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 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, studies were excluded if they 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:

- Spina Bifida
- Meningomyelocele
- Myelomeningocele
- Bone density
- Prevention
- Spinal Dysraphism
- Walking
- Bone and Bones
- Bone
- Osteoporosis
- Vibration
- (‘Spinal Dysraphism’[Mesh] OR ‘Meningomyelocele’[Mesh]) AND ‘Vibration’[Mesh]
- Standing
- Vibrating platform
- 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]

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
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 (Szalay, 2010; Marreiros, 2010; Okurowska-Zawada, 2009; Dosa, 2007; Khoury, 2002; Parsch, 1991; Boytim, 1991; Locke, 1989; Drabu, 1985; Kumar, 1984; Anschuetz, 1984; Reikerås, 1981; Drumbold 1981; Townsend, 1979; Quilis, 1974; Korhonen, 1971). By reviewing the reference lists of selected papers, we selected two additional articles (Drennan, 1971; James, 1970) (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; Apkon, 2009; Okurowska-Zawada, 2009; Ausili, 2008; Taskinen, 2007; Boyle, 2006; Pluskiewicz, 2004; Tucherman, 2002; Mingin, 2002; Quan, 1998; Koch, 1992; Rosenstein, 1987) (Table 2). The articles Pluskiewicz, 2004 and Tucherman, 2002 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; Quan, 2003; Sholas, 2005; Ausili, 2008) (Table 3).

Because all of the studies had small sample sizes 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) (Table 4).

An article that met our inclusion criteria, but was not obtained using the search strategy was selected (Liptak, 1992). 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. 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.

The most common fracture site is the distal femur.

Occurrence of fractures in relation to the mechanism of injury
Many fractures result from minor stress or are spontaneous. Thus, the true incidence of fractures is probably higher than presently measured.
recorded because not all fractures are recognized.\textsuperscript{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 were the following: fall (35\%), transfer (28\%), cast immobilization (37\%), and unknown (21\%).\textsuperscript{10} In our previous study, we showed that spontaneous fractures were the principal mechanism of injury (64.4\%).\textsuperscript{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.\textsuperscript{1} Lock et al. detected 66 fractures in 37 of 186 patients. Only seven (9\%) were associated with a history of known trauma.\textsuperscript{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\textsuperscript{1,4,10,14,15} and in non-ambulatory patients.\textsuperscript{4,10} James verified that in asymmetrically affected patients with SB, the paralytic limb was more likely to be fractured than the active limb.\textsuperscript{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.\textsuperscript{14}

### Environmental factors

Okurowska-Zawada et al. showed that body fat levels were higher in MMC patients with fractures than in those without fractures.\textsuperscript{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.\textsuperscript{18,39} Previous studies from general paediatric populations have reported that maternal dietary folate intake during pregnancy positively correlates with BMD of the child.\textsuperscript{40}
### Table 3  Search strategy used

<table>
<thead>
<tr>
<th>Prevention and treatment of osteoporosis</th>
<th>Articles</th>
</tr>
</thead>
<tbody>
<tr>
<td>'Myelomeningocele'[All Fields] OR 'Spina bifida'[All Fields] OR 'Meningomyelocele' [All Fields] AND 'Bone density'[All Fields] AND 'Prevention'[All Fields]</td>
<td>3 records identified</td>
</tr>
<tr>
<td>'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' TO '2011/06/10'[PDAT])</td>
<td>19 records identified</td>
</tr>
<tr>
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<td>11 records identified</td>
</tr>
<tr>
<td>'Spinal Dysraphism'[Mesh] OR 'Meningomyelocele'[Mesh] AND 'Vitamin D'[Mesh]</td>
<td>1 record identified</td>
</tr>
<tr>
<td>'Spinal Dysraphism'[Mesh] OR 'Meningomyelocele'[Mesh] AND 'Diphosphonates'[Mesh]</td>
<td>3 records identified</td>
</tr>
<tr>
<td>'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]</td>
<td>7 records identified</td>
</tr>
<tr>
<td>'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' TO '2011/06/10'[PDAT]) AND ('humans'[MeSH Terms] AND English[lang])</td>
<td>23 records identified</td>
</tr>
</tbody>
</table>

