Bone Quality in Children with Severe Neurological Impairment and Intellectual Disability

Diagnostic methods and determinants of low bone quality

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Bone Quality in Children with Severe Neurological Impairment and Intellectual Disability

Diagnostic methods and determinants of low bone quality

Botkwaliteit bij kinderen met ernstige meervoudige beperkingen

Een onderzoek naar diagnostische methoden en factoren die samenhangen met lage botkwaliteit

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List of abbreviations

BA	Bone Age
BF	Body Fat
BMC	Bone Mineral Content
BMD	Bone Mineral Density
BMI	Body Mass Index
BUA	Broadband Ultrasound Attenuation
CI	Confidence Interval
CP	Cerebral Palsy
CT	Computed Tomography
CV	Coefficient of Variation
DICOM	Digital Imaging and Communications in Medicine
DXA	Dual Energy X-ray Absorptiometry (NL: DEXA)
DXR	Digital X-ray Radiogrammetry
DXR-BMD	Digital X-ray Radiogrammetry Bone Mineral Density
GI	Gastro Intestinal
GMFCS	Gross Motor Functioning Classification System
ID	Intellectual Disability
ISCD	International Society for Clinical Densitometry
IQ	Intelligence Quotient
MRI	Magnetic Resonance Imaging
NAGCPP	North American Growth in Cerebral Palsy Project
PBI	Paediatric Bone Index
pQCT	peripheral Quantitative Computed Tomography
RCT	Randomized Controlled Trial
SI	Stiffness Index
SIGN	Scottish Intercollegiate Guidelines Network
SD	Standard Deviation
SDS	Standard Deviation Score
SOS	Speed of Sound
T-score	Standard Deviation Score in comparison to the mean of healthy young adults
QCT	Quantitative Computed Tomography
QUI	Quantitative Ultrasound Index
QUS	Quantitative Ultrasonography
WHO	World Health Organisation
Z-score	Standard Deviation Score in comparison to the mean of persons with the same age and gender

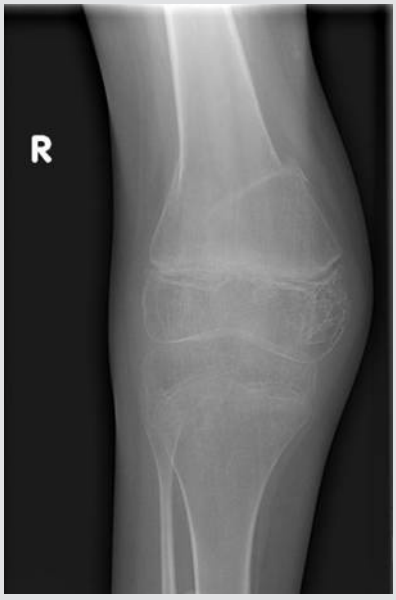
Chapter 1

Introduction and outline of the thesis

This thesis addresses bone quality in children with severe neurological impairment and intellectual disability (ID). In clinical practice severe problems concerning bone health are encountered in this group of severely disabled children as the following case report illustrates.

Alex is a 16-yr old boy with severe neurological impairment and ID of unknown origin. He has severe epilepsy, spasticity and contractures of upper and lower extremities, and scoliosis, leading to severe limitation of his mobility. Moreover, he suffers from chronic constipation, gastro-oesophageal reflux disease and recurrent airway infections.
To control his contractures, spasticity and scoliosis, at night he lays in an individualized orthesis. During one of the daily care moments his mother tries to reposition him in a better way. She puts her arms underneath both shoulders and knees to lift him. During this, she hears a snap and Alex starts to cry. Inspection of the legs shows no abnormalities but palpation and movement of the right leg are clearly painful. Because a fracture is suspected, a radiograph is made (Figure 1).

Figure 1. Radiograph of the right knee of Alex



It shows a femoral fracture just above the knee joint and osteopenic highly translucent bone with a small cortex. A plaster bandage is put on. Fracture healing is slow. After six weeks of plaster only minimal callus is seen. Subsequently, dual energy X-ray absorptiometry (DXA) is performed to determine bone mineral density (BMD). The DXA shows a very low bone density (BMD Z-score −3.8), but the DXA operator describes the examination as less accurate because Alex is not able to attain the appropriate posture because of his contractures. Moreover, it is difficult for him to lie still during the measurements. Alex is treated with oral bisphosphonates for 10 months. A new fracture occurs at the right femur, so intravenous treatment with bisphosphonates is started. A third fracture at the same femur occurs after 3 months of therapy with bisphosphonates. Because all fractures occur during care taking, splints are constructed to protect his legs during washing and dressing.

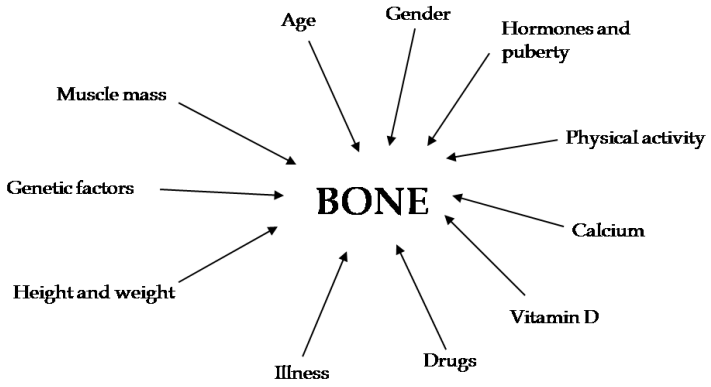
This case report illustrates many additional clinical experiences concerning the enormous impact of fractures on the quality of life of severely disabled children and their caretakers. Evidence is accumulating that the development of fractures is a consequence of processes that start early in life [1-2]. This provides a rationale to study bone quality in childhood, because it is considered an important risk factor of fragility fractures [3-4]. In this way, knowledge may be increased on the aetiology of low bone quality and indicate ways of prevention of fractures at an early stage.

Bone quality and bone mineral density

Bone quality and bone mineral density (BMD) are both aspects of bone health. Bone quality can consequently be defined in terms of bone microstructure, bone geometry, bone turnover and bone material properties [5]. BMD or bone mass concerns the calcium (and other minerals) content per section of bone (in gram/cm^2).

To adapt to mechanical stress and to maintain calcium homeostasis, bone is put through a constant process of remodelling. Bones will adjust their strength in proportion to the amount of mechanical stress put on them. Normal bones can detect and repair small amounts of micro damage by a process in which "remodelling units" remove and replace bone in a coordinated manner. Osteoclasts are responsible for absorbing bone tissue, while osteoblasts replace bone tissue.

Figure 2. Determinants for bone health



Low BMD or osteoporosis arises if a longer existing mismatch occurs between the rates of bone resorption and bone formation [6]. It has been described as "a disease characterized by low bone mass and micro-architecture deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk". Osteoporosis in adults is considered a multifactorial disorder involving a broad variety of aetiological factors (Figure 2) [7-8].
Foundation for skeletal health is established early in life. In healthy children, in spite of constant remodelling of bone tissue, there is an accrual of bone mass throughout childhood and early adulthood, resulting in a peak bone mass. Scarce literature is present on a suboptimal accrual and lower peak bone mass in children with motor disabilities, resulting in early occurrence of fractures [2, 9-10]. Therefore, it seems important to monitor bone quality in children with severe neurological impairment and ID, in order to estimate fracture risk and to take preventive measures or even start intervention.

Description of the study population

Children with severe neurological impairment and ID have severe motor problems as well as an intellectual disability. They are defined in this thesis as children with a moderate to severe intellectual disability (estimated intelligence quotient (IQ) < 55) and a Gross Motor Functioning Classification System (GMFCS) level IV or V [11].

The GMFCS is a five level classification system that is widely used for children with cerebral palsy (CP) and describes gross motor function on the basis of self-initiated movement [11]. Children classified in level IV may walk indoors for short distances with physical assistance, but mostly rely on wheeled mobility. Children with GMFCS level V have severe limitations in head and trunk control, and in self-mobility. These children are entirely wheelchair depended [12-13].
Although the origin of their intellectual and motor disabilities may differ, e.g. in some children the handicap is caused by deprivation of oxygen during birth and in others by a known genetic disorder, or by a severe trauma, they have in common that they are prone to an accumulation of additional health problems. Epilepsy, chronic constipation, gastro-oesophageal reflux disease, dysphagia, recurrent airway infections, growth retardation, contractures, scoliosis of the spine and visual impairment are frequently observed, as well as polypharmacy [9, 14-19]. And although their life expectancy remains reduced in comparison to children without these profound handicaps, in recent years improvement of medical care, including the introduction of the percutanous gastrostomy catheter has caused a considerable improvement in life expectancy. A 5 year increase was observed between 1995 and 2002 [20-21]. It is expected, that a rise in fracture incidence will be observed in this population, increasingly growing older.

Diagnostic methods

In Table 1, the definition of osteoporosis by the World Health Organisation (WHO) is shown. This definition is based on BMD measurements with DXA. In the general adult population we are accustomed to measure bone quality, expressed in bone mineral density using DXA only.

Table 1. Definition of osteoporosis according to the World Health Organization (WHO).

T-score *	**Interpretation**
$T \leq -2.5$	Osteoporosis
$-2.5 < T \leq -1$	Osteopenia
$T > -1$	Normal Bone Mineral Density

* T-score: Standard Deviation Score of BMD outcome in comparison to the young adult mean BMD
BMD: Bone Mineral Density as measured by dual energy X-ray absorptiometry

In children, who by definition have not reached their peak bone mass yet, age and sex adjusted Z-scores are used to describe bone mass measurements instead of T-scores. Measurement of BMD in children using DXA requires specific software and each device has its own reference values. As a result, in the Netherlands, paediatric DXA is only available in academic hospitals, hampering availability of the method. Moreover, in clinical practice, the DXA method has not shown to be very feasible in children with severe neurological impairment and ID. Its accuracy can be diminished by a variability in skeletal size and body composition [22-24]. Therefore, a more generally available, easily applicable and safe diagnostic method is wanted for this group. This method should be suitable to evaluate bone health in the course of time.

Aims of the current study

The primary aim of our study was to establish the prevalence of low bone quality in children with severe neurological impairment and ID, and to identify which children could be most at risk for low bone quality and subsequent fractures, requiring a study of bone quality associated determinants in this specific population.
The feasibility of the golden standard method DXA, for assessing bone quality in this group was studied. In addition, other measurement methods, e.g. quantitative ultrasound (QUS) and automated radiogrammetry, were investigated in the scope of this thesis.

Outline of the thesis

This thesis can be divided into three main parts. In chapter 2 studies on low bone mineral density in children with severe neurological impairment and ID are reviewed.
The second part of the thesis describes our evaluations of diagnostic methods; DXA measurement (chapter 3), QUS (chapter 4) and automated radiogrammetry (chapter 5).
The last section of the thesis (chapter 6) describes the prevalence of low bone quality and its determinants in severely handicapped children.
In chapter 7 the results of the studies in this thesis are discussed and subsequent recommendations for further research and clinical practice are presented.

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Chapter 2

Epidemiology of low bone mineral density and fractures in children with severe cerebral palsy: a systematic review

Dev Med Child Neur 2009; 51(10): 773-778.

Abstract

Children with severe cerebral palsy (CP) are at risk for developing low bone mineral density (BMD) and low-impact fractures. The aim of this study was to provide a systematic literature review on the epidemiology of fractures and low BMD in children with severe CP, with an emphasis on risk factors. Gross Motor Function Classification System (GMFCS) levels IV and V were criteria for severe cerebral palsy.

The literature (PubMed) was searched and eligible studies were given a level of evidence score using the Scottish Intercollegiate Guidelines Network (SIGN) criteria.

Seven studies were found concerning epidemiology of fractures, 11 studies described epidemiology of low BMD, and 14 studies concerned risk factors. The methodological quality of most of these studies was poor. Five studies were considered well conducted, with low risk of confounding and bias. In these studies, the incidence of fractures in children with moderate to severe CP approached 4% per year, whereas the prevalence of low BMD in the femur was 77%. Limited ambulation, feeding difficulties, previous fractures, anticonvulsant use, and lower body fat mass were associated with low BMD Z-scores.

There is only a limited amount of high-quality evidence on low BMD and fractures in children with severe CP.

Introduction

Children with severe cerebral palsy (CP) may have an intellectual disability in addition to severe motor impairment. These children frequently experience health problems such as epilepsy, recurrent pulmonary infections, gastro-oesophageal reflux and constipation [1, 2]. In addition to the above, children with multiple disabilities are prone to develop low bone mineral density (BMD) [3, 4]. The underlying pathophysiology in these patients is complex, and several risk factors for the development of low BMD, such as immobility, low calcium intake, low vitamin D status and anticonvulsant use, are frequently observed in this group [5]. Most of these risk factors for developing low BMD are present from early childhood, so osteopenia primarily results not from true losses in bone mineral, but from a diminished growth rate of bone mineral compared with healthy children [6].
Earlier studies in children with primary osteoporosis or osteoporosis associated with chronic disease or its treatment have shown a relationship between decreased bone density and increased fracture incidence [7, 8]. In children with a profoundly low BMD, these fractures can occur without significant trauma [9]. Moreover, the lack of verbal communication in severely disabled children may lead to diagnostic delay of fractures and, therefore, increased morbidity.
To acquire a greater insight into fracture risk in children with severe CP it is necessary to evaluate not only fracture incidence and risk factors, but also the prevalence of low BMD and the determinants causing this condition.
The aim of this review is to provide a structured and comprehensive overview of the current literature on the prevalence of low BMD and the incidence of fractures in children with severe CP, with an emphasis on the risk factors.

Method

Searching

For this survey, we divided our search into the following two main subjects: fractures and low BMD. Studies concerning low BMD were further divided into prevalence studies and studies concerning determinants. Studies concerning both prevalence and determinants were reviewed for both subjects separately.
Articles were identified through the Medline database using PubMed by combining search terms for cerebral palsy (‘generalized cerebral palsy’, ‘cerebral palsy’,

'mental retardation', 'multiple disability', 'intellectual disability', 'learning disability') with keywords for fracture ('fractures', 'fracture') or keywords for bone mineral density ('bone mineral density', 'bone density', 'osteoporosis', 'osteopenia'). Search results were limited to human and paediatric studies published in the English language. Studies described in this review were published between 1950 (start of Medline) and February 2009.

Selection

Types of studies

All types of study designs (e.g. cross-sectional, cohort, or case–control), except case reports and case series, were considered for inclusion in this review.

Studied patients

Children (aged 0–18y) with severe CP were the subject of our search. Severe CP was defined as level IV or V according to the Gross Motor Function Classification system and a history of clinically diagnosed CP [10].

Outcome measures

Incidence rate of fractures, prevalence of low BMD (Z-score below –2) and predictive or associative factors for fractures and low BMD were our primary outcome measures. Statistical significance was set at $p<0.05$.

The mean Z-score for BMD was a secondary outcome measure. The individual Z-score was calculated by comparing BMD values with age- and sex-related reference values.

Validity assessment

The abstracts of the studies identified by the literature search were read to identify relevant studies for full review. Studies needed to concern children with moderate to severe CP and also had to provide data on fractures or bone density. In addition, we scrutinized the reference lists of the identified publications to find additional studies.

After review, we recorded information about the year of publication, study design, number of included participants, representativeness of the study population, applied diagnostic methods, and outcome measures.

Quality assessment

The quality of the eligible studies was assessed by taking into account the study design, the size and representativeness of the study population (i.e. the presence of selection bias), the validity of outcomes (risk of confounding or bias) and the quality of the statistical analysis. Two of the authors evaluated the levels of evidence of the articles independently using the previously published criteria developed by the Scottish Intercollegiate Guidelines Network (SIGN; Table 1) [11].

