modest increases in skeletal loading, but these studies are subject to methodological criticisms because of the small number of patients included and the use of different parameters that prevent comparisons between programmes. We must also consider that the bone response in children with flaccid paralysis could be different from others conditions, such as cerebral palsy, implying that studies are needed to clarify the effects of standing in a standing frame and on vibrating platforms on patients with SB. Liptak *et al.* analysed 39 children who used a parapodium and 29 children in wheelchairs with MMC in a comparative study and showed that early use of the parapodium did not protect against fractures.[37] The most ideal mobility device remains controversial. Weight bearing during ambulation should not be confused with passive weight bearing using a device, such as a standing frame.[25] To determine whether it is worthwhile to encourage patients who have high-level SB to walk at an early age, Mazur and colleagues compared 36 patients who participated in a walking programme with 36 patients matched for age, sex, level of lesion, and intelligence for whom a wheelchair was prescribed early in life. The patients who walked earlier had fewer fractures.[33] Ausili *et al.* showed that BMD in the lumbar and femoral neck regions was improved in MMC patients who participated in athletic activities in comparison with those who did not.[26]

No studies are available concerning the amount of weight bearing and ambulation necessary to maintain or increase BMD[10] to guide prescription of this treatment in patients with SB.

For paediatric patients who fail to respond adequately to these general measures, pharmacological therapy for osteoporosis may be considered. Few studies have evaluated the effect of pharmacological treatment on BMD and fractures in patients with SB.

Global programmes should include attention to nutritional factors, particularly adequate intake of calcium and vitamin D. The impairment in ambulation and functioning in paediatric patients with SB may cause them to spend more time inside, which may increase the risk for low serum calcidiol and osteopenia. Non-ambulatory children and children with frequent fractures and low BMD should be considered for routine monitoring of risk and vitamin D deficiency screening.[67,68] During adolescence, when dairy consumption decreases, vitamin D intake is less likely to be adequate, and this deficiency may adversely affect calcium absorption.[9] A review of controlled trials documented an increase in the BMC of adolescents who took calcium supplements.[69] However, constipation secondary to neuropathic bowel is a frequent problem in patients with SB, and supplementation with calcium may exacerbate it. This side effect should be considered, and treatment of constipation in MMC children should be given when appropriate.[70] Moreover, patients with MMC have hypercalciuria linked to immobilization,[11] which is a known metabolic risk factor associated with renal calculi. Matlaga *et al*. have established that many patients with MMC undergoing percutaneous nephrolithotomy will be found to have calculi that are metabolically derived rather than calculi secondary to chronic bacteriuria with urea-splitting organisms.[71] Consequently, in patients with SB, metabolic calculi may be exacerbated by oral calcium administration. Restriction of dietary calcium is not recommended in children with hypercalciuria, as it puts the growing child at risk for negative calcium balance and poor bone mineralization.[72] Hypercalciuria was also found in 43% of children with recurrent urinary tract infection.[73]

Therapy for bone fragility in childhood has been limited to conservative measures, such as optimizing calcium and vitamin D intake, even though adequate calcium and vitamin D intake may not be enough to treat osteoporosis,[74] particularly in patients with a high fracture risk. To date, no outcome study on the use of vitamin D has proven convincingly that this vitamin is insufficient for patients with a high fracture risk. Thus, the impact of vitamin D on BMD is currently unknown.[25]

Hydrochlorothiazide is known to reduce urinary calcium loss and increase BMD in non-MMC patients,[75,76] and a positive association between hypercalciuria and fractures has been identified in SB patients.[11] In a prospective randomized, double-blinded controlled study of 20 children with MMC with ages ranging from 6 to 16 years, Quan *et al.* recorded no positive effects of hydrochlorothiazide on forearm BMD compared to placebo-treated controls, despite a tendency for decreased urine calcium excretion.[34] However, only 13 of the patients completed the year-long protocol, and only six patients belonged to the hydrochlorothiazide group. Thus, at this time, it is unknown as to whether pharmacological therapy with hydrochlorothiazide increases BMD.