1 record identified that met all eligibility requirements (Quan, 2003)
2 records identified that met all eligibility requirements (Ausili, 2008; Mazur, 1981)
1, Adult patients (Valloton, 2006)
3, Review articles (Webb, 2010; Lubicky, 2005; Roussos, 2001)
2, No intervention (Mountain, 2010; Semler, 2007)
2, Other subject (Mountain, 2010; Geertzen, 2009)
6, Other subject (Mountain, 2010; 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 (Valloton, 2006)
3, Review articles (Webb, 2010; Lubicky, 2005; Roussos, 2001)
2, No intervention (Mountain, 2010; Semler, 2007)
2, Other subject (Mountain, 2010; Semler, 2007)
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)
11 records excluded:
1, No intervention (Quan, 1998)
1, Other subject (Quan, 1998)
3 records excluded:
1, No intervention (Duprez, 1996)
1, Review articles (Osebold, 1982)
1, Review articles (Osebold, 1982)
1, Non-English studies (Sholas, 2005)
2, No intervention (Marreiros, 2010; Anschuetz, 1984)
3, Other subject (Funk, 2011; Semler, 2007; Osebold, 1982)
1, Review articles (Osebold, 1982)
2, No intervention (Marreiros, 2010; Quan, 2003)
2, Other subject (Semler, 2007; VanSickle, 2001)
2, No intervention (Marreiros, 2010; Anschuetz, 1980; Apkon, 2009; Mingin, 2002; Quan, 2003; Ozard, 2008; Mingin, 2002; Quan, 2003; Osborn, 1989; Petersen, 1987; Pettit, 1980; Griffiths, 1983; Pettit, 1979; Elwood, 1977)
1, Review articles (Osebold, 1982)
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1, Review articles (Osebold, 1982)
2, No intervention (Marreiros, 2010; Anschuetz, 1980; Apkon, 2009; Mingin, 2002; Quan, 2003; Osborn, 1989; Petersen, 1987; Pettit, 1980; Griffiths, 1983; Pettit, 1979; Elwood, 1977)
1, Review articles (Osebold, 1982)
Association between fractures and prolonged inactivity

In paediatric patients with SB, there is an association between fractures and prolonged inactivity secondary 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 SB43 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 neurological interventions.1,4

Dosa et al. found that while neither shunted hydrocephalus nor cognitive subscores on the Functional Independence Measure were associated with fractures,4

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). 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.

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.

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 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).

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.

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

| 1. | Personal history of spontaneous fracture |
| 2. | Non-ambulatory status |
| 3. | Higher level of neurological involvement |
| 4. | Physical inactivity (e.g. postoperative inactivity) |
| 5. | Contractures |
| 6. | Hypercalciuria |
| 7. | Higher body fat levels |

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). A limitation of this study is its evaluation of BMD in the radius, which is less often fractured in this population.

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Total body BMC increases nearly three-fold in females and more than triples in males between 8 and 17 years of age. 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. 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. Comparisons between MMC children who underwent conduit urinary diversion (ileal or colonic) or were managed with intermittent catheterization showed no significant difference in BMD. In a comparison of BMD in MMC children with or without bladder...
Marreiros et al. Osteoporosis in spina bifida

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.\textsuperscript{24,25,54,57} Reference Z-scores for the distal lateral femur are available for children aged 3 years and older.\textsuperscript{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.\textsuperscript{59}