Table 1. Level of evidence rating system: Sign criteria[11]

Level of evidence score	
1++	High-quality meta-analyses, systematic reviews of RCTs or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews of RCTS or RCTs with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2-	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies, e.g. case reports, case series
4	Expert opinion

RCT, randomized controlled trial.

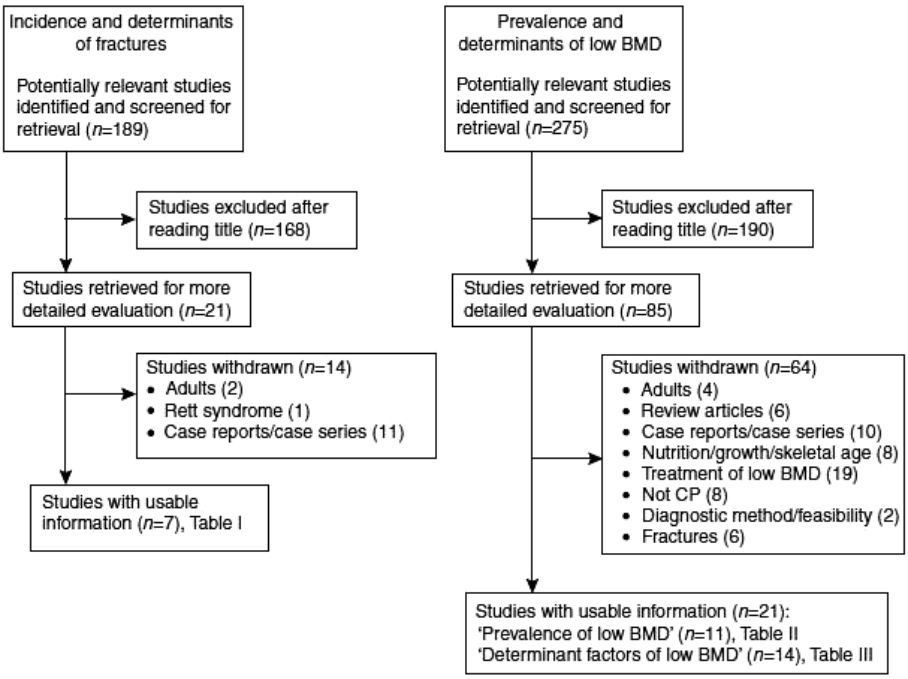
The highest levels of evidence in the SIGN grading system are accorded to randomized controlled trials and meta-analyses of randomized controlled trials. In the current review, concerning observational nonintervention studies, the highest possible score according to this rating system for this purpose was 2++, which is given for high-quality case–control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal.

Results

Trial flow

In Figure 1 we present a flow diagram, according to the Quoroum guidelines [12], that summarizes the results of our literature search.

Figure 1. Flow diagram (Quorum guidelines) modified for epidemiological studies [12].



Study characteristics

Incidence and determinants of fractures

The characteristics and levels of evidence of the seven publications on fractures are presented in Table 2.

Table 2: Incidence and determinants of fractures in children with severe CP

Reference	Study design	Study population (*n*)	Incidence rate fractures	Determinants	Level of evidence score[a]
Presedo et al. [17]	Cross-sectional file study	*n*=156 children with CP referred to hospital for fracture treatment. Control group: 100 children with CP without fractures	–	Use of antiepileptic drugs (p=0.001) Diminished ambulatory status (p=0.001) Osteopenia (on radiograph) (p=0.001) Quadriplegia (p=0.005)	2–
Ko et al. [20]	Case–control, retrospective, 12mo	*n*=19 children with CP with long-bone fracture. Control group: 90 children with CP without fracture, in residential care	–	Lower weight for age Z-score (p=0.01) Recent postoperative immobilization (p=0.04)	2–
Stevenson et al. [13]	Prospective cohort study, median duration of follow-up 1.6y (total 600 person-years)	*n*=364 children with moderate to severe CP, GMFCS III, IV and V (population based, identified through multiple methods including clinical samples, parent-to-parent organizations, local United Cerebral Palsy Associations, school systems, public service announcements, physical therapists, local physicians, equipment vendors, newspaper advertisements)	4/100/y (4% per year)	Higher body fat (p=0.03) Gastrostomy (p=0.05) Previous fracture (p=0.10)	2+

Table 2 (continued)

Reference	Study design	Study population (*n*)	Incidence rate fractures	Determinants	Level of evidence score[a]
Leet et al. [19]	Cross-sectional questionnaire study	*n*=418 children with CP in outpatient clinic/ rehabilitation centre	Prevalence: 50 (12%) patients sustained 66 fractures	Mixed tone (spastic and hypotonic) CP ($p<0.01$) Feeding tube[b] Seizure disorder[b] Valproic acid[b] Standing equipment in therapy[b] Older age at time of fracture and valproic acid use explained 5% of variance. Equation fracture=−0.01 + (valproic acid × 0.17) + (age × 0.15)	2–
Bischof et al. [16]	Cross-sectional	*n*=20 children and young adults in residential care with spastic quadriplegia and with long-bone fracture, 20 controls from same cohort without long-bone fracture	Prevalence: 20 out of a cohort of 88 residents (23%) sustained 56 fractures	Use of anticonvulsant therapy ($p=0.002$)	2–
Henderson [15]	Prospective cohort study, mean follow-up 3.8y	*n*=43 children with spastic quadriplegia (population based)	Males<6y=3.8/100/y (normal population 1.7) Males >6y=4.5/100/y (normal population 4.3) Females >6y=2.7/100/y (normal population 3.0)	Following spica casting incidence rate 8.6/100/y ($p=0.007$) Previous fracture incidence rate 8.3/100/y ($p=0.04$)	2–
Brunner et al [27]	Retrospective file study 20y	*n*=37 children and young adults with CP at paediatric orthopaedic centre with fracture without significant trauma (± 4000 CP patients/y)	0.065% per year (fractures without significant trauma)	–	2–

[a]See Table I for Sign criteria. [b]Significance (p value) not included in the article.

Prevalence and determinants of low bone mineral density

In Table 3 the characteristics of the 11 remaining articles on prevalence of low BMD are presented. The 14 articles on determinants of low BMD are more extensively described in Table 4.

Methodological quality

We did not find any high-quality systematic reviews, cohort, case–control or cross-sectional studies. Five studies were considered well conducted with a low risk of confounding or bias and a level of evidence score of 2+ [4, 6, 13-15]. In four of these studies the data presented had been collected as part of the North American Growth in Cerebral Palsy Project (NAGCPP), a project that started in 1996 at six separate sites in the USA and Canada [4, 13-15]. To obtain a representative population-based sample, multiple recruitment methods have been used to identify potentially eligible children: hospitals, newspapers, special education teachers, physical therapists and regional United Cerebral Palsy newsletters. All other reviewed studies had used selected populations (children at orthopaedic clinics or institutionalized children) rather than population-based samples, and, therefore, were more prone to selection bias. The five well-conducted studies also differed from the other studies in including a more extensive description of the statistical methods that had been used to analyze the data.

In 16 studies, the study design was not reported, while in two studies an incorrect design was formulated [16, 17]. Determining the applied study design was difficult in some cases because of unclear descriptions of methods or because of the use of multiple designs in one study. For example, sometimes it was not clear whether the determinants had been assessed at a distinct point in time or over a period of time, and some cross-sectional studies included small intervention studies or follow-up studies [13, 16, 18].

None of the articles reported a power calculation to determine the population size necessary to answer the research question. As 95% confidence intervals for prevalences of low BMD were not reported in any study (Table 3), these were calculated by us using the reported size of the study population because they provide valuable additional information in estimating the validity of the outcomes.

In the group of studies concerning fractures, three studies were file studies and two studies had used a questionnaire to collect data. Such studies are sensitive to information bias.

Table 3: Prevalence of low bone mineral density in children with severe CP

Reference	Study design	Study population (*n*)	Diagnostic method	Prevalence of low BMD (Z-score<−2 SD)	Level of evidence score[a]
Modlesky et al. [28]	Cross-sectional	*n*=12 children with CP, non-ambulatory hospital population, 10 age- and sex-matched control patients	Dual Energy X-ray Absorptiometry of the distal femur	Z-scores were not calculated in this study. areal BMD and bone mineral content were markedly lower in children with CP than in controls (37% vs. 46%, $p<0.001$)	2–
Ali et al. [22]	Cross-sectional	*n*=30 children with CP, outpatient orthopaedic clinic	Dual Energy X-ray Absorptiometry of lumbar spine	20/30 (66.6%) (95% CI 49.8–83.5%) Mean Z-score −2.14, SD 1.08	2–
Henderson et al. [6]	Prospective observational	*n*=69 children with moderate to severe spastic CP	Dual Energy X-ray Absorptiometry of distal femur and lumbar spine	Mean BMD Z-scores distal femur: 2.0–5.9y: −2.4, SD 0.4 6.0–11.9y: −3.0, SD 0.2 12.0–19.4y: −3.4, SD 0.4) Mean BMD Z-scores lumbar spine: 2.0–5.9y: −2.8, SD 0.3 6.0–11.9y: −1.7, SD 0.2 12.0–19.4y: −2.3, SD 0.4	2+
Binkley et al. [29]	Cross-sectional	*n*=13 CP patients in long-term residential care (26 controls)	Peripheral quantitative computed tomography of the tibia	Z-scores were not calculated in this study. Cortical bone mineral content, cortical area, cortical thickness, periosteal circumference, endosteal circumference, and polar strength–strain index were greater in the control group ($p<0.05$)	2–

Table 3 (continued)

Reference	Study design	Study population (*n*)	Diagnostic method	Prevalence of low BMD (Z-score<−2 SD)	Level of evidence score[a]
Hartman et al. [21]	Cross-sectional	*n*=87 institutionalized children/young adults with moderate to severe intellectual disabilities	Bone quantitative ultrasound of distal radius and midshaft tibia	22/82 (27%) (95% CI 17.6–37.8%) (considering measurement of either radius or tibia)	2–
King et al. [3]	Cross-sectional	*n*=48 non-ambulatory patients with spastic quadriplegia in residential care and outpatient departments	Dual Energy X-ray Absorptiometry of the lumbar spine	28/48 (58%) (95% CI 43.2–72.4%) Mean Z-score −2.37, SD 0.21 ≤ 18y: mean Z-score −2.32, SD 0.23	2–
Henderson et al. [4]	Cross-sectional	*n*=62 children with moderate to severe CP (population-based sample)	Dual Energy X-ray Absorptiometry of distal femur and lumbar spine	Femur 48/62 (77%) (95% CI 65.0–87.1%) Mean Z-score distal femur: −3.1, SD 0.2 Mean Z-score lumbar spine: −1.8, SD 0.1	2+
Tasdemir et al. [30]	Cross-sectional	*n*=24 children with CP: nine ambulant, 15 non-ambulant; 19 controls	Quantitative computed tomography of the lumbar spine	Mean BMD values were lower in patient group than in controls	2–

Table 3 (continued)

Reference	Study design	Study population (*n*)	Diagnostic method	Prevalence of low BMD (Z-score<−2 SD)	Level of evidence score[a]
Wilmhurst et al. [31]	Cross-sectional	*n*=27 children with CP attending schools for children with learning difficulties. Divided in four groups depending on mobility	Quantitative computed tomography of the lumbar spine and quantitative ultrasound of the calcareous	Mean broadband ultrasound attenuation (BUA) Z-scores: Mobile with abnormal gait: −1.07, SD 0.30 Mobile with frame/rollator: −1.85, SD 0.51 Non-mobile but stands in a frame: −2.46, SD 0.15 Non-mobile or weight bearing: −3.09, SD 0.24. Mean spinal bone mineral density Z-scores: Mobile with abnormal gait: −1.08, SD 0.32 Mobile with frame/rollator: −2.12, SD 0.59 Non-mobile but stands in a frame: −1.45, SD 0.38 Non-mobile or weight bearing: −2.79, SD 0.47	2−
Henderson et al. [23]	Cross-sectional	*n*=139 heterogeneous group of children with spastic CP, orthopaedic outpatient clinic	Dual Energy X-ray Absorptiometry of proximal femur and lumbar spine	Mean BMD Z-score: Proximal femur: −0.92, SD 0.14 Lumbar spine: −0.80, SD 0.10	2−
Shaw et al. [32]	Case series	*n*=9 non-ambulant children with severe CP	Dual Energy X-ray Absorptiometry (*n*=8), peripheral quantitative computed tomography (*n*=1) of the lumbar spine	BMD SD scores ranged from −8.9 to −2.5	3

[a]See Table I for Sign criteria.

In eight out of the 14 studies in which determinants (for fractures or low bone mineral density) were described and analysed, a multiple regression analysis had been performed. The other studies used linear regression analyses or t-tests only, so little could be said about the interference between different determinants in these studies.

Study outcomes

Incidence rate and determinants of fractures

The prevalence of fractures reported in two studies was 12% (95% CI 8.9–15.1%) [19] and 23% (95% CI 14.0–31.5%) [16]. The incidence of fractures was reported in two other studies and varied between 2.7% (95% CI −0.3 to 5.7%) and 4.5% (95% CI 1.0–7.9%) [13, 15]. The most frequently reported determinants were use of antiepileptic drugs, immobilization, fracture in history and use of a feeding tube (Table 3) [13, 15-17, 19, 20].

In a study by Stevenson et al. (level of evidence 2+), the incidence of fractures in children with moderate to severe CP (n=261) was 4% per year (95% CI 1.5–6.2%) [13]. A higher percentage body fat and the presence of a gastrostomy catheter were significantly associated with a higher number of reported fractures. Determinants that did not have a significant relation were sex, Gross Motor Function Classification System (GMFCS) level, race, anticonvulsant use, height Z-score, and weight Z-score.

Prevalence of low BMD

The prevalence of low BMD of the distal femur, defined as a Z-score lower than −2, was 77% (95% CI 65.0–87.1%) in a study by Henderson et al. (level of evidence score 2+)[4]. The mean Z-score for BMD of the distal femur was −3.1 0.2 (SD) and for BMD of the lumbar spine was −1.8 ± 0.1 (Table 3).

In three other studies, a prevalence of 27% [21], 58% [3], and 66%[22] was found. In seven other studies only mean BMD Z-scores were calculated for children with different levels of CP and mobility and of different ages. Mean BMD Z-scores varied in these studies between −3.4 (distal femur in children with moderate to severe CP aged 12–19y) [6] and −0.8 (lumbar spine in children with spastic CP) [23]. In a second study by Henderson et al. [6], which we assigned a level of evidence 2+, mean BMD Z-scores in the distal femur ranged from −2.4 to −3.4 with increasing age.

Determinants of low BMD

The most commonly studied determinants were GMFCS level, feeding difficulties, previous fracture and use of antiepileptic drugs (Table 4) [3, 21, 24, 25].

Two studies by Henderson et al. were assigned a level of evidence score of 2+ [4, 14]. Based on the outcomes of a study on predicting low BMD [15], a regression equation was developed for predicting BMD Z-score from the variables weight Z-score, age, GMFCS level, feeding difficulties, previous fracture and use of anticonvulsants (R^2=0.55, p=<0.0001) [14, 15]. In the other study on bone density and metabolism, the authors reported a significant association between GMFCS score (p<0.001), feeding difficulties (p=0.003), previous fracture (p< 0.001), and anticonvulsant use (p=0.003) and the BMD Z-score measured in the distal femur [4]. In addition, a significant relation was described between low triceps skinfold Z-score and low BMD Z-score measured in the lumbar spine [4, 14].

Factors that did not have a significant relation to low BMD according to both studies were age, sex, race, temporary immobilization, health status, calcium intake, serum transthyretin, serum 25-hydroxyvitamin D, serum N-telopeptides, serum osteocalcin and phosphorus, calcium and alkaline phosphatase levels.