Reducing hypercalciuria has occasionally been the aim of bisphosphonate therapy even in patients with normal calcium concentrations[77] and is being considered with increasing frequency in children with secondary osteoporosis. In a case series, Sholas *et al.* analysed the effects of oral alendronate in 10 non-ambulatory children (one with SB) aged 3–17 years. This study showed that disabled, non-ambulatory children tolerate alendronate, and it may decrease fractures in those at risk of severe disuse osteopenia.[35] A similar conclusion was drawn from a retrospective, uncontrolled trial by Steelman *et al.*, who used a single-day low-dose pamidronate infusion every 3 months. Pamidronate treatment increased BMD and decreased the fracture rate of symptomatic paediatric osteoporotic patients ($n = 18$) aged 6–21 years with only one of whom had SB.[36]

Low BMD among children may not indicate accelerated bone loss[41] but rather a failure to achieve the expected peak bone mass, bone loss or a combination of the two.[78,79] It is important to acknowledge that the use of antiresorptive drugs, such as bisphosphonates, may not be the optimal approach. Therefore, an understanding of the pathogenesis of low bone mass in paediatric patients with SB is needed.[41] In this way, in children who fail to gain adequate bone mineral,[41] PTH would be an alternative because it is the most effective anabolic agent for bones in adults.[61] However, PTH has a black box warning against its use in children and adolescents because it has caused osteosarcoma in a significant proportion of young rats.[80] The previously mentioned study by Quan *et al.* demonstrated that full-time wheelchair users and limited ambulators had elevated urinary pyridinoline and thus greater bone reabsorption compared to normal ambulatory patients.[5] This finding could differentiate the pathophysiological mechanisms involved in osteoporosis in this population from other cases of paediatric osteoporosis, and it suggests a potential beneficial role for bisphosphonates. However, the potential benefits of bisphosphonate therapy should be analysed and weighed against the potential adverse effects. Flu-like symptoms in children can occur with

the initiation of bisphosphonates.[81] Some of the most serious side effects associated with bisphosphonates, such as uveitis and thrombocytopenia and oesophageal or oral ulcerations, which were documented in adult studies, are rare in children.[61] The gastrointestinal symptoms associated with oral agents should be weighed in patients with SB because the Arnold-Chiari II malformation can compromise deglutition. Munns and colleagues have described adverse respiratory events associated with the first pamidronate cycle in four infants with severe osteogenesis imperfecta who were less than 2 years of age with pre-existing reactive airway disease.[82] In excess, bisphosphonates can induce the oversuppression of bone turnover[83] and can cause acute post-infusion hypocalcemia and hypophosphatemia.[84] Iatrogenic osteopetrosis was detected in a child who was treated for $2\frac{3}{4}$ years with more than four times the usual pamidronate dosage.[83] In children with osteogenesis imperfecta, pamidronate disodium has been associated with an increased risk of delayed osteotomy healing.[85] Osteonecrosis of the jaw has been described among adults; however, there were no cases identified in children receiving bisphosphonates.[61,74,86] Extrapolating the literature from other diagnoses[87,88] and reviewing clinical experiences suggest a potential benefit of using bisphosphonates in paediatric patients with SB; however, bisphosphonates are neither the current standard of care nor are they approved by the United States Food and Drug Administration for this purpose.[25,41] Moreover, there is no literature detailing which factors should be used to determine the suitable length of pharmacological treatment after bisphosphonate treatment is initiated.[61,89]

To our knowledge, there are no studies evaluating the use of calcitonin in SB treatment. This polypeptide has been confirmed to be more effective in preventing vertebral fractures than hip fractures in patients with osteoporosis.[90] Therefore, it may not be the first treatment option of choice for patients with MMC, in which fractures are more common in the lower extremities. Also, the lack of documentation of vertebral fractures suggests a possible protective effect on vertebral fractures among patients with SB who use wheelchairs.[4,12]

Most of the articles identified had small sample sizes and lacked the scientific power of clinical trials. No studies of paediatric patients with SB compare two different methods of osteoporosis treatment (pharmacological vs. non-pharmacological) and two pharmacological agents.