Although several studies have been conducted to assess BMD in paediatric populations, there is no consensus for predicting fracture risk,\textsuperscript{41,47,57,60} particularly in those with chronic conditions\textsuperscript{45} such as SB.\textsuperscript{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.\textsuperscript{47} According to some authors, osteoporosis can be suspected clinically in patients who suffer a low-impact fracture.\textsuperscript{61,62} Both the emphasis on the presence of fracture by the definition of osteoporosis used by the ISCD\textsuperscript{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.\textsuperscript{57,61} Thus, unlike in adults, the diagnosis of osteoporosis in children depends on a history of fracture.\textsuperscript{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.\textsuperscript{47,61} To prevent fractures secondary to postoperative inactivity,\textsuperscript{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.\textsuperscript{6} The period of immobilization after a surgical intervention should be reduced, if possible,\textsuperscript{6,15} and weight-bearing should be allowed as soon as possible,\textsuperscript{1,10} depending on X-rays signs of consolidation.\textsuperscript{10} There is limited evidence that passive weight-bearing in children with SB improves BMD,\textsuperscript{25} although standing with the use of a standing frame appears to increase BMD in children with cerebral palsy.\textsuperscript{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.\textsuperscript{65}

Data from physical therapy research,\textsuperscript{66} including investigations of standing on vibrating platforms\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{26}

No studies are available concerning the amount of weight bearing and ambulation necessary to maintain or increase BMD\textsuperscript{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.\textsuperscript{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.\textsuperscript{9} A review of controlled trials documented an increase in the BMC of adolescents who took calcium supplements.\textsuperscript{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.\textsuperscript{70} Moreover, patients with MMC have hypercalciuria linked to immobilization,\textsuperscript{11} which is a known metabolic risk factor associated with renal calculi. Matlaga \textit{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.\textsuperscript{71} Consequently, in patients with SB, metabolic calcium 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.\textsuperscript{72} Hypercalciuria was also found in 43\% of children with recurrent urinary tract infection.\textsuperscript{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,\textsuperscript{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.\textsuperscript{25}

Hydrochlorothiazide is known to reduce urinary calcium loss and increase BMD in non-MMC patients,\textsuperscript{75,76} and a positive association between hypercalciuria and fractures has been identified in SB patients.\textsuperscript{11} In a prospective randomized, double-blinded controlled study of 20 children with MMC with ages ranging from 6 to 16 years, Quan \textit{et al.} recorded no positive effects of hydrochlorothiazide on forearm BMD compared to placebo-treated controls, despite a tendency for decreased urine calcium excretion.\textsuperscript{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\textsuperscript{77} and is being considered with increasing frequency in children with secondary osteoporosis. In a case series, Sholas \textit{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.\textsuperscript{35} A similar conclusion was drawn from a retrospective, uncontrolled trial by Steelman \textit{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.\textsuperscript{36}

Low BMD among children may not indicate accelerated bone loss\textsuperscript{41} but rather a failure to achieve the expected peak bone mass, bone loss or a combination of the two.\textsuperscript{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.\textsuperscript{41} In this way, in children who fail to gain adequate bone mineral,\textsuperscript{41} PTH would be an alternative because it is the most effective anabolic agent for bones in adults.\textsuperscript{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.\textsuperscript{80} The previously mentioned study by Quan \textit{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.\textsuperscript{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 bisphosphate therapy should be analysed and weighed against the potential adverse effects. Flu-like symptoms in children can occur with the initiation of bisphosphonates. 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. 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. In excess, bisphosphonates can induce the over-suppression of bone turnover and can cause acute post-infusion hypocalcemia and hypophosphatemia. Iatrogenic osteoporosis was detected in a child who was treated for 2 1/2 years with more than four times the usual pamidronate dosage. In children with osteogenesis imperfecta, pamidronate disodium has been associated with an increased risk of delayed osteotomy healing. Osteonecrosis of the jaw has been described among adults; however, there were no cases identified in children receiving bisphosphonates. Extrapolating the literature from other diagnoses and reviewing clinical experiences suggests 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. Moreover, there is no literature detailing which factors should be used to determine the suitable length of pharmacological treatment after bisphosphate treatment is initiated.

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. 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.

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. Weight bearing during ambulation and sports activity should also be stimulated because it may reduce fractures and increase BMD 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. 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 and low BMD. The risk factors for fractures include higher level neurological involvement, non-ambulatory status, contractures, hypercalciuria, higher body fat levels, postoperative inactivity, and a previous spontaneous fracture. 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