Discussion

This review confirms that low BMD is a serious problem in children with severe CP, with mean Z-scores ranging from −3.4 in the distal femur to −0.8 in the lumbar spine [4, 6, 23], a prevalence of BMD Z-scores below −2 of 77% (95% CI 65.0–87.1%) [4], and an annual incidence of fractures of 4% [13]. Significant determinants of low BMD were limited ambulation, feeding difficulties, previous fracture, anticonvulsant use, and lower fat mass (measured at the triceps skinfold) [4, 14].

However, the evidence is still limited because most identified studies were either (low-quality) file studies or case reports. No high-quality studies have been published, but five studies were considered well conducted with a low risk of confounding or bias. Four of them were found to be acceptable because of the representative population-based study population (no selection bias), and all five had a clear description of methods and statistical procedures.

The paucity of valid research can, to a large extent, be explained by the fact that research in children with severe CP requires complicated logistics. Study protocols

Table 4: Determinants of low BMD in children with severe CP

Reference	Study design	Study population (*n*)	Diagnostic method	Determinants of low BMD (Z-score < −2 SD)	Level of evidence score[a]
Ali et al. [22]	Cross-sectional	*n*=30 children with CP, outpatient orthopaedic clinic	Dual Energy X-ray Absorptiometry of lumbar spine	IGF-1 (p=0.09) IGFBP-3 (p=0.05) (correlation was limited to 25 osteopenic patients)	2–
Jekovec-Vrhovšek et al. [33]	Cross-sectional	*n*=67 children and young adults with CP in residential care, divided in three groups based on fracture history and anticonvulsant medication use	Quantitative ultrasound of the calcaneus	Significantly higher values of the quantitative ultrasound index (QUI) were found in the group without long-bone fractures and not taking anticonvulsant medication. The lowest QUI values were in the group with long-bone fractures and taking anticonvulsant medication	2–
Hartman et al. [21]	Cross-sectional	*n*=87 institutionalized children/ young adults with moderate to severe retardation	Bone quantitative ultrasound distal radius and midshaft tibia	Radius BMD: Female gender (p=0.003) Height for age (p=0.008) Tibia BMD: Age (p=0.03) Fracture history (p=0.04)	2–
Henderson et al. [14]	Cross-sectional	*n*=107 children with moderate to severe CP (population based sample)	Dual Energy X-ray Absorptiometry of distal femur	Predicted BMD Z-score=−0.75 + (0.19 × weight Z-score) − (0.091 × age) + 0 if GMFCS III, −0.71 if GMFCS IV, −0.86 if GMFCS V, −0.81 if moderate/severe feeding difficulty, −0.53 if previous fracture and −0.31 if on anticonvulsants R^2=0.55 (p<0.0001)	2+

Table 4 (continued)

Reference	Study design	Study population (*n*)	Diagnostic method	Determinants of low BMD (Z-score < −2 SD)	Level of evidence score[a]
Ünay et al. [34]	Cross-sectional	*n*=40 children with CP, 40 children in healthy control group	Dual Energy X-ray Absorptiometry of the lumbar spine	Mean BMD value was significantly lower in children with CP than in the control group. BMD was significantly lower in tetraplegic than in hemiplegic children	2–
King et al. [3]	Cross-sectional study	*n*=48 non-ambulatory patients with spastic quadriplegia in residential care and outpatient departments	Dual Energy X-ray Absorptiometry of the lumbar spine	Fracture history (p=0.05)	2–
Henderson et al. [4]	Cross-sectional	*n*=117 children with moderate to severe cerebral palsy (62 population-based sample, 55 hospital and school population)	Dual Energy X-ray Absorptiometry of distal femur and lumbar spine	Distal femur BMD: GMFCS level (p<0.001) Increasing difficulty in feeding (p=0.003) Use of anticonvulsant medications (p=0.003) Lumbar spine BMD: GMFCS (p=0.03) Triceps skinfold Z-scores (p=0.003)	2+
Tuckerman et al. [35]	Cross-sectional	*n*=10 immobile children residential setting and orthopaedic clinic (7 children with CP), 20 controls	Dual Energy X-ray Absorptiometry of lumbar spine	No difference in bone density between healthy control participants and immobile children	2–

Table 4 (continued)

Reference	Study design	Study population (*n*)	Diagnostic method	Determinants of low BMD (Z-score < −2 SD)	Level of evidence score[a]
Ihkkan et al. [36]	Cross-sectional	*n*=69 children with spastic cerebral palsy, 26 controls	Dual Energy X-ray Absorptiometry of total body	BMD values of lower extremities were lower in tertraplegic children than in control and hemiplegic children ($p<0.5$)	2–
Chad et al. [24]	Cross-sectional	*n*=17 white children with spastic CP (referral by clinicians and advertisement)	Dual Energy X-ray Absorptiometry of total body, total proximal femur and femoral neck	Non-independent ambulators ($p<0.05$)	2–
Duncan et al. [37]	Retrospective file study (case series)	*n*=19 non-ambulatory children with CP in a rehabilitation clinic	Radiological diagnosis of osteopenia		3
Baer et al. [25]	Cross-sectional	*n*=338 children with cognitive delays, living at home, divided in four groups depending on ambulatory status and anticonvulsant use	Radiograph of left hand and wrist	Mean Z-scores were lower for all groups than the predicted norm ($p<0.001$), and significantly lower among non-ambulatory children regardless of anticonvulsant use ($p<0.001$)	2–

Table 4 (continued)

Reference	Study design	Study population (*n*)	Diagnostic method	Determinants of low BMD (Z-score < −2 SD)	Level of evidence score[a]
Henderson et al. [23]	Cross-sectional	*n*=139 children with spastic CP in paediatric orthopaedic outpatient clinic	Dual Energy X-ray Absorptiometry of proximal femur and lumbar spine	Distal femur BMD: Functional level of walking (p<0.001) Age when child first walked (p<0.005) Immobilization (p=0.07) Nutritional score (p=0.02) Lumbar spine BMD: Functional level of walking (p<0.001) Age when child first walked (p<0.005) Quadriplegia versus di/hemiplegia (p<0.001) Immobilization (p=0.005) Use of antiepileptic drugs (p=0.005) Nutritional score (p<0.001) Calcium intake<500 mg/d (p<0.05)	2–
Nishiyama et al. [38]	Cross-sectional	*n*=118 institutionalized patients (30 children) with severe intellectual disability and/or physical disabilities divided in three groups depending on ambulatory status	Microdensitometry of second metacarpal	Bone width, bone pattern area and bone salt density were decreased in patients, most prominent in group 1 (bed-ridden patients). Patients receiving anticonvulsants showed lower bone pattern area and bone salt density (p<0.05 and 0.01)	2–

[a]See Table I for Sign criteria.
IGF, insulin-like growth factor; IGFBP, insulin-like growth factor-binding protein.

are minutely examined by medical ethics committees because the studies involve a vulnerable patient group. Moreover, it is difficult to obtain a sufficiently large and representative study population if the patient group is relatively small, and parental consent rates for research are usually rather low. Indeed, most studies we reviewed used small and selected patient populations. The NAGCPP can be regarded as an example of how a representative study population can be achieved. The best way to obtain more valid data on bone quality and risk factors for low BMD in children with severe CP is by longitudinal research. A high-quality cohort study achieving a level of evidence score of 2++ on the Sign criteria would require recruitment in a representative community setting, for example through day-care centres and special schools. Bone density measurements should be performed annually over a longer period of follow-up (e.g. 5 y) to determine changes in BMD over time and should be combined with repetitive assessment of determinants of low BMD. The measurements should impose a minimal burden on the children, so that parents or caregivers will be more likely to cooperate and will not readily drop out. This could be achieved by performing bone density measurement at home to avoid transportation of the child to a hospital. The research population should be towards the top of the calculated size to compensate for the drop-out of children who die or become too ill to participate in the study. Another and more convenient way to overcome the problem of small numbers might be implementing protocols for systematic data collection on low BMD and aetiological factors in hospitals and care facilities. Although this will not give a representative study population, in this way a larger group of children can be recruited over a longer period of time for data collection.

The only well-conducted study on fracture incidence in children with CP was a prospective cohort study with a median follow-up of 1.6 years. The annual incidence of fractures found in this study (4%) seems to be accurate and corresponds to results found in other studies [15]. This percentage is higher than the fracture rate in healthy children, which is around 2.5%. This is notable because children without disabilities are more prone to accidents in the playground, whereas children with CP are often wheelchair bound and unable to walk [13].

Significant negative associations between BMD Z-score and limited ambulation, feeding difficulties, previous fracture, anticonvulsant use and lower fat mass correspond to existing theories and clinical practice. Stevenson et al. found that higher body fat was significantly associated with the number of fractures that occurred during follow-up [13]. This association is not confirmed by other studies in

children with severe CP [20]. A possible explanation could be that after inserting a gastrostomy catheter, which was also found to be a significant association, a rapid increase in fat mass may be observed in previously malnourished children [26]. Malnutrition is a known risk factor for fractures and low BMD.

In our clinical experience, not all predictive factors for developing low BMD in this population have been studied. For example, daylight exposure and amount of exercise were not assessed in any of the studies. These factors could be assessed by using diaries in which caregivers record the amount of time the children spend daily on activities or being outdoors. To provide reliable data, this should preferably be done in different seasons and over a substantial period of time (e.g. 2 wks).

Conclusion

Implications for practice

Children with CP who are not independently ambulant, who have had previous fractures, who have feeding difficulties, or who use anticonvulsive drugs are at a high risk for developing low BMD. We recommend monitoring BMD in such cases. If BMD is found to be low, parents and caregivers need to be cautious to avoid fractures. Furthermore, we recommend optimization of calcium intake and determination of vitamin D status in these children. Interventions that increase muscle mass are advisable.

Implications for research

Longitudinal research is required to determine predictive factors for low BMD in this group. A practical way to acquire relevant data is by implementing protocols for systematic data collection and registration of low BMD and aetiological factors in children with CP, for example by paediatricians and physicians for people with intellectual disabilities.

The feasibility and reliability of new diagnostic methods such as quantitative computed tomography (with less interference of bone shape and size) need to be tested in children with severe CP.

Strategies to prevent bone loss and optimize peak bone mass, for example by increasing muscle mass or vitamin D supplementation, should be developed and evaluated.

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Chapter 3

Lumbar spine and total body dual energy X-ray absorptiometry in children with severe neurological impairment and intellectual disability: A pilot study of artefacts and disrupting factors.

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Abstract

Background: Children with severe neurological impairment and intellectual disability (ID) are susceptible for developing low bone mineral density (BMD) and fractures. BMD is generally measured with dual energy X-ray absorptiometry (DXA).
Objective: To describe the occurrence of factors that may influence the feasibility of DXA and the accuracy of DXA outcome in children with severe neurological impairment and ID.
Materials and methods: Based on literature and expert opinion, a list of disrupting factors was developed. Occurrence of these factors was assessed in 27 children who underwent DXA measurement.
Results: Disrupting factors that occurred most frequently were movement during measurement (82%), aberrant body composition (67%), small length for age (56%) and scoliosis (37%).The number of disrupting factors per child was mean 5.3 (range 1-8). No correlation was found between DXA outcomes and the number of disrupting factors.
Conclusion: Factors that may negatively influence the accuracy of DXA outcome are frequently present in children with severe neurological impairment and ID. No systematic deviation of DXA outcome in coherence with the amount of disrupting factors was found, but physicians should be aware of the possible influence of disrupting factors on the accuracy of DXA.

Introduction

Reduced bone health in children with severe neurological impairment and intellectual disability (ID) has raised concern and research interest during recent years [1-3]. It is established that children with moderate to severe cerebral palsy (CP), who often experience many additional health problems, have an increased risk of developing low bone mineral density (BMD). They, therefore, have an increased risk of low-impact fractures [1, 4-5].

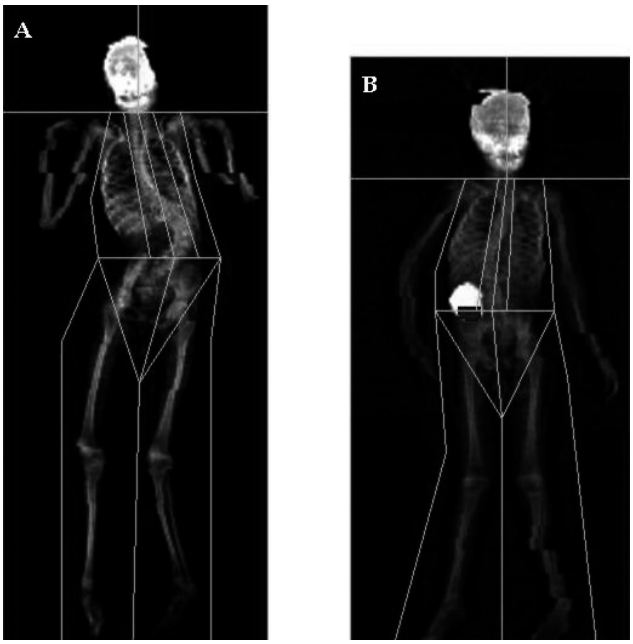
To determine BMD, dual energy X-ray absorptiometry (DXA) is generally accepted as the method of choice. With DXA after determining the bone mineral content (BMC) of body parts or the total body, a subsequent BMD is calculated by dividing BMC by bone area. However, it is known that in children the accuracy of the BMD outcome is diminished by several factors, such as variability in skeletal size and body composition [6-7]. Several studies have reported on additional artefacts and their influences on DXA results in the general population or in other patient groups [8-12]. The shape of the scanning X-ray beam, pencil beam versus fan beam, may also influence the accuracy of the measurement. As its name suggests, pencil beam scanners use a fine pencil beam of x-rays combined with a single detector scanning the patient in a raster fashion back and forth. While the detector moves over the patient the body parts not scanned may be fixated to reduce movement artefacts. The fan beam technology, in comparison, uses a wider X-ray beam that is detected using an array of detectors. The pencil beam method is found to be more accurate with less interference of magnification errors compared with the fan beam method [13-14]. The most important advantage of the fan beam technology, is that it offers a shorter scan time [15-16]. Disrupting factors may lead to both underestimation and/or overestimation of BMD [6, 9, 11, 17-19].

DXA is also used to determine body composition, e.g. lean body mass, percentage body fat (BF). The disrupting factors influence these parameters as well [14]. Operator-related artefacts, e.g. incorrect region of interest or inappropriate reference database, can be minimised by employing an experienced and trained operator who is familiar with the DXA equipment and software [9, 12]. However, patient-related artefacts are more difficult to deal with, e.g. severe contractures or orthopaedic hardware following scoliosis operation [11-12, 20]. While performing DXA measurements in children with severe neurological impairment and ID, we noticed that disrupting factors are frequently present (Figure 1). As far as we are aware, there are no studies on the frequency of factors that may negatively

influence accuracy of DXA outcomes in children with severe neurological impairment and ID. It is not clear whether these factors may lead to a systematic under-diagnosis or over-diagnosis of low BMD in this group and whether these factors were associated with low BMD. This limits our knowledge of the feasibility of DXA in this specific group of children.

Our main objective was to describe which factors reduce the accuracy of DXA outcome and to determine their frequency in a group of children with severe neurological impairment and ID. To observe whether these factors might lead to systematically skewed outcomes, we studied the correlation between the individual number of disrupting factors and DXA outcome values; total body BMC, BMC of the extremities, lumbar spine or total body BMD values, lumbar spine and total body Z-scores and body fat percentage. We also investigated whether children with moderate or severe ID and with low or normal BMD differed in the presence of the most prevalent disrupting factors.

Figure 1: Two examples of dual energy X-ray absorptiometry in children with severe neurological impairment and ID.



A. An 11-year-old girl with severe scoliosis.
B. A 5-year-old girl with an intracorporal medical device

Materials and methods

Study design

This study consisted of two separate parts. First, a checklist with known disrupting factors was developed. Then we assessed the presence of these disrupting factors in 34 children with severe neurological impairment and ID, who underwent DXA examination within the framework of a larger study on validation of nutritional assessment techniques. The framework study was approved by the Dutch Central Committee on Research Involving Human Subjects (The Hague, the Netherlands, P05.0102C).