Practice points and recommendations for research

While recognizing the uncertainties and limitations of the studies concerning fracture and osteoporosis in paediatric patients with SB, we can draw some conclusions that can be useful for physicians involved in the care of children with SB. Children with SB should have their fracture risk evaluated at each consultation by the medical team. Thus, calcium and vitamin D intake should be evaluated by the physician. In the presence of vitamin D deficiency and/or poor dietary calcium intake, it would be suitable to replace such deficits, but routine calcium and vitamin D supplementation is not recommended.[10,91] Weight bearing during ambulation and sports activity should also be stimulated because it may reduce fractures[33] and increase BMD[26] in MMC, respectively. If a fragility fracture occurs despite vitamin D supplementation and physiotherapy, no guidelines are available for further management.

Future issues to be addressed concerning the issue of osteoporosis in children with SB include a determination of what and how many specific processes underlie this condition. Research should establish a relationship between low BMD and fracture risk.[25] Currently, there is no universal treatment regimen for osteoporosis in SB. The experience of world centres specialized in treating children with SB who suffer from multiple fractures or osteoporosis has not been disseminated, which makes it impossible to compare data among different centres. Thus, there is a need to properly evaluate the efficacy of non-pharmacological and pharmacological osteoporosis treatment through randomized clinical trials. Who should be treated and the appropriate duration of treatment are not well known. Whether low BMD alone is adequate for drug therapy in children is far less clear. We think that bone fragility is a critical area for future research in SB.

Conclusion

Paediatric patients with SB are at risk of fractures[1,3,4,6,10–16,18,20–23] and low BMD.[25] The risk factors for fractures include higher level neurological involvement,[1,4,10,14,15] non-ambulatory status,[4,10] contractures,[14] hypercalciuria,[11] higher body fat levels,[11] postoperative inactivity,[1,3,4,6,10,13,15,16,18,20–22] and a previous spontaneous fracture.[4] There is no evidence to substantiate measuring BMD to evaluate fracture probability in paediatric patients with SB. Serious limitations were observed in the number and quality of studies concerning osteoporosis prevention and treatment in paediatric patients with SB.