Checklist

We used Medline to develop an overview of reported disrupting factors and artefacts. Disrupting factors according to five experts on (paediatric) DXA measurements were added. The respondents were a paediatric DXA operator, a paediatric-endocrinologist, a paediatric radiologist, an internist-endocrinologist and a radiotherapist. All had a vast experience with DXA measurements for diagnostic and research purposes (experience, mean 17 years) and two of them were familiar with the target population (years of experience, mean 5.5 years). They were asked to answer the following in a questionnaire:

- Which factors negatively influence the accuracy of DXA results?
- To what extent do these factors disrupt the DXA results in children with severe neurological impairment and ID (from "hardly disrupting" to "extremely disrupting" on a five point scale).

All disrupting factors and artefacts were recorded in a checklist for clinical purposes (supplement A).

Participants

Children, aged between 2 and 19 years, with severe neurological impairment and ID, known to have a moderate to severe ID (IQ< 55) and a gross motor functioning classification system (GMFCS) [21] of level IV or V were recruited through children's day care centres.

DXA scan

Measurements of bone mineral content (BMC), bone mineral density (BMD) and body fat percentage (BF) were performed by pencil beam DXA (Lunar, DPXL/

PED, Winconsin, USA). DXA values of the lumbar spine, total body and body fat percentages were compared with normative data of healthy Caucasian children, as obtained by Van der Sluis et al., and were converted to age and gender related Z-scores [22]. There were no reference values for BMC values available. Low BMD was diagnosed if a Z-score of −2.0 or below was obtained. High body fat was defined as a BF Z-score equal to or higher than 2.0. All DXA measurements were done by the same well trained operator, experienced in working with children with intellectual disabilities. None of the children received sedating medication prior to the measurement. One of the researchers (RR) assisted during all DXA measurements and a parent or caregiver, was also present to reassure the child. To prevent movement during the recording, the child was manually immobilized by the researcher and parent/carer. Attention was paid not to influence the DXA measurements. The operator aimed at obtaining an optimal scanning result; therefore artefacts were removed if possible (e.g. metal objects on clothing) or otherwise excluded from the scan results (e.g. projection of the gastrostomy catheter onto a lumbar vertebra). All artefacts for which adjustment of the scan was needed were counted.

Evaluation of artefacts and disrupting factors included in the checklist

After the scan, the operator recorded specific details and presence of artefacts on the test outcome form. During DXA measurements, the child's level of movement was recorded on a four point scale (from 4 points when a child was lying completely still to 1 point when the child was moving to an extreme degree).
Factors regarding growth and nutritional status had been assessed within the framework of the larger study on nutritional assessment techniques [23]. In brief, body height (cm) was measured with a flexible tape line and compared with Dutch reference values as provided by Growth Analyser 3.5 (Dutch Growth Foundation, 2007). A child was diagnosed with "small bones" if body height was below the 5th centile for age group. Triceps and subscapular skin fold thicknesses (mm) were measured with a Harpenden skin fold calliper (John Bull, England); these sites are most commonly included in equations on body fatness. Skin fold thickness was measured three times at each site. Mean values were calculated and used for further analyses. Centile scores in comparison with matched healthy gender groups and age groups were calculated using the Dutch reference values of Gerver and De Bruin [24] and categorised as low (≤ 3rd rcentile), normal (between 3rd

and 97th centile) or high (≥ 97th centile). If there was a substantial discrepancy in outcome between centiles of subscapular and triceps skin folds (e.g. triceps in the low and subscapular in the normal centile group or triceps in the normal and in the subscapular high centile group), the child was considered to have an aberrant subcutaneous fat distribution.
Medical history and medication were recorded from patient files. Data on lumbar spine surgery, presence of intracorporal devices, use of contrast agents, presence of calcinosis and use of calcium tablets were recorded.
Mobility according to the Gross Motor Function Classification System [21] and the presence of contractures or scoliosis were assessed by observation and performing physical examination if necessary.

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences for Windows 15.0 (SPSS Inc., Chicago, IL., USA).
Descriptive statistics are reported as number of cases and percentages. Pearson correlations coefficients were calculated for DXA outcome measures (BMC, BMD, BF) and the number of disrupting factors per child. After dichotomizing BMD Z-scores in low (≤ -2) and normal (> -2), an unpaired t-test was performed to assess the difference in mean number of disrupting factors in these groups. Fisher exact test was used to determine proportional differences between the presence of disrupting factors in children with moderate and severe intellectual disability, low and normal total body BMD Z-score and low and normal BMD lumbar spine Z-score. A p-value of less than 0.05 was considered statistically significant.

Results

The disrupting factors and artefacts according to literature findings and expert opinion are presented in Table 1.

Table 1. List of factors that might disrupt outcome of DXA measurements in children with severe neurological impairment and ID, including observed frequencies in the study group (N=27).

Factors		**N**	**%**
▪ Contractures		5	19
▪ Scoliosis		10	37
▪ Movement during measurement	• Complete immobilisation • Some movement • Considerable movement • Extreme movement	5 11 7 4	19 41 26 15
▪ Orthopaedic hardware		1	3
▪ Aberrant body composition (fat-lean mass)	Substantial difference between triceps and subscapular skinfold centile	18	67
▪ Small bones (length for age)	• <p5 height for age	15	56
▪ Intracorporal medical devices	• Intrathecal pump • Gastrostomy catheter • Gastrostomy catheter with projection on lumbar spine	1 14 2	4 52 7
▪ (Crush) fractures		0	0
▪ Other vertebral anomalies (e.g. spondylodesis, osteoarthritis, spinal implants, laminectomy)		2	7
▪ Jewellery or objects on clothing		1	4
▪ Dense metal objects (e.g. bullet, large collection of clips)		0	0
▪ Metastatic lesions		0	0
▪ Vascular/aortic calcification or calcified tendonitis and anostosis		0	0
▪ Calcinosis or calculi		1	4
▪ Use of contrast agents or undissolved calcium tablets in GI-tract		0	0

Information on the presence or absence of all disrupting factors and outcome of the DXA measurement were available from 27/34 children. In three children skin fold thickness was not assessed and in four children no information was present on movement during examination; therefore, they were excluded from analysis. Patient characteristics are summarised in Table 2. The children all had moderate to severe intellectual disabilities as well as severe motor disabilities: most scored level V on the Gross Motor Functioning and Classification System [21] and were unable to walk independently.

Table 2. Patient characteristics (N=27)

		N	%	Mean (range)
Gender	Female	14	51.9	
	Male	13	48.1	
Age in years				8.5 (3-17)
Severity of intellectual disability	Moderate (IQ <50)	2	7.4	
	Severe (IQ< 35)	25	92.6	
GMFCS*	Level IV	2	7.4	
	Level V	25	92.6	
Body weight in kilogram				24.4 (10-55)

*GMFCS: Gross Motor Function Classification System [21]

The mean amount of distorting factors and artefacts per child was 5.3 (range 1-8). Five children (18.5%) had a mean of 4.6 contractures (range 2-8). In ten children scoliosis was apparent (37.0%) and in one child (3.7%) the scoliosis was corrected with osteosynthesis materials in situ. An example of DXA measurement of one of the children with severe scoliosis is shown in Figure 1A. Fourteen children (58.8%) had an intracorporal medical device, all of them in the form of a gastrostomy catheter, but only in two children (7.4%) did the catheter projected onto the lumbar spine. One of these two had, in addition, an intrathecal pump for baclofen medication (Figure 1B). During DXA examination five children (18.5%) were completely immobile and 26 children (81.5%) were moving with severity of movement varying from some movement to extreme movement. In our study population 15 children (55.6%) had a Z-score lower than −2 SD for length for age and 13 out of these 15 children had a Z-score lower than −2.5 SD. Nine children (29.0%) had a subscapular skin fold on or above the 97th centile for their age and gender group and 15 children (48.5%) had a triceps skin fold on or below the

3rd centile for their age and gender group. After categorizing skin fold outcomes of subscapular and triceps measuring sites in either low (≤ 3rd centile), normal (between 3rd and 97th centile) or high (≥ 97th centile), an aberrant body composition was identiefied in 21 children (67.6%). In none of the children did the triceps skin fold thickness exceeded the subscapular skin fold thickness.

Despite of the disrupting factors, BMD results as well as body composition results could be produced for lumbar spine and total body in all 27 children. The mean BMC of the total body was 757 gram (SD 421). The mean BMC of the left arm was 36 gram (SD 30), of the right arm 37 gram (SD 34), left leg 68 gram (SD 58), right leg 73 gram (SD 69). The mean BMD Z-score for total body DXA was −1.30 (SD 1.79) and the mean BMD Z-score for the lumbar spine (L2-L4) was −2.41 (SD 1.18). A significant correlation between absolute BMD values of the total body and of the lumbar spine was observed (p=0.001). This correlation was not present between both BMD Z-scores (p=0.455).

The mean percentage body fat measured by DXA (N=23) was 25.2% (SD 12.3). Six children (22.2%) had high body fat, defined as a body fat standard deviation score equal to or more than 2 SD.

There was no significant correlation between the amount of disrupting factors and the BMC value of the total body (p=0.432), or the BMC values of the different extremities (left arm p=0.637, left leg p=0.743, right arm p=0.543, right leg p=0.929). The BMD value of the total body (p=0.226), the BMD Z-score of the total body (p=0.755), the BMD value of the lumbar spine (p=0.492) and the BMD Z-score of the lumbar spine (p=0.192) were not correlated with the number of disrupting factors as well. Also, no correlation was found between body fat percentage and the amount of disrupting factors (p=0.148). Comparison of children with and without low BMD (defined as Z-score < −2.0) in total body or lumbar spine showed no significant difference in mean number of disrupting factors (Table 3).

Table 3. Mean number of disrupting factors in children with and without low BMD (N=27)

	Total body BMD Z-score		**Lumbar spine BMD Z-score**	
	Low (≤ −2.0)	Normal (> −2.0)	Low (≤ −2.0)	Normal (> −2.0)
	(N=11)	(N=16)	(N=18)	(N=9)
Mean number of disrupting factors	5.5 (SD 2.25)	5.1 (SD 1.50)*	5.6 (SD 1.98)	4.7 (SD 1.32)**

* *p*=0.65
** *p*= 0.24
BMD: Bone mineral density

There were no significant proportional differences in presence of scoliosis, movement during measurement, aberrant body composition, small length and presence of a gastrostomy catheter when comparing children with moderate to severe ID, children with low and normal total body BMD Z-score or children with low and normal BMD lumbar spine Z-score (Table 4).

Table 4. Proportional differences between presence of scoliosis, movement during measurement, aberrant body composition, small length and presence of a gastrostomy catheter in children with moderate to severe intellectual disability, low and normal total body BMD Z-score and low and normal BMD lumbar spine Z-score (N=27).

	Intellectual disability			**Total body BMD Z-score**			**Lumbar spine BMD Z-score**		
	Moderate	Severe		Low (≤ −2.0)	Normal (> −2.0)		Low (≤ −2.0)	Normal (> −2.0)	
	(N=2)	(N=25)		(N=11)	(N=16)		(N=18)	(N=9)	
			Fisher exact Test			Fisher exact test			Fisher exact test
Scoliosis	0	10	0.516	5	5	0.687	8	2	0.406
Movement during measurement	2	20	1.000	9	13	1.000	14	8	0.636
Aberrant body composition	0	18	0.103	6	12	0.411	12	6	1.000
Small length (<p5)	1	14	1.000	8	7	0.239	11	4	0.448
Gastrostomy catheter	0	14	0.222	5	8	0.704	9	5	1.000

BMD: Bone mineral density

Discussion

As expected, factors that may negatively influence the accuracy of DXA measurements, were frequently present in children with severe neurological impairment and ID, with a mean of 5.3 factors in 27 children. The most frequently

occurring factors were movement during measurement, scoliosis, contractures, gastrostomy catheters, aberrant body composition and a height below the 5th centile for age. The prevalences of these factors did not differ between children with low or normal BMD values. We found no systematic overestimation or underestimation of BMC, BMD or BF outcome relating to the amount of disrupting factors. Therefore, it remains unknown to what extent DXA outcomes are influenced if one or more artefacts are present.

Published studies on disrupting factors in DXA examination are mostly descriptive and frequently performed in older patients or postmenopausal women [10, 17-18, 25-26]. Most studies describe only one of the factors in detail and we found no study determining the total amount of disrupting factors present in specific patient groups. Therefore, it remains unknown whether the number of disrupting factors is higher in our population than in others. Our finding of a mean of five disrupting factors per child, however, implies that DXA outcomes in children with severe neurological impairment and ID may be prone to inaccuracy. The lack of correlation between the amount of disrupting factors and BMD might be explained by the relatively small study population (n=27) and the fact that the disrupting factors may lead to both overestimation and underestimation of bone density [6, 9, 11, 17-19, 27]. The question whether BMD outcome in children with severe neurological impairment and ID deviates in a systematic way as a result of disrupting factors can, therefore, not be thoroughly answered. Additional information on the presence of artefacts is, however, important to interpret the results of the individual bone density and body composition measurements, not only for single measurements but especially for repeated measurements in which the presence of disrupting factors may differ.

The power and strength of the statistical techniques performed in this pilot study were limited by the small study population, e.g. regression analysis and prediction models could not be used because of the small sample size. We, therefore, recommend a study to be conducted with a more appropriate sample size so that more sophisticated statistical techniques can be used to further clarify the associations between disrupting factors and DXA outcomes.

Most of the reported disrupting factors are hard to avoid, but movement during measurement might be diminished by giving sedative medication in advance [27] or by placing sand cushions or straps to prevent movement. However, considering that these measures impose restraints that undoubtedly will increase stress, and knowing that sedatives might cause side effects like cardiorespiratory depression or

vomiting and aspiration [28], the advantages and disadvantages of those measures need to be assessed on an individual basis. When, despite measures to prevent it, considerable or extreme movements occur during measurement, DXA outcome is unreliable. The measurement should either be repeated when the child is more at ease or an alternative diagnostic method less susceptible to movement (e.g. quantitative ultrasound or automated radiogrammetry) should be used.

In our study a pencil beam DXA method was used (Lunar, DPXL/PED). With a pencil beam DXA, the body parts not being scanned at that moment can be manually fixated to prevent movement. This enhances the accuracy of the bone and soft tissue measurements. The pencil beam method, therefore, may be more accurate than the fan beam method in severely handicapped children.

The accuracy of DXA is largely dependent on the experience of the operator, appropriate regions of interest and, when possible, artefact removal. We, therefore, recommend that all clinical centres where DXA is performed in children with severe neurological impairment and ID designate an operator with special interest to gain experience with these children. The operator needs to routinely record disrupting factors and present these together with the scan results to the referring physician. It may be recommended that the checklist developed as part of our study (supplement A) is adopted by manufacturers of DXA systems as part of the results printout.

Regarding intracorporal devices and metallic implants, we feel that the usability of DXA can be improved if the software enables more accurate corrections. After deleting the very high density pixels (caused by these artefacts) from the scans, alternative sub-regions that give an estimate of its "BMC equivalent" should be added to reduce interference with the DXA outcome. It is recommended that the manufacturers adapt their DXA software accordingly.

In the Netherlands, it is common to measure bone density in children by performing DXA of the lumbar spine and total body [22]. However, Henderson et al. have indicated that measurement of the BMD of the distal femur projected in a lateral plane in children with moderate to severe CP or muscular dystrophy has a strong correlation with fracture history [29]. This specific scanning technique may diminish the amount of disrupting factors as well, e.g. no projection of scoliosis or intracorporal devices on the lumbar spine, fewer positioning problems due to contractures and probably less movement during examination because patients are lying on their side. Development of reference values for distal femur BMD for the different DXA devices and standardisation of the measurement procedure may be

an important step in standardising diagnosis of low bone mineral density in children with severe neurological impairment and ID.

Conclusion

In children with severe neurological impairment and ID, frequently occuring disrupting factors may influence the feasibility of DXA and the accuracy of its outcome. Because treatment of low bone density in practice is reserved for children with (low impact) fractures, this distortion presumably has had limited effect on treatment frequency. However, alterations in artefacts over time may complicate comparison of successive outcome values in an individual child. In addition, the effectiveness of preventive measures can only be determined if accurate and reliable bone density measurements are available. Therefore, either more information on the impact of individual disrupting factors is necessary, or other methods or localisations for bone density measurement less prone to distortion are needed for this population.

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Supplement A: Checklist of artefacts and disrupting factors during DXA in children with severe neurological impairment and ID

Name patient:

Date of birth:

Date of examination:

Name operator:

Height: …….. cm
Centile height for age: p…
P value < p5: yes/no

Contractures *: yes/no
Location(s) of contracture(s): …….

Orthopaedic operations in patient history: yes/no

Recent use of contrast agent
(e.g. CT/MRI with contrasts, scintigraphy): yes/no

Location DXA measurement:

☐ Total body
☐ Lumbar spine
☐ Proximal femur
☐ Distal femur

Movement during measurement *: yes/no

☐ Completely still
☐ Some movement
☐ Considerable movement
☐ Extreme movement

Aberrant body composition *:

Triceps skinfold: …. mm

Centile for age: p …

p value <p5: yes/no

Subscapular skinfold: …. mm

Centile for age: p …

p value <p5: yes/no

Intracorporal medical devices (*e.g. gastrostomy catheter, intrathecal baclofen pump*)

Present: yes/no

Kind of device: ……

Projection on region of interest: yes/no

Scoliosis *: yes/no

Orthopaedic hardware present *: yes/no

Vertebral crush fracture(s) present: yes/no

Other vertebral anomalies present

(*e.g. spondylodesis, osteoarthritis*): yes/no

Jewellery or metal objects on clothing: yes/no

Dense metal objects present

(*e.g. bullets, collection operation clips*): yes/no

Calcinosis of calculi present: yes/no

Undissolved calcium tablets in GI tract present: yes/no

Calcifications present (*e.g. vascular/aorta, tendinitis*): yes/no

Metastatic lesions: yes/no

* *Factors considered very or extremely disrupting by expert opinion*.

One or more yes answers on this checklist may implicate that the DXA outcome is less reliable; the extent of disruption depends on the factor involved and the degree of disturbance (e.g. movement).

In case of doubt concerning the interpretation of these results contact the operator for consultation.

Chapter 4

Feasibility of quantitative ultrasound measurement of the heel bone in people with intellectual disabilities

Res Dev Disabil 2010; 31(6): 1283-1290

Abstract

Low bone mineral density (BMD) and fractures are common in people with intellectual Disabilities (ID). Reduced mobility in case of motor impairment and the use of anti-epileptic drugs contribute to the development of low BMD. Quantitative ultrasound (QUS) measurement of the heel bone is a non-invasive and radiation-free method for measuring bone status that can be used outside the hospital.
QUS might be used for screening purposes to identify people with intellectual disability with poor bone status, who are in need of supplementary examination and treatment.
To investigate feasibility of QUS in this group, QUS of the heel bone was performed on-site in 151 people with ID living in residential care.
Measurements were successfully performed in at least one foot in 94.7%, were interpretable (resulting in a stiffness index) in 91.6%, and induced barely or no stress in 90.4% of the study population. Measurements generally took less than ten minutes. In 93 persons bone status of both feet had been measured. The "mean percentage of the absolute difference" between outcomes of both feet was 15.5% (± 15.3% SD, range 0-76.5%).
Ultrasound measurement of the heel bone is a feasible and non-stressful method for measuring bone status in people with ID. Since the mean difference between outcomes of the left and right foot were large, measurement of both feet is recommended to prevent inaccurate interpretation.

Introduction

People with Intellectual Disabilities (ID) are prone to developing osteoporosis or low bone mineral density (BMD). In people with ID low BMD often develops at an earlier age than in the general population [1-2]. Increased frequencies of low BMD are present in persons with any degree of ID [3-7]. In the Netherlands the prevalence of low BMD is 5.2% in males and 16.6% in women in the general population over 55 years of age [8-9]. In comparison, the prevalence of low BMD was 20% in young adult males with mild to moderate ID [4] and even 77% in children with ID and moderate to severe cerebral palsy (CP) [3]. Important determinants of low BMD in people with ID are limited ambulancy and anticonvulsant drug use [3, 10-11]. Due to the increasing lifespan of people with ID [12-14], the prevalence of low bone mineral density may increase even further in the nearby future.

A reduced BMD in combination with an increased risk of falling, e.g. due to motor or visual impairment, causes an increased fracture incidence in people with ID compared to that of the general population [15-16]. In high risk groups, such as older women and people with impaired mobility, bone status should therefore be assessed to determine fracture risk.

In large-scale screening studies in the general population, quantitative ultrasound measurement of the bone (QUS) has been used to identify people at risk for developing osteoporosis and fractures [17-18]. Advantages of QUS are its non-invasiveness, lack of radiation and its portability. Bone status can be measured outside the hospital [19-21] and QUS can be applied to different parts of the extremities, such as the heel bone, radius, tibia or finger. However, the calcaneus or heel bone is the most commonly used site of measurement [22-24].

Earlier studies in the general population have shown that QUS results can vary between the left and right foot [25-26]. In most people the right foot is dominant and therefore may have a higher bone density than the non-dominant foot. As a result larger studies frequently opt for measurement of the left foot [18], so that the lowest value of bone density is measured. It is however unknown whether differences in QUS results between the feet present in a similar way in people with ID. Foot dominance is more difficult to determine and might be less pronounced in people with ID, resulting in less obvious left and right differences. On the other hand hemiplegia or other unilateral disrupting factors that are known to influence bone density [27], are more frequently present in people with ID and might lead to increased differences between QUS results of the feet.

The variables measured with QUS are speed of sound (SOS), a variable related to velocity of the ultrasound signal, and broadband ultrasound attenuation (BUA), a variable reflecting the weakening of the ultrasound signal while travelling through the bone [19]. Both variables, but in particular BUA, are found to be predictive of fracture risk, independent of BMD as measured with dual energy X-ray absorptiometry (DXA) [17, 28]. This can be explained by the fact that QUS variables also depend on bone structure and composition besides bone density [22]. Some QUS devices provide additional variables like a stiffness index (SI) or quantitative ultrasound index (QUI) which are parameters derived from linear combinations of BUA and SOS.

Since measurement can be performed on the spot, QUS seems a promising method for screening bone status in people with ID. Although several studies have applied QUS to determine bone quality in people with ID, we have found no studies specifically determining its usability, applicability and side effects in this group [11, 29-32]. Therefore, we determined whether ultrasound measurement of the heel bone is a feasible method for determining bone status in people with ID. While in the literature the definition of feasibility strongly depends on the diagnostic method or intervention that is used, we defined feasibility by number of successful recordings, interpretability of the outcome and acceptability by the client.

Materials and methods

Study protocol and population

From November 2007 until January 2008, a device for measuring bone status with QUS was available for feasibility testing at ASVZ, a residential facility for people with ID. During that period, physicians providing medical care for this group were invited to refer patients for examination of bone status. No inclusion or exclusion criteria were applied. A total number of 151 persons with ID were referred with a mean (± SD) age of 47.0 ± 18.1 yr (range 3 months-84 years) of whom eight were children (<19 years). Measurements were done after informed consent of parents or legal representatives. Consent for measurement of bone status was obtained by the care giving physician; therefore we are not aware of the percentage of people who refused to participate. This study was part of a larger project on the prevalence and risk factors of osteoporosis, and its study protocol has been approved by the Institutional Review Board. The feasibility outcome measures were analyzed anonymously

After referral, age and gender were noted on a registration form. Referred children were assessed as well, although paediatric reference values for BMD were unavailable.

The level of intellectual disability (ID) was retrieved from the patient files and scored as mild, moderate, severe or profound. Mobility was assessed according to the Gross Motor Function Classification System (GMFCS), a 5 level classification system that is widely used for children with CP and describes gross motor function on the basis of self-initiated movement [33]. GMFCS levels are distinguished according to functional limitations, the need for assistive mobility devices (walkers, crutches, canes) or wheeled mobility and, to a lesser extent, quality of movement [34]. Children in level 1 walk without limitations in all settings, whereas children in level 5 have severe limitations in head and trunk control, and in self-mobility. Children in level 4 may walk for short distances with physical assistance of an adult at home but rely more on wheeled mobility (pushed by an adult or operate a powered chair) outdoors, at school and in the community [35]. The diagnosis 'severe neurological impairment and ID' implicates that people had profound intellectual disability and GMFCS level IV or V. Clinical characteristics of the study population are listed in Table 1.

Table 1. Clinical characteristics of study population (N=151).

		N	**%**
Gender	Male	63	41.7
	Female	88	58.3
Level of Intellectual Disability	Mild	29	19.2
	Moderate	38	25.2
	Severe	43	28.5
	Profound	41	27.2
GMFCS*-level	I	44	29.1
	II	34	22.5
	III	16	10.6
	IV	16	10.6
	V	41	27.2
Severe neurological impairment and ID	yes	33	21.9
Previous fracture	yes	46	30.5
Use of anti-epileptic drugs	yes	72	48.0

* Gross Motor Function Classification System [33]

Calcaneal ultrasound measurement

Bone density of the heel bone was measured using the Lunar Achilles (type Insight, GE Healthcare, Clinical systems Ultrasound, Hoevelaken, the Netherlands), a device that uses transverse ultrasound transmission [36]. Measurements generally took place in the living unit of the client. Frequently more than one client in a group participated and was studied. After introducing the researcher to the clients, the device was shown and a volunteer was asked from the study participants. Occasionally one of the accompanying staff members volunteered to undergo the measurement. Clients with oppositional or defensive behaviour were invited to watch the procedure in one or more other clients. If they persisted in their rejection, the measurement was abandoned.

Measurements started with positioning the client in either a chair or wheelchair in front of the QUS devices with bare feet. After thoroughly spraying the ankle with alcohol, one foot was placed in the device. Then the two membranes on either side of the ankle automatically filled with lukewarm water, enabling the transducers on both sides of the ankle to transmit and receive the ultrasound signal. If possible, bone status of both feet was determined. In case only one foot could be measured, preferably the left foot was measured, which is the non-dominant foot in most people.

According to the specifications provided by the manufacturer, the repeated in vivo measurement precision of the Lunar Achilles Insight, expressed as the coefficient of variation (CV), is < 2.0%.

Three measurement outcomes were obtained: speed of sound (SOS), broadband ultrasound attenuation (BUA) and stiffness index (SI). The Lunar device uses built-in reference values based on age and gender, supplied by the manufacturer and obtained from healthy German adults, to calculate T- and Z-scores of the stiffness index. The T-score results from the comparison of the participants' bone status with the average peak value in healthy young people and the Z-score provides a context for a participants' bone status by comparing individual measurement values with the mean value for people of the same age and gender. No reference values for children (<19 year) are available in the software, therefore for them only stiffness indexes are provided, but no Z-scores.

When the ultrasound signal does not reach the receiving transducer, for example if too little alcohol is used or if the water level in the membranes is insufficient, the lunar device displays the result "out of range". This can also occur when bone mass is either extremely high, and the signal cannot pass through the bone, or when

bone mass is extremely low and therefore not measurable. After obtaining an out of range result, the measurement procedure was repeated after checking the water level of the membranes and thoroughly spraying with alcohol a second time.

Aspects of feasibility

Feasibility was operationalised according to the following aspects: number of successful recordings (including cooperation), interpretability of the results, clients' perceived stress and duration of the measurement. First it was determined in which percentage of participants the measurement could be successfully performed in at least one foot according to the instructions in the manual. Possible causes for failed measurements were recorded, e.g. uncooperative behavior or anatomical deformity of the foot. Results were considered interpretable if a stiffness index was provided by the device. At the time of the study, no instruments were available to determine the level of perceived stress during the recording. Therefore, a simple five point scale was developed and filled out. A score of one indicates that the procedure is experienced as not being stressful, two as barely stressful, three as stressful, four as considerably stressful and five as highly stressful. The stress score was based on consensus between the client's opinion and the observations by the accompanying staff member and the researcher. Duration of the measurement was determined by recording starting and finishing times of each measurement. Time necessary for clarification of the procedure, taking off shoes and socks and making the subject feel comfortable was included.

Analysis and statistics

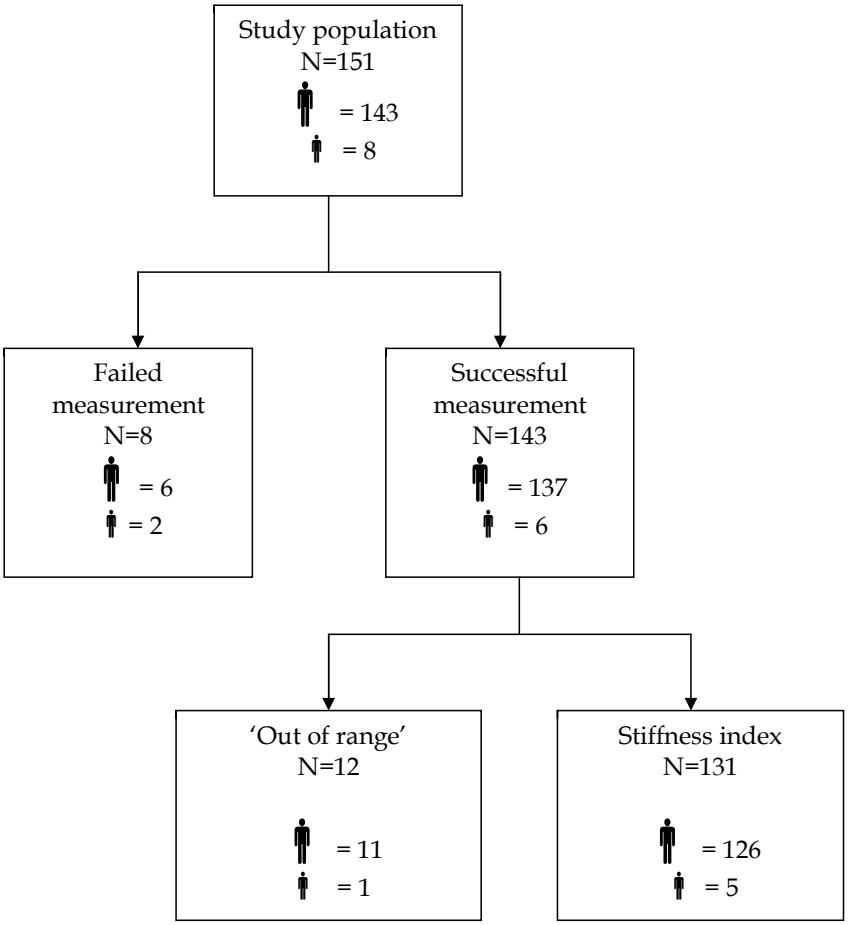
Results are expressed as mean ± standard deviation or 95% confidence interval (CI). T-tests, Pearson Chi-square tests and Mann-Whitney tests were used to calculate differences between groups with different measurement outcomes. A p-value below 0.05 was considered statistically significant.

To study differences between left and right feet if possible, the percentage of absolute difference between both feet was calculated by the following equation [25-26]:

$$\frac{|leftstiffness - rightstiffness|}{\left(\frac{leftstiffness + rightstiffness}{2}\right)} \times 100\%$$

Previously a difference of 11% (± 9.25 SD) has been reported in otherwise healthy children [26]. Since no specific definitions for substantial difference were found in the literature, a substantial difference was defined as an absolute difference between the feet equal to or above 25%.