References

1 Parsch K. Origin and treatment of fractures in spina bifida. Eur J Pediatr Surg 1991;1(5):298–305.

2 Molnar GE, Murphy KP. Spina bifida. In: Molnar GE, Alexander MA (eds.) Pediatric rehabilitation. Philadelphia, PA: Hanley & Belfus; 1999. p. 219–44.
3 Anschuetz RH, Freehafer AA, Shaffer JW, Dixon Jr. MS. Severe fracture complications in myelodysplasia. J Pediatr Orthop 1984; 4(1):22–4.
4 Marreiros H, Monteiro L, Loff C, Calado E. Fractures in children and adolescents with Spina Bifida – experience of a Portuguese tertiary care hospital. Dev Med Child Neurol 2010;52(8):754–9.
5 Quan A, Adams R, Ekmark E, Baum M. Bone mineral density in children with myelomeningocele. Pediatrics 1998;102(3):E34.
6 Drummond DS, Moreau M, Cruess RL. Post-operative neuropathic fractures in patients with myelomeningocele. Dev Med Child Neurol 1981;23(2):147–50.
7 Rosenstein BD, Greene WB, Herrington RT, Blum AS. Bone density in myelomeningocele: the effects of ambulatory status and other factors. Dev Med Child Neurol 1987;29(4):486–94.
8 Faulkner RA, Bailey DA, Drinkwater DT, McKay HA, Arnold C, Wilkinson AA. Bone densitometry in Canadian children 8–17 years of age. Calcif Tissue Int 1996;59(5):344–51.
9 Osteoporosis prevention, diagnosis, and therapy. NIH Consensus Development Panel on osteoporosis prevention, diagnosis, and therapy. JAMA 2001;285(6):785–95.
10 Akbar M, Bresch B, Raiss P, Fürstenberg CH, Bruckner T, Seyler T, *et al.* Fractures in myelomeningocele. J Orthop Traumatol 2010;11(3):175–82.
11 Okurowska-Zawada B, Konstantynowicz J, Kulak W, Kaczmarski M, Piotrowska-Jastrzebska J, Sienkiewicz D, *et al.* Assessment of risks factors for osteoporosis and fractures in children with meningomyelocele. Adv Med Sci 2009;54(2):247–52.
12 Dosa NP, Eckrich M, Katz DA, Turk M, Liptak GS. Incidence, prevalence, and characteristics of fractures in children, adolescents, and adults with spina bifida. J Spinal Cord Med 2007;30:S5–9.
13 Khoury JG, Morcuende MD. Dramatic subperiosteal bone formation following physeal injury in patients with myelomeningocele. Iowa Orthop J 2002;22:94–8.
14 Boytim MJ, Davidson RS, Charney E, Melchionni JB. Neonatal fractures in myelomeningocele patients. J Pediatr Orthop 1991; 11(1):28–30.
15 Lock TR, Aronson DD. Fractures in patients who have myelomeningocele. J Bone Joint Surg Am 1989;71(8):1153–7.
16 Drabu KJ, Walker G. Stiffness after fractures around the knee in spina bifida. J Bone Joint Surg Br 1985;67(2):266–7.
17 Kumar SJ, Cowell HR, Townsend P. Physeal, metaphyseal, and diaphyseal injuries of the lower extremities in children with myelomeningocele. J Pediatr Orthop 1984;4(1):25–7.
18 Reikerås O, Hellum C. Fractures in children with myelomeningocele. Arch Orthop Trauma Surg 1981;98(1):25–8.
19 Townsend PF, Cowell HR, Steg NL. Lower extremity fractures simulating infection in myelomeningocele. Clin Orthop Relat Res 1979;(144):255–9.
20 Quilis AN. Fractures in children with myelomeningocele. Acta Orthop Scand 1974;45(6):883–97.
21 Korhonen BJ. Fractures in myelodysplasia. Clin Orthop Relat Res 1971;79:145–55.
22 Drennan JC, Freehafer AA. Fractures of the lower extremities in paraplegic children. Clin Orthop Relat Res 1971;77:211–7.
23 James CC. Fractures of the lower limbs in spina bifida cystica: a survey of 44 fractures in 122 children. Dev Med Child Neurol Suppl 1970;22:88–93.
24 Szalay EA, Cheema A. Children with spina bifida are at risk for low bone density. Clin Orthop Relat Res 2011;469(5):1253–7.
25 Apkon S, Fenton L, Coll JR. Bone mineral density in children with myelomeningocele. Dev Med Child Neurol 2009;51(1):63–7.
26 Ausili E, Focarelli B, Tabacco F, Fortunelli G, Caradonna P, Massimi L, *et al.* Bone mineral density and composition in a myelomeningocele children population: effects of walking ability and sport activity. Eur Rev Med Pharmacol Sci. 2008;12(6): 349–54.
27 Taskinen S, Fagerholm R, Mäkitie O. Skeletal health after intestinal bladder augmentation: findings in 54 patients. BJU Int 2007; 100(4):906–10.