Figure 1. Flow diagram feasibility results.



The picture of the larger male implicates number of adults; the picture of the smaller male implicates number of children.
Failed measurements are defined as technically not successful measurements.
"Out of range" implicates that either the ultrasound signal did not reach the receiving transducer or there was minimal signal alteration.
Stiffness index is a parameter derived from linear combination of BUA (broadband ultrasound attenuation) and SOS (speed of sound).

Results

Feasibility

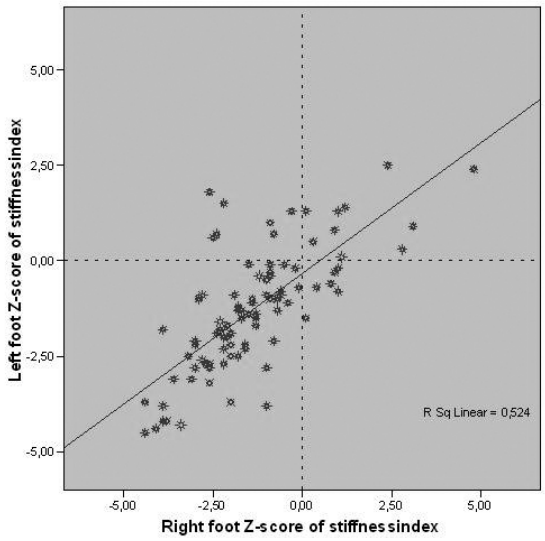
In 143 out of 151 participants (94.7%; 136 adults and seven children) the measurement could be successfully performed in at least one foot (Figure 1) and in 93/151 (61.6%; 92 adults and one child) in both feet. In seven participants (4.6%) the measurement could not be done at all because of defensive behaviour (consisting of verbal aggression and non-compliance). In one patient the feet could not be positioned into the device because of severe deformities. Characteristics of the participants with successful measurements (N=143) were not different from those in whom measurement was not possible because of defensive behaviour or deformities of the feet (N=8) (table 2, left panel).

In 12/143 participants (8.4%) the measurement result was "out of range", implicating that the receiving transducer did not establish any alterations in the ultrasound signal. This might occur when bone mass is either extremely high not allowing the signal to pass through the bone, or when bone mass is extremely low. Three of the 12 people with "out of range" results had deformities of the feet (e.g. clubfoot) and two other people had oedematous feet.
A stiffness index was therefore provided for 131/143 persons (91.6%) (Figure 1). The twelve participants with 'out of range' results had a significantly more severe ID and more severe motor disability as measured with the GMFCS than those for whom a stiffness index was provided. The proportion of people with severe neurological impairment and ID was significantly higher in the group with 'out of range' result than in the group with a measurable stiffness index ($p<0.0001$). (Table 2, right panel).
In four persons data on stressfulness were not available. The procedure was scored as "not stressful" by 108/147 participants (73.4%), "barely stressful" by 25 (17.0%), "stressful" by nine (6.1%) and "considerably stressful" by one participant (0.7%). The procedure was scored "highly stressful" by four persons (2.7%) with defensive behaviour. Their anxiety made it impossible for them to cooperate and therefore the measurement was aborted in these participants. The mean duration of the measurements was 6.7 minutes (range 5 – 20 minutes); 137/143 completed measurements (97.2%) took less than ten minutes.

Table 2. Comparison of demographics between groups with different measurement outcomes.

	Measurement not successful (N=8)	**Measurement successful (N=143)**		**"Out of range" (N=12)**	**Measurable stiffness index (N=131)**	
Gender (N=male/ female)	2/6	61/82	p=0.324 (Pearson X^2)	5/7	54/77	p= 0.942 (Pearson X^2)
Mean age yrs [SD]	42.3 [16.6]	47.7 [18.1]	p=0.408 (t-test)	39.4 [14.2]	47.9 [17.6]	p= 0.105 (t-test)
GMFCS N (%)						
I	2 (25.0%)	42 (29.4%)	p=0.394 (Mann-Whitney test)	0 (0%)	42 (32.1%)	p=0.0001 (Mann-Whitney test)
II	4 (50.0%)	30 (21.0%)		0 (0%)	30 (22.9%)	
III	1 (12.5%)	15 (10.5%)		1 (8.3%)	14 (10.7%)	
IV	0 (0%)	16 (11.2%)		0 (0%)	16 (12.2%)	
V	1 (12.5%)	40 (28.0%)		11 (91.7%)	29 (22.1%)	
Severity ID						
Mild	0 (0%)	29 (20.3%)	p=0.364 (Mann-Whitney test)	0 (0%)	29 (22.1%)	p < 0.008 (Mann-Whitney test)
Moderate	1 (12.5%)	37 (25.9%)		3 (25%)	34 (26.0%)	
Severe	6 (75.0%)	37 (25.9%)		1 (8.3%)	36 (27.5%)	
Profound	1 (12.5%)	40 (28.0%)		8 (66.6%)	32 (24.4%)	
Severe neurological impairment and ID	0 (0%)	33 (23.1%)	P=0.124 (Pearson X^2)	8 (66.7%)	25 (19.1%)	P < 0.0001 (Pearson X^2)

Figure 2. Comparison of values Z-score of stiffness index in the left and right foot (N=92).



Z-score indicates how many standard deviations the individual stiffness index is above or below the mean stiffness index for the age en gender related reference population.
Stiffness index is a parameter derived from linear combination of BUA (broadband ultrasound attenuation) and SOS: (speed of sound)
'R Sq Linear' is the square of the correlation coefficient between left and right stiffness index Z-scores.

Outcome

In the children with a measurable stiffness index (N=6) the measured values could not be converted into Z-scores because of the lack of paediatric reference values. In the adults with a measurable stiffness index (N=125, namely the 136 adults with a stiffness index minus 11 adults with "out of range" results) Z-scores of the stiffness index could be determined. In 92/125 (74.4%) of the adult participants Z-scores of the stiffness index of both feet were available.

Mean Z-scores were −1.33 (SD 1.77, range −4.50 to +4.80) for the left foot (N= 111) and −1.62 (SD −4.70 to +4.80) (N=106) for the right foot.

Linear regression showed a moderate but significant correlation between left and right Z-score values (R^2= 0.52, p< .0001) (Figure 2). However, large individual differences in stiffness index were observed between both feet. The mean percentage of absolute difference between both feet was 15.5% (± 15.3% SD, range 0-76.5%). Level of ID (p=0.54), GMFCS score (p=0.27) and stressfulness of the recording (p=0.11) were not significantly different between people with

substantial (≥ 25%) and people with small or absent differences in outcome between both feet (data not shown).

Discussion

This study in which bone status was measured in 151 people (8 children and 143 adults) with mild to profound ID living in residential care, shows that quantitative ultrasound of the heel bone is a feasible method. Successful measurements were performed in 94.7% and interpretable outcome was obtained from 91.6%. Measurements generally took less than ten minutes and were not or barely stressful in 90.4% of the participants.

Defensive behaviour (N= 7, 4.6%) or severe anatomical deformities of the feet (N=1, 0.7%) were the main reasons for unsuccessful measurements. Earlier studies described the same obstacles with comparable frequencies [6]. In the study of Aspray et al. 7.5% of the measurements were unsuccessful because of deformity of the heel and another 7.5% because of behavioural problems [32]. A different composition of the study population and the use of a different ultrasound device may have been the cause of these slightly higher numbers compared to those of the present study. Overall, the frequency of failure due to anatomical deformities of the feet is relatively low. Performing the measurement at another site of the body less prone to deformities (e.g. the forearm) could even increase its feasibility. However, not all QUS devices are capable of measuring different sites of the body. Failure rate of the recording due to defensive or oppositional behaviour might be further diminished by investing even more time into the clarification procedure and by demonstrating the measurement on another person. We noticed that while performing the measurement in an acquaintance, people became interested in the procedure and the device and were more willing to participate. Additionally, medication diminishing anxiety might be considered to increase feasibility of the recording. We feel however, that sedative medication should exclusively be reserved for patients in whom detailed information on bone mineral status is required. In those cases screening with QUS should be omitted and bone density should be measured with dual energy X-ray absorptiometry (DXA), because DXA results are required to diagnose osteoporosis and to evaluate effectiveness of therapeutic measures. [37].

In our study 12 persons had an 'out of range' outcome. These people were significantly less mobile and more severely cognitively disabled than those in whom a stiffness index was obtained. Most of them were people with severe neurological impairment and ID. Although feasibility in this group is lower than in other persons with ID, an interpretable result was achieved in 25 out of 33 persons with severe neurological impairment and ID. Therefore QUS screening should not be rejected for this group, which has a high risk of poor bone status.

We noticed that some people had large individual differences in stiffness index between the left and right foot; the mean percentage of the absolute difference was 15.5% (± 15.3 SD, range 0-76.5%), which can not be explained by the precision error of the device (CV <2%). The cause of this difference may be structural, e.g. in case of hemiplegia, or the result may be disrupted, for example by movement during the measurement. While small movements of the foot during measurement can not always be observed and were not specifically scored, we were unable to determine the direct influence of movement on differences between the left and right foot. We found however no correlation with severity of intellectual disability, GMFCS level or experienced stress, factors that might be related to movement and motor abilities. In our present study we aimed to measure bone status in at least one foot. Therefore only during analysis of the results we found that differences in bone QUS parameters between the feet can be frequently present and sometimes large. Future research in this population should thus include default measurement of both feet, in order to eliminate the influence of left-right differences on study outcome.

While the main purpose of our present study was to confirm feasibility of QUS in people with ID, we felt that including a control group for this aspect was not necessary. A control group with age and gender related healthy persons would undoubtedly strengthen the outcomes of a prevalence study on low bone status in people with ID and is therefore recommended in future research. The rating of stress used in our study was rather subjective. A self formulated 5-point scale was used, while no comparable and easy-to-use stress scales were available in literature. The reliability of this stress score would have been augmented if separate scores would have been assigned by two independent raters rather than the consent opinion in the present study. Another limitation of the study is the non-representativeness of the selected population. While using a convenience sample of people referred for examination by their physician, the bone quality outcomes found in this study may not be applicable to the overall population of people with ID. The

influence of the convenience sample on feasibility outcomes is considered limited. The composition of our study group was heterogeneous with different levels of ID and motor disability and a wide age range.
We conclude that quantitative ultrasound measurement of the heel bone seems a feasible and non-stressful method for measuring bone status in people with ID. Further research on its value as a screening instrument for assessing bone quality in people with intellectual disability is recommended. Preferably this research should be population based with a control group of people without ID and measurements in both feet. Also we recommend prospective research in which QUS outcomes can be related to fracture incidence to establish fracture risk in people with ID.

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Chapter 5

Automated radiogrammetry measuring bone quality and bone maturation in severely disabled children

Submitted

Abstract

Children with severe neurological impairment and intellectual disability (ID) are prone to low bone quality and fractures. In search of a diagnostic method available in every hospital and easy to apply, we investigated whether automated radiogrammetry is a feasible method to assess bone quality in this specific group of children.

Hand radiographs were made in 95 children with severe neurological impairment and ID (mean age 11.4 year SD 4.8) at outpatient paediatric clinics in four hospitals in the Netherlands. BoneXpert © software (version 1.14) was used to determine the paediatric bone index (PBI), a method previously validated in a population of healthy children. Automated bone age determination was assessed as part of the PBI measurements.

A PBI was succesfully obtained in 60 children (63.2%). Severe contractures of the hands were the most common cause of unsuccessful measurement. In 36/56 (64%) of the children chronological age diverged more than one year in either direction. This mostly concerned delayed bone maturation (n=26).

The authors conclude that automated radiogrammetry is feasible to evaluate bone quality in disabled children before severe contractures occur. Since bone maturation frequently deviated in this group of severely disabled children, comparison to bone age related reference values is recommended.

Introduction

Children with severe neurological impairment and intellectual disability (ID) are susceptible to develop low bone mineral density (BMD), which can lead to the occurrence of fractures that may originate from a limited or even unknown trauma [1-5].

In both adults and children, BMD is generally measured with dual energy X-ray absorptiometry (DXA) [3-4], but measurement in children requires specific software and adapted reference values [6-7]. In the Netherlands, paediatric DXA is only available in tertiary care centres, which restricts the use of DXA for this specific group. In addition, a various number of disrupting factors negatively influencing the reliability of DXA results can be present, especially in this group of children, such as contractures, scoliosis or movement during measurement [chapter 3]. Therefore, screening bone quality in these children prone to low BMD using a diagnostic method that is generally available in hospitals, easy to apply and less depending on disrupting factors, would be an important and relevant addition to diagnostic possibilities.

Moreover, severely handicapped children may have a slower growth velocity, whereas their skeletal maturation can be either delayed or accelerated [2, 8-10]. This may influence the validity of bone density outcomes of diagnostic methods that generally use chronological age related reference values, like DXA or Quantitative Ultrasound (QUS) [11].

With automated radiogrammetry of plain hand radiographs, bone quality can be measured with web-based software [12] and is expressed as Paediatric Bone Index (PBI). This PBI is determined by geometrical calculations similar to the determination of digital X-ray radiogrammetry bone mineral density (DXR-BMD). The DXR-BMD has shown to correlate well with peripheral DXA measurements of the forearm, with DXA of the femoral neck in adults and with DXA of the lumbar spine and total body in children [12-15]. PBI reference values have been developed in a large group of healthy children (N=2398) [12]. These reference values are gender and bone age related [12]. In children treated for acute lymphoblastic leukaemia and growth hormone deficiency automated radiogrammetry has shown to be easily applicable with a negligible effective radiation dose [15]. However, no data have been published so far on the use of this method in children with severe neurological impairment and ID.

Therefore, the aim of this study was to determine whether the automated radiogrammetry method is feasible in children with severe neurological impairment and ID and to what extent bone age differs from chronological age in this group.

Methods

Study design

The current study was part of a cross-sectional multicenter study on bone quality in children with severe neurological impairment and ID, in which four Dutch hospitals participated. Together these four hospitals cover a large part of the southwest of the Netherlands.
Ethics approval of this study was obtained by the ethics committees of the Erasmus University Medical Center Rotterdam (MEC-2005-182) and of each participating hospital.

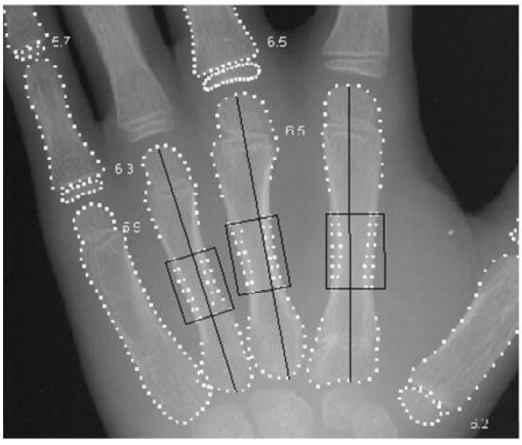
Study population

Children with severe neurological impairment and ID, known to have a moderate or severe intellectual disability (IQ< 55) and a Gross Motor Functioning Classification System (GMFCS) level IV or V, visiting the outpatient paediatric clinic of the participating hospitals, were eligible for inclusion. GMFCS is a 5 level classification system that is widely used for children with cerebral palsy and describes gross motor function on the basis of self-initiated movement [16]. Children in level IV may walk short distances with physical assistance of an adult at home but rely on wheeled mobility outdoors. Children in level V depend on a wheelchair for their mobility and have severe limitations in head and trunk control [16-17]. Concerning the aetiology of their disability children were subdivided into five groups. The first group consisted of children with a congenital cause e.g. lisencephaly, in the second group children with perinatal complications e.g. solutio placentae were presented and the third group consisted of the acquired disabilities like meningitis or trauma. Two additional groups were presented by children with either a combination of congenital and acquired causes and children with an unknown cause of their disability.
Ninety five children were included from June 2006 till January 2009.