28 Boylu U, Horasanli K, Tanriverdi O, Kendirci M, Gumus E, Miroglu G. Evaluation of bone mineral density after ileocystoplasty in children with and without myelomeningocele. Pediatr Surg Int 2006;22(4):375–9.
29 Pluskiewicz W, Drozdzowska B. An interesting study conducted in a group of immobile children with neuromuscular disease. J Clin Densitom 2004;7(3):355.
30 Tuckerman K, Hofmaster P, Rosen CJ, Turi M. Bone density in ambulatory and immobile children. J Clin Densitom 2002;5(4): 327–34.
31 Mingin GC, Nguyen HT, Mathias RS, Shepherd JA, Glidden D, Baskin LS. Growth and metabolic consequences of bladder augmentation in children with myelomeningocele and bladder exstrophy. Pediatrics 2002;110(6):1193–8.
32 Koch MO, McDougal WS, Hill DE, Braren HV, Donofrio MN. Long-term metabolic effects of urinary diversion: a comparison of myelomeningocele patients managed by clean intermittent catheterization and urinary diversion. J Urol 1992;147(5):1343–7.
33 Mazur JM, Shurtleff DB, Menelaus MB, Colliver J. Orthopedic management of high-level spina bifida. Early walking compared with early use of a wheelchair. J Bone Joint Surg AM 1989; 71(1):56–61.
34 Quan A, Adams R, Ekmark E, Blaum M. Bone mineral density in children with myelomeningocele: effect of hydroclorothiazide. Pediatr Neprhol 2003;18(9):929–33.
35 Sholas MG, Tann B, Gaebler-Spira D. Oral bisphosphonates to treat disuse osteopenia in children with disabilities: a case series. J Pediatr Orthop 2005;25(3):326–31.
36 Steelman J, Zeitler P. Treatment of symptomatic pediatric osteoporosis with cyclic single-day intravenous pamidronate infusions. J Pediatr 2003;142(4):417–23.
37 Liptak GS, Shurtleff DB, Bloss JW, Baltus-Hebert E, Manitta P. Mobility aids for children with high-level myelomeningocele: parapodium versus wheelchair. Dev Med Child Neurol 1992;34(9): 787–96.
38 Rosenblum MF, Finegold DN, Charney EB. Assessment of stature of children with myelomeningocele, and usefulness of arm-span measurement. Dev Med Child Neurol 1983;25(3):338–42.
39 Shurtleff DB, Walker WO, Duguay S, Peterson D, Cardenas D. Obesity and myelomeningocele: anthropometric measures. J Spinal Cord Med. 2010;33(4):410–9.
40 Tobias JH, Steer CD, Emmett PM, Tonkin RJ, Cooper C, Ness AR. Bone mass in childhood is related to maternal diet in pregnancy. Osteoporos Int 2005;16(12):1731–41.
41 Bachrack LK. Osteoporosis and measurement of bone mass in children and adolescents. Endocrinol Metab Clin North Am 2005;34(3):521–35.
42 Steer CD, Emmett PM, Lewis SJ, Smith GD, Tobias JH. Methylenetetrahydrofolate Reductase (MTHFR) C677T polymorphism is associated with spinal BMD in 9-year-old children. J Bone Miner Res 2009;24(1):117–24.
43 Franchis R, Buoninconti A, Mandato C, Pepe A, Sperandeo MP, Sperandeo MP, *et al.* The C677T mutation of the 5,10-methylenetetrahydrofolate reductase gene is a moderate risk factor for spina bifida in Italy. J Med Genet 1998;35(12):1009–13.
44 Garoufi AJ, Prassouli AA, Attilakos AV, Voudris KA, katsarou ES. Homozygous MTHFR C677T gene mutation and recurrent stroke in an infant. Pediatr Neurol 2006;35(1):49–51.
45 Bachrach LK. Consensus and controversy regarding osteoporosis in the pediatric population. Endocr Pract 2007;13(5):513–20.
46 Specker BL, Schoenau E. Quantitative bone analysis in children: current methods and recommendations. J Pediatr 2005;146(6): 726–31.
47 Lewiecki EM, Gordon CM, Baim S, Leonard MB, Bishop NJ, Bianchi ML, *et al.* International Society for clinical Densitometry 2007 adult and pediatric official positions. Bone 2008;43(6):1115–21.
48 Bogunovic L, Doyle SM, Vogiatzi MG. Measurement of bone density in the pediatric population. Curr Opin Pediatr 2009; 21(1):77–82.
49 Fewtrell MS, on behalf of the British Pediatric and Adolescent Bone Group. Bone densitometry in children assessed by dual X-ray absorptiometry (DXA): uses and pitfalls. Arch Dis Child 2003;88(9):795–8.
50 Fewtrell MS, Gordon I, Biassoni L, Cole TJ. Dual x-ray absortiometry (DXA) of the lumbar spine in a clinical pediatric setting:

does the method of size-adjustment matter? Bone 2005;37(3): 413–9.
51 Sheridan KJ. Osteoporosis in adults with cerebral palsy. Dev Med Child Neurol 2009;51:S38–51.
52 Carter DR, Bouxsein ML, Marcus R. New approaches for interpreting projected bone densitometry data. J Bone Miner Res 1992;7(2):137–45.
53 Cowell CT, Lu PW, Lloyd-Jones SA, Briody JN, Allen JR, Humphries IR, *et al.* Volumetric bone mineral density – a potential role in pediatrics. Acta Paediatr Suppl 1995;411:12–6.
54 Henderson RC, Lark RK, Newman JE, Kecskemthy H, Fung EB, Renner JB, *et al.* Pediatric reference data for dual X-ray absorptiometric measures of normal bone density in the distal femur. AJR Am J Roentgenol 2002;178(2):439–43.
55 Meyer S, Landau H. Precocious puberty in myelomeningocele patients. J Pediatr Orthop 1984;4(1):28–31.
56 Trollmann R, Strehl E, Dörr HG. Precocious puberty in children with myelomeningocele: treatment with gonadotropin-releasing hormone analogues. Dev Med Child Neurol 1998;40(1): 38–43.
57 Szalay EA, Harriman D. Adapting pediatric DXA scanning to clinical orthopaedics. J Pediatr Orthop 2006;26(5): 686–90.
58 Bouchard J, D'Astous J. Postoperative heterotopic ossification in children: a comparison of children with spina bifida and with cerebral palsy. Can J Surg 1991;34(5):454–6.
59 Kanis JA, McCloskey EV, Johansson H, Strom O, Borgstrom F, Oden A. How to decide to treat. Best Pract Res Clin Rheumatol 2009;23(6):711–26.
60 Clark EM, Tobias JH, Ness AR. Association between bone density and fractures in children: a systematic review and meta-analysis. Pediatrics 2006;117(2):e291–7.
61 Bachrach LK, Ward LM. Clinical review: bisphosphonate use in childhood osteoporosis. J Clin Endocrinol Metab 2009;94(2): 400–9.
62 Landin LA. Fracture patterns in children. Analysis of 8,682 fractures with special reference to incidence, etiology and secular changes in a Swedish urban population 1950–1979. Acta Orthop Scand Suppl 1983;202:1–109.
63 Diagnosis of osteoporosis in men, premenopausal women, and children. Writing Group for the ISCD Position Development Conference. J Clin Densitom 2004;7(1):17–26.
64 Stuberg WA. Considerations related to weight-bearing program in children with developmental disabilities. Phys Ther 1992;72(1): 35–40.
65 Ward K, Alsop C, Caulton J, Rubin C, Adams J, Mughal Z. Low magnitude mechanical loading is osteogenic in children with disabling conditions. J Bone Miner Res 2004;19(3):360–9.
66 Chad KE, Bailey DA, Mckay HA, Zello GA, Snyder RE. The effect of a weight-bearing physical activity program on bone mineral content and estimated volumetric density in children with spastic cerebral palsy. J Pediatr 1999;135(1):115–7.
67 Baer MT, Kozlowski BW, Blyler EM, Trahms CM, Taylor ML, Hogan MP. Vitamin D, calcium, and bone status in children with developmental delay in relation to anticonvulsant use and ambulatory status. Am J Clin Nutr 1997;65(4):1042–51.
68 Misra M, Pacaud D, Petryk A, Collett-Solberg PF, Kappy M. Vitamin D deficiency in children and its management: review of current knowledge and recommendations. Pediatric 2008;122(2): 398–417.
69 Wosje KS, Specker BL. Role of calcium in bone health during childhood. Nutr Rev 2000;58(9):253–68.
70 Rendeli C, Ausili E, Tabacco F, Focarelli B, Pantanella A, Di Rocco C, *et al.* Polyethylene glycol 4000 vs. lactulose for the treatment of neurogenic constipation in myelomeningocele children: a randomized-controlled clinical trial. Aliment Pharmacol Ther 2006;23(8):1259–65.