Automated radiogrammetry

Automated radiogrammetry analysis was performed on a posterior anterior radiograph of the left (non-dominant) hand. In case less contractures were present, the right hand was used. In order to get optimal results, one of the authors (SM) was present during all X-ray examinations. Preferably the radiographs were digital in DICOM format, but traditional film X-rays could also be used after scanning with the VIDAR Diagnostic Pro Advantage Scanner (VIDAR, Herndon, VA, USA). Automated radiogrammetry was performed with BoneXpert© (version 1.14, Visiana, Holte, Denmark, www. BoneXpert.com). This method determines the bone edges of the middle three metacarpals and a minimum of eight other hand bones (Figure 1). BoneXpert can determine automatically either the Greulich and Pyle bone age or the Tanner and Whitehouse bone age. In this study the Greulich and Pyle method was used which has proven a robust method of automatic determination of bone age in an earlier study [18]. Valid and consistent bone ages of a minimum of 8 bones were required to assess bone age [19]. PBI was calculated using the three middle metacarpals by a formula containing the average values for transverse cortical area (A), bone width (W) and bone length (L): $PBI = A/(W^{1.33} L^{0.33})$ [12]. Individual PBI outcomes were compared to reference values determined in healthy bone age and gender related children and expressed in standard deviation score (SDS) [12].

Figure 1. Preview of hand radiograph from a girl with bone borders used for calculating bone age and paediatric bone index (in metacarpals II through IV) outlined by BoneXpert.



The small numbers represent the given bone age for the individual bones used in calculating bone age.

Feasibility

Feasibility was specified in terms of successful determination of PBI. The authors considered the method feasible, if the PBI SDS would be obtained in at least 70% of the children.

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences for Windows 15.0 (SPSS Inc., Chicago, IL., USA). Results were expressed as mean ± standard deviation. T-tests and Pearson Chi-square tests were used to calculate differences between groups. A p-value of less than 0.05 was considered statistically significant.

Difference between chronological age and bone age was calculated as automated bone age (years) minus chronological age (years). Based on clinical experience, a difference of one year or more, in either direction, was defined as relevant.

Results

Patient characteristics are summarized in Table 1. Mean age of the children was 11.4 years (SD 4.8) and 53 (55.8%) of the children were male. GMFCS level V was present in 80%. The most common causes for their disability were either congenital (40%) or perinatal (31%). Mean weight of the children was 32.2 kilogram (± 12.5 SD) and 82.1% of the children had epilepsy.

Table 1. Characteristics of the study population (n=95)

Age* (yrs)		11.4 (4.8)
Weight* (kg)		32.3 (12.5)
Gender	Male/female	53 /42
Epilepsy		78
GMFCS	Level IV/V	19 /76
Aetiology of disability	Congenital	38
	Perinatal	29
	Acquired	7
	Combination of congenital and acquired	4
	Unknown	16

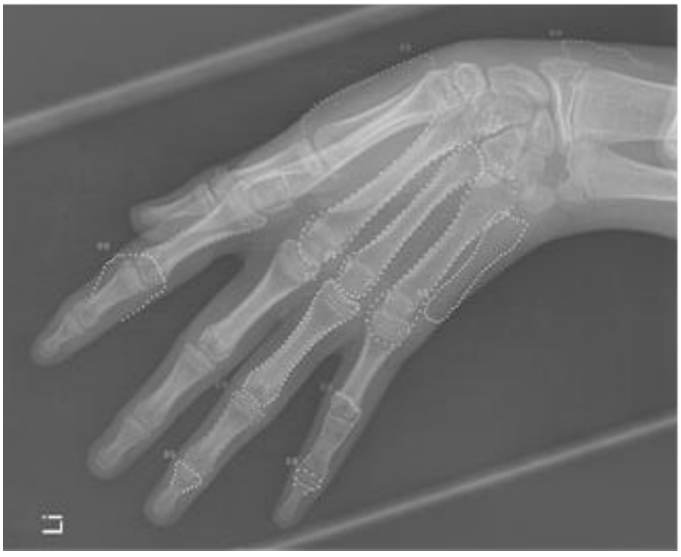
* mean with standard deviation in parentheses

Hand radiographs were obtained from all 95 children. From 60 (63.2%) radiographs the PBI SDS could be calculated. Determination was not possible in 35 children. Causes of an unsuccessful measurement are described in Table 2. Contractures of the hand causing crossed projection of the metacarpals on the radiograph (Figure 2) were most common.

Table 2. Reasons for failure PBI SDS measurement (N=35).

Reason for failure	**N**	**%**
Missing bone age	2	5.7
Contractures of the hand causing crossed projection of the metacarpals	17	48.6
Excessive sharpening giving lack of contrast between bone tissue and surrounding soft tissue	8	22.9
Anatomical deformities of the bones (not possible to determine exact margins of regions of interest)	3	8.6
Unclear	5	14.3

Figure 2. Example of a hand radiograph with projection of the metacarpals.

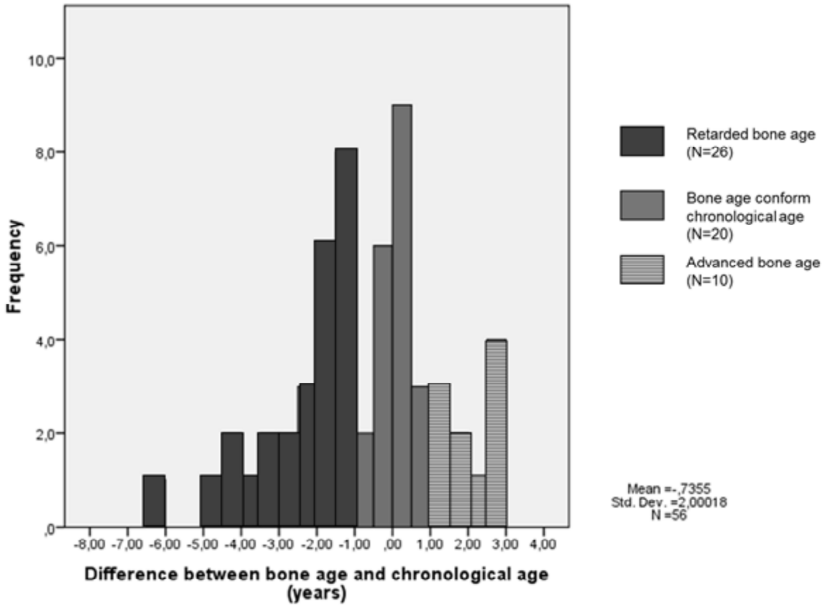


Correct positioning of the dotted lines on the bone edges and correct positioning of the regions of interest were not possible.

Assessment of bone quality was more frequently unsuccessful in children with more severe motor disabilities, scored as GMFCS level V (p=0.03, X2-test). Age, gender, aetiology of the intellectual disability, weight and epilepsy did not influence feasibility.

In order to determine bone age successfully, at least eight hand and wrist bones were required, compared to three metacarpal bones in determining PBI. In four children bone age could not be measured. Bone age and chronological age diverged more than one year in 36/56 (64%) of the study group. In 26 children bone maturation was delayed and in 10 children bone maturation was accelerated (Figure 3). A strong correlation was found between chronological age and bone age ($p<0.0001$). On the other hand individual differences between both values varied from a bone age three years ahead of chronological age till six years behind (Figure 3).

Figure 3. Histogram of differences found between chronological age and bone age (N=56)



Chronological age: age in years at time of measurement;Bone age: automated bone age in years as determined by BoneXpert software from the hand X-ray; Frequency: number of children

Discussion

In 60 out of 95 children with severe neurological impairment and ID (63.2%) PBI SDS was successfully determined. This is slightly lower compared to the minimum of 70% we determined on forehand judging this diagnostic method feasible for this group.
Determination of bone quality appeared more difficult in children with a GMFCS level V. These children suffer from severe contractures, which appeared to be the most common cause for unsuccessful measurement (17/35, 49%). This made correct identification of bone edges, necessary for automated assessment of the PBI, impossible. Although this reduces the usability of the automated radiogrammetry method in the most severely handicapped paediatric group it is important to realise that in children with severe contractures and deviant posture other bone diagnostic methods are difficult to apply as well (chapter 3 and 4) [20]. In severely disabled children with multiple determinants for low bone quality, e.g. use of anti-epileptic drugs, severe immobility and feeding problems, it is recommended to monitor bone development and bone quality over time [21-22]. Automated radiogrammetry, being an easily applicable diagnostic method with limited radiation use, appears to be particularly suitable for this purpose [11, 15]. It has shown to be attainable in longitudinal research, since in earlier studies on children treated for acute lymphoblastic leukaemia and growth hormone deficiency this method was able to detect changes in bone quality during treatment [15].
Another important advantage of the BoneXpert method is the automated bone age determination, which results in absence of interobserver variation. Bone age and chronological age were found to diverge in a substantial part of the children, i.e. in 36/56 children (64.3%) the difference was more than one year. Comparing the PBI outcome value to bone age related reference values appears to result in more accurate outcome measures, because skeletal growth and maturation, and bone mineral accrual appear to be closely related [23]. Because PBI increases with age, the 26 children with bone age retardation would have had a lower PBI SDS if their PBI outcome had been compared to reference values of children with the same chronological age. Likewise, the ten children, in whom bone age was ahead of chronological age, presumably would have had higher PBI SDS values when using chronological age related reference values. Bone age retardation may be due to malnutrition, a chronic disease, growth hormone deficiency or hypothyroidism

[24-25]. Early or precocious puberty, sometimes observed in children with severe neurological impairment and ID [26], may explain bone age advancement [25, 27]. These important aspects of growth in children with severe neurological impairment and ID may also have consequences for interpreting outcome of other diagnostic methods on bone mineral density and bone quality [11]. Preferably, bone quality outcome in this group should be compared to bone age related reference values instead of chronological age related ones and manufacturers of both DXA and QUS should integrate the possibility of correcting outcome for bone age in their software.

We conclude that automated radiogrammetry is a successful method to obtain results on bone quality in children with severe neurological impairment and ID before severe contractures occur. It can be used to evaluate bone maturation and bone quality over time, thus enhancing insight in the pathofysiology of low bone quality in this vulnerable population.
An ideal diagnostic method for measuring bone quality has not yet been found for older and more deformed children who are particularly at risk for low bone quality and fragility fractures. Furthermore, it is important to realise that when other diagnostic methods are used in this group, bone maturation should be taken into account when interpreting bone outcome.

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Chapter 6

Prevalence of low bone quality and its determinants in children with severe neurological impairment and intellectual disability

Submitted

Abstract

Prevalence and determinants of low bone quality were assessed by automated radiogrammetry in children with severe neurological impairment and intellectual disability (ID).
Paediatric Bone Index (PBI), a measure of bone quality, was determined on a regular radiograph of the hand (BoneXpert software © version 1.14) in sixty children at outpatient paediatric clinics in the Netherlands. The children had an estimated IQ less then 55 and a GMFCS level more than III.
Potential determinants were collected from patient files, interviews with parents and physical examination. Their relation with bone quality was analysed using regression analysis.
The study population consisted of young, mainly prepubertal children, in whom 73% were diagnosed GMFCS level V and 80% suffered from epilepsy. Bone quality was strikingly lower in these severely disabled children as compared to bone age and gender matched healthy children. The mean PBI standard deviation score (SDS) was −1.85 (SD 1.9). In 48% of the children the PBI SDS was below −2.0. A severe motor handicap (GMFCS level V) in combination with use of anticonvulsant medication, appeared most predictive for a low PBI SDS (p=0.007).
Children with severe neurological impairment and ID are at high risk for low bone quality. In these children imaging techniques to determine bone status should be implemented in routine paediatric care.

Introduction

Low bone mineral density (BMD) and low impact fractures are frequently present in children with severe neurological impairment and intellectual disability (ID) [1-5]. Low BMD in children, like its equivalent osteoporosis in adults, is a multifactorial disorder involving a broad variety of etiological factors. In children with moderate to severe cerebral palsy (CP), limited ambulation, feeding difficulties, anticonvulsant use, and lower body fat mass have been associated with low BMD Z-scores [6, 7]. In children with severe neurological impairment and ID several other factors might contribute to the development of low BMD, such as diminished intake of calcium [8, 9], limited exposure to sunlight [10], use of progestagens to induce amenorrhoea [11] or use of a ketogenic diet due to severe epilepsy [12].
With automated radiogrammetry bone quality can be measured from a hand radiograph using web-based software [13]. Children can be examined in their local hospital and next to bone quality bone age can be determined to investigate bone maturation which can frequently deviate in severely disabled children [14].
In this study we measured bone quality with automated radiogrammetry in children with severe neurological impairment and ID to determine prevalence of low bone quality and to assess which determinants are associated with low bone quality.

Methods

Study design

In a cross-sectional multicenter study, four Dutch hospitals participated. Together these four hospitals cover a large part of the southwest Netherlands.
Ethics approval of this study was obtained from the ethics committee of the Erasmus University Medical Centre Rotterdam (MEC-2005-182) as well as the ethics committees of each participating hospital.

Study population

All children with severe neurological impairment and ID visiting the outpatient clinics of the participating hospitals were eligible for inclusion. Severe neurological impairment and ID was defined as a moderate to severe intellectual disability (estimated intelligence quotient (IQ) < 55) and a Gross Motor Functioning Classification System (GMFCS) level IV or V. The GMFCS is a five level classification

system that is widely used for children with cerebral palsy and describes gross motor function on the basis of self-initiated movement [15]. Children classified in level IV may walk indoors for short distances with physical assistance, but mostly rely on wheeled mobility. Children with GMFCS level V have severe limitations in head and trunk control and in self-mobility, and are entirely wheelchair dependent [16, 17].

Children with Down syndrome or Prader Willi syndrome were excluded, because these syndromes are known to influence bone metabolism [18-20]. Children with a malignancy diagnosed in the previous five years and children with untreated rickets were excluded as well.

At least two weeks before a regular visit to the paediatrician, parents or caregivers of eligible children received verbal information and written patient information about the study. After written informed consent by the legal representative of the child was received, the measurements were carried out in the hospital following a subsequent visit to the paediatrician.

Data collection

Patient characteristics and possible determinants were collected from patient files, interviews with parents or caregivers and a physical examination. A radiograph of the hand was made in order to assess bone quality and bone age.

Determinants

The following information was retrieved from patient files: drug use in present and past (anticonvulsants, corticosteroids, spasmolytics, bisphosphonates, hormonal treatment with either negative or positive effect on bone density), supplementation of calcium or vitamin D, numbers of years of anticonvulsant use, ketogenic diet, epilepsy, and hypogonadism. These data were verified during the interview with parents/caregivers. Also, parents were asked to estimate the time (in hours per week) spent by their children performing physical activity (e.g. swimming, active physiotherapy, horse riding) and the time spending outdoors (in hours per week). Mean daily intake of calcium was assessed with a specific food frequency questionnaire [21], which was sent beforehand to the parents.

Weight was measured with a standard clinical balance that was present in the outpatient clinic. Height was measured with a flexible tape measure in supine position. If scoliosis or contractures were present, the curves of the back or extremities were followed. Body Mass Index (BMI) was calculated using the

following formula, BMI = weight (kg)/ (length (m))^2. The BMI was compared to reference values of healthy Dutch children as provided by Growth Analyser 3.5 (Dutch Growth Foundation, 2007). Pubertal stage was assessed according to Tanner by visual inspection [22].

Bone quality and bone age measurement

Automated radiogrammetry analysis was performed on a regular posterior-anterior radiograph of the hand with the least contractures. Correct position of the hand was flat, palm down on the film with fingers stretched and slightly spread. The radiographs were digital in DICOM format or traditional radiographs on film. Radiographs on film were used after scanning with a VIDAR Diagnostic Pro Advantage Scanner (VIDAR, Herndon, VA, USA).

To ascertain Paediatric Bone Index (PBI), automated radiogrammetry was performed with BoneXpert© (version 1.14, Visiana, Holte, Denmark, www.BoneXpert.com), a software program originally designed to automatically determine bone age. Bone age (years) was calculated after determining bone edges of 13 bones in the wrist and hand, ascertaining bone age for each bone individually and then averaging the outcomes [14]. Valid and consistent bone ages of a minimum of eight bones were required to assess bone age [23]. BoneXpert uses either the Greulich and Pyle or the Tanner and Whitehouse method. In this study we used Greulich and Pyle which has proven a robust method for automatic determination of bone age in an earlier study [14]. If automated bone age determination was not possible, bone age was determined manually with the Greulich and Pyle method by a paediatric radiologist, who was blinded for chronological age and severity of handicap [24].

PBI was determined by geometrical calculations similar to digital X-ray radiogrammetry bone mineral density (DXR-BMD), which has shown to correlate well with peripheral DXA measurements of the forearm [25, 26] and with DXA femoral neck BMD in adults [27]. The formula for calculating PBI contains the average values for transverse cortical area (A), bone width (W) and bone length (L): $PBI = A/(W^{1.33} L^{0.33})$ [26]. Reference values of automated radiogrammetry have been developed in a large group of healthy children (N= 2398) [26]. Individual PBI outcomes were compared to reference values as determined in healthy bone age (instead of chronological age) and gender related children resulting in a standard deviation score (PBI SDS) [26]. In this study a PBI SDS value equal to or below −2.0 was defined as too low.

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences for Windows 15.0 (SPSS Inc., Chicago, IL., USA).
Linear regression was used to determine the associations between the different variables and the PBI SDS outcome. After this, a multiple regression analysis was performed with determinants that were found to be significantly or nearly significantly associated with PBI SDS.
P-values of less than 0.05 were considered statistically significant and p-values of less than 0.10 nearly significant.

Results

From June 2006 till January 2009 95 children were included in this study. In 35 children (37%) bone quality measurement with PBI SDS failed. Assessment of bone quality was more frequently unsuccessful in children with more severe motor disabilities, defined as GMFCS level V (p=0.03, X2-test) (chapter 5).
In this study we used the data of 60 children with measurable PBI SDS for the analysis. Mean age of these children was 10.9 yrs (SD 4.3). The mean PBI standard deviation score (SDS) was −1.85 (SD 1.9). In 29/60 children (48.3%) the PBI SDS was below −2.0. Patient characteristics are summarized in Table 1.

Table 1. Patient characteristics (n=60)

		N	%	mean (SD)
Age (yrs) *				10.9 (SD 4.3)
Gender	Male/female	32/28	53.3/46.7	
GMFCS	Level IV/ V	16/44	26.7/73.3	
Etiology of disability	Congenital	30	50.0	
	Perinatal	16	26.7	
	Acquired	3	5.0	
	Combination of congenital and acquired	3	5.0	
	Unknown	8	13.3	
Epilepsy		48	80.0	
Bone age(yrs)*				9.7 (3.9)
PBI SDS *				−1.85 (1.9)

* mean with standard deviation in parentheses
GMFCS: gross motor functioning and classification system
PBI SDS: Paediatric Bone Index standard deviation score

Determinants of low bone quality

Possible determinants are presented in Table 2. PBI SDS was significantly associated with anticonvulsants (p=0.009), and GMFCS level (p=0.052) nearly significant. Physical activity including physiotherapy was nearly significant inversely related to PBI SDS (p=0.079). Without physiotherapy no relation was found.

Table 2. Lineair regression analysis on determinants of Paediatric Bone Index Standard

	Standardized coefficients (β)	**R square**	**P-value**
Patient characteristics			
Age	0.01	0.001	0.824
Gender	0.47	0.015	0.352
GMFCS-level	−1.10	0.064	*0.052***
Medication use			
Anti-convulsants	−1.35	0.112	*0.009**
Spasmolytics	0.27	0.003	0.655
Hormonal treatment	0.71	0.028	0.203
Vitamin D suppletion	−0.32	0.005	0.604
Calcium suppletion	−1.07	0.028	0.205
Conditions			
Epilepsy	−0.72	0.023	0.251
Hypogonadism	−0.30	0.001	0.831
Ketogenic diet	0.79	0.003	0.690
Measurements			
Tanner Stage	0.14	0.013	0.396
Years of anticonvulsant use	−0.01	0.001	0.823
Calcium intake (mg per day)	0.001	0.016	0.345
Time spent outdoors (hours/week)	0.03	0.005	0.581
Physical activity (hours/week)	−0.18	0.052	*0.079***
Physical activity minus physiotherapy (hours/week)	−0.13	0.028	0.204
BMI for age (Z-score)	0.054	0.003	0.676

* Significant; $P < 0.05$.
** Nearly significant; $P<0.10$.
GMFCS: gross motor functioning and classification system
BMI: Body Mass Index = weight (kg)/(length (in m))^2

Multiple regression analysis was performed using the variables 'anticonvulsant use' and 'GMFCS level' with PBI SDS as outcome variable (Table 3). The prediction model using both variables was significant (p=0.007) with a goodness-of-fit of 15.8% (R square 0.158). Table 3 also shows that anticonvulsant use significantly diminishes the PBI SDS outcome with 0.31 (p=0.014), whereas children with GMFCS level V have a nearly significant decrease of PBI SDS outcome of 0.22 in comparison with level IV children (p=0.08).

Table 3. Multiple regression analysis with PBI SDS as dependent variable.

Model	**R square**	**P-value Model**	**Predictor**	**Standardized coefficients (β)**	**95% CI**	**P-value**
1	0.112	*0.009**	Anti-convulsants	−0.33	−2.3,−0.3	0.09**
2	0.158	*0.007**	Anti-convulsants GMFCS	−0.31 −0.22	*−2.2, −0.3* *−2.0, 0.1*	*0.01** *0.08***

* Significant; $P < 0.05$.
** Nearly significant; $P<0.10$.
PBI SDS: paediatric bone index standard deviation score

Discussion

Prevalence of low bone quality and associated determinants were studied in 60 children with severe neurological impairment and ID with a mean age of 10.9 years. The mean paediatric bone index (PBI), as measured with automated radiogrammetry, was much lower compared to bone age and gender matched healthy children (PBI SDS −1.85), whereas 29 of the 60 children had a PBI SDS lower than -2. Anticonvulsant use was found to be a significant negative determinant of bone quality (p= 0.0009) and GMFCS level a nearly significant determinant (p=0.079). The prevalence percentage of low bone quality found (48%) presumably underestimates the actual frequency of low bone quality in the whole group (n=95). A previous article described that recordings of PBI failed more often in older children with more severe motor disability (chapter 5). While motor dysfunction is known to be an important risk factor of low bone density [6, 7, 28, 29], children in whom the measurement failed are prone to have poor muscle load

and poor bone quality [28, 29]. Therefore, the prevalence of 48.3% found in this study must be considered a minimal prevalence.
The nearly significant association between physical activity and PBI SDS was inverse, suggesting that more physical activity was associated with lower bone quality. However, without physiotherapy no relation was found. The same applied to the single variable physiotherapy. Also, physiotherapy consisted partly of passive movements. Therefore, physical activity as possible determinant was not included in the multiple regression analysis.
Our finding that anticonvulsant use and severe motor disability (GMFCS level V) are determinants of low bone quality is consistent with previous studies in children with moderate to severe CP [6, 30]. In this study, other observed determinants, like limited calcium intake, low body weight, feeding difficulties and minimal physical activity were not associated with low bone quality. This might be explained by our relatively small and rather homogeneous study population, resulting in a lack of variance in comorbid conditions, drug use, food intake, and physical activity.
These data implicate that subdivisions are not required within the group of children with severe neurological impairment and ID because all children with this diagnosis are at risk for low bone quality and therefore eligible for follow-up of bone quality.

Recommendations for clinical practice

At present, there is insufficient information on the effect of single or combinations of commonly used anticonvulsants on bone health in children [31]. Obviously, one should aim for a minimum amount of medication with the most optimal effect on often severe convulsions. Also, the older enzyme inductive anticonvulsant, e.g. phenytoin and phenobarbital, who have a negative effect on bone quality by inducing liver enzymes and increasing vitamin D catabolism should be avoided [32, 33].
We recommend that imaging techniques to determine bone status should be implemented in routine paediatric care for children with severe neurological impairment and ID.

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Chapter 7

General discussion

This thesis describes the results of studies on methods assessing bone quality in children with severe neurological impairment and intellectual disability (ID), and the results of a clinical study concerning prevalence of low bone quality and its determinants in this group of severely disabled children.
Throughout this chapter, directions for future research and recommendations are given in grey textboxes.

Overview of the main results

In the review study (chapter 2), only a limited amount of high-quality data on low bone mineral density (BMD) and fractures in children with cerebral palsy (CP) was found. In the selected studies, the incidence of fractures in children with moderate to severe CP approached 4% per year, whereas the prevalence of low BMD, defined as a Z-score below -2 measured with dual energy X-ray absorptiometry (DXA), was 77% in the femur. Limited ambulation, feeding difficulties, previous fractures, anticonvulsant use, and lower body fat mass were associated with low BMD Z-scores.
Our study on the applicability of DXA (chapter 3) showed that factors negatively influencing the accuracy of the DXA outcome are frequently present in children with severe neurological impairment and ID. The mean amount of disrupting factors per child was five, and factors occurring most frequently were movement during measurement (82%), aberrant body composition (67%), small height for age (56%), and scoliosis (37%).
Quantitative Ultrasound measurement of the heel bone (QUS) was found a feasible and non-stressful method for measuring bone quality in (mainly adult) persons with ID (chapter 4). Measurements were successfully performed in at least one foot in 95% and induced barely or no stress in 90% of the study population.
With automated radiogrammetry, bone quality could be obtained successfully in 63% of the children with severe neurological impairment and ID (chapter 5). Severe contractures of the hands were the most common cause of unsuccessful measurement. In addition, bone age was determined and in 64% of the children chronological age diverged more than a year from bone age.
Bone quality, measured with automated radiogrammetry, was found to be strikingly lower in this group of severely disabled children compared to bone age and gender matched healthy children (chapter 6); in almost 50% of the children the standard

deviation score was below −2.0. A severe motor handicap (Gross Motor Function Classification System (GMFCS) level V) in combination with use of anticonvulsant medication, was associated with low bone quality (p=0.007).

Diagnostic methods

Diagnosing bone quality in children with severe neurological impairment and ID is challenging. In Table 1 an overview is given of the advantages and disadvantages of the current diagnostic methods in this group [1-7]. Results from the performed studies in this thesis are included.

The golden standard for measuring bone mineral density in adults is dual energy X-ray absorptiometry (DXA). DXA measures an areal rather than a true volumetric bone density. This complicates the use in children because it does not take into account the depth of bones and three-dimensional growth. In large bones DXA BMD will be an overestimation; in small bones it will be an underestimation of true volumetric BMD. To correct for these deviations, calculations adjusting for body size are used [8].

DXA has proven less applicable in children with severe neurological impairment and ID by the presence of artefacts and disrupting factors, especially for measurements of the lumbar spine and total body. In the North American Growth in Cerebral Palsy study, Henderson and colleagues measured BMD of the distal femur in 619 children with moderate to severe cerebral palsy (CP) [9]. This concerns an alternative region located just above the lower epiphysis of the femur near the knee joint. Generally in adults the proximal femur or the femoral neck is evaluated. The distal femur measurement is performed with the child positioned on its side. To maintain the correct position foam blocks and wedges are used as support [10]. This specific scanning technique may diminish the amount of disrupting factors mentioned earlier. In addition, a correlation between distal femur BMD and fracture risk was found in children with CP, with a 10-20% increased risk of fracture with each 1.0 decrease in BMD Z-score of the distal femur [9, 10]. Therefore, it is recommended that when DXA is used in children with severe motor disabilities, preferably the BMD of the distal femur is measured.

Table 1. Aspects of current diagnostic methods of bone health

Diagnostic method	Measured Parameter	Measured site	Advantages	Disadvantages	Status of method
DXA	Bone mineral density (g/cm^2)	Total body, lumbar spine, (distal) femur	• Short scanning time • Low radiation	• Distorting factors • No differentiation between cortical and trabecular bone • Measures areal bone density (not a true density)	Golden standard
QUS	Speed of sound (m/s) Broadband ultrasound attenuation (dB/MHz)	Heelbone	• No radiation • Low costs • Mobile apparatus • Characterizes other material properties of bone (besides bone density)	• Limited availability reference values for children • Limited correlation with DXA • Correlation with fracture risk not established	Screening
QCT	Volumetric bone mineral density (mg/cm^3)	Lumbar spine	• Measures volumetric bone density (bone shape) • Differentiation between cortical and trabecular bone	• High radiation • Limited paediatric reference values • Susceptible to motion artefacts • Expensive	Diagnostic
pQCT	Volumetric BMD (mg/cm^3)	Forearm, tibia	• Low radiation • Short scanning time • Differentiation between cortical and trabecular bone	• Appendicular bone • Limited availability • Limited paediatric reference values • Correlation with fracture risk not established	Diagnostic
MRI	Volumetric bone mineral density (mg/cm^3)	Lumbar spine	• No radiation • Assessment of trabecular microarchitecture	• Expensive • Not readily available • Susceptible to motion artefacts	Experimental
Automated Radiogrammetry	Paediatric Bone Index ($\mu m^{0.33}$)	Metacarpals	• Only hand radiograph needed • Low radiation • Bone age determination	• Good quality hand radiography necessary (e.g. contractures) • Limited evidence of correlation with other methods and fracture risk	Experimental

DXA: Dual X-ray Absorptiometry; QUS: Quantitative Ultrasound; QCT: Quantitative Computed Tomography; pQCT: peripheral quantitative Computed Tomography; MRI : Magnetic Resonance Imaging

To be able to use BMD measurement of the distal femur in Dutch hospitals, reference values should be developed for each DXA device and standardization of the measurement procedure must be implemented in clinical practice.

A technical advantage of magnetic resonance imaging (MRI) and quantitative computed tomography (QCT) in comparison to DXA is the possibility to distinguish between the two main types of bone, e.g. trabecular and cortical bone. Trabecular and cortical bone differ in their rates of bone accrual during normal growth and trabecular bone is more rapidly affected by disease or therapy. Therefore, when studying the response to therapeutic interventions, separate analysis of both bone types may provide additional information on treatment effects on bone tissue [6, 11]. On the other hand, both MRI and QCT measurements are very sensitive to movement [7]. In the study on disrupting factors in DXA more than 80% of the disabled children moved to some extent during the measurement. This will obviously disturb the outcome of MRI and QCT as well and implies the necessity of sedation during this type of measurements. An additional disadvantage of QCT is the amount of radiation used. In peripheral QCT (pQCT) the lower forearm or tibia is measured. This results in less radiation exposure. However, the method is not widely available and present data on pQCT are not sufficient for the prediction of fractures [7, 8]. Therefore, these measurements appear not feasible in these children.

The use of quantitative ultrasound (QUS) in children was complicated by the lack of available QUS devices with apparatus specific paediatric reference values. Although reference values were developed for tibial QUS in Dutch children [12], in the meantime this QUS device was out of production. Only recently, additional reference data for different QUS devices measuring the heel bone have become available [13, 14]. A recent study of Lee et al. provided more information on longitudinal changes in QUS parameters during growth. In this study the calcaneal QUS measures, speed of sound (SOS) and broadband ultrasound attenuation (BUA), increased with increasing skeletal age [14]. In adults QUS measures have shown to correlate with hip fracture risk [15], however few data are present in children [8]. Also, it