71 Matlaga BR, Kim SC, Watkins SL, Kuo RL, Munch LC, Lingeman JE. Changing composition of renal calculi in patients with neurogenic bladder. J Urol 2006;175(5):1716–9.
72 Srivastava T, Schwaderer A. Diagnosis and management of hypercalciuria in children. Curr Opin Pediatr 2009;21(2):214–9.
73 Biyikli NK, Alpay H, Guran T. Hypercalciuria and recurrent urinary tract infections: incidence and symptoms in children over 5 years of age. Pediatr Nephrol 2005;20(10):1435–8.
74 Ward L, Tricco AC, Phuong P, Cranney A, Barrowman N, Gaboury I, *et al.* Bisphosphonate therapy for children and adolescents with secondary osteoporosis in childhood and adolescence. Cochrane Database Syst Rev 2007;(4):CD005324.
75 Reusz GS, Dobos M, Vásárhelyi B, Sallay P, Szabó A, Horváth C, *et al.* Sodium transport and bone mineral density in hypercalciuria with thiazide treatment. Pediatr Nephrol 1998;12(1):30–4.
76 Voskaki I, al Qadreh A, Mengreli C, Sbyrakis S. Effect of hydrochlorothiazide on renal hypercalciuria. Child Nephrol Urol 1992; 12(1):6–9.
77 Schoemaker LR. Expanding role of bisphosphonate therapy in children. J Pediatr 1999;134(3):264–7.
78 Soyka LA, Misra M, Frenchman A, Miller KK, Grinspoon S, Schoenfeld DA, *et al.* Abnormal bone mineral accrual in adolescent girls with anorexia nervosa. J Clin Endocrinol Metab 2002; 87(9):4177–85.
79 Bachrach LK, Katzman DK, Litt IF, Guido D, Marcus R. Recovery from osteopenia in adolescent girls with anorexia nervosa. J Clin Endocrinol Metab 1991;72(3):602–6.
80 Vahle JL, Sato M, Long GG, Young JK, Francis PC, Engelhardt JA, *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(3): 312–21.
81 Munns CF, Rajab MH, Hong J, Briody J, Hogler W, McQuade M, *et al.* Acute phase response and mineral status following low dose intravenous zoledronic acid in children. Bone 2007;41(3): 366–70.
82 Munns CF, Rauch F, Mier RJ, Glorieux FH. Respiratory distress with pamidronate treatment in infants with severe osteogenesis imperfecta. Bone 2004;35(1):231–4.
83 Whyte MP, Wenkert D, Clements KL, McAlister WH, Mumm S. Bisphosphonates-induced osteopetrosis. N Eng J Med 2003;349(5): 457–63.
84 Högler W, Yap F, Little D, Ambler G, McQuade M, Cowell CT. Short-term safety assessment in the use of intravenous zoledronic acid in children. J Pediatr 2004;145(5):701–4.
85 Munns CF, Rauch F, Zeitlin L, Fassier F, Glorieux FH. Delayed osteotomy but not fracture healing in pediatric osteogenesis imperfecta patients receiving pamidronate. J Bone Miner Res 2004; 19(11):1779–86.
86 Van den Wyngaert T, Huizing MT, Vermorken JB. Bisphosphonates and osteonecrosis of the jaw: cause and effect or a post hoc fallacy? Ann Oncol 2006;17(8):1197–204.
87 Bachrach SJ, Kecskemethy HH, Harcke HT, Hossain J. Decreased fracture incidence after 1 year of pamidronate treatment in children with spastic quadriplegic cerebral palsy. Dev Med Child Neurol 2010;52(9):837–42.
88 Henderson RC, Lark RK, Kecskemethy HH, Miller F, Harcke HT, Bachrach SJ. Bisphosphonates to treat osteopenia in children with quadriplegic cerebral palsy: a randomized, placebo-controlled clinical trial. J Pediatr 2002;141(5):644–51.
89 Batch JA, Couper JJ, Rodda C, Cowell CT, Zacharin M. Use of bisphosphonate therapy for osteoporosis in childhood and adolescence. J Paediatr Child Health 2003;39(2):88–92.
90 Mehta NM, Malootian A, Gilligan JP. Calcitonin for osteoporosis and bone pain. Curr Pharm Des 2003;9(32):2659–76.
91 Shaw NJ. Management of osteoporosis in children. Eur J Endocrinol 2008;159:S33–9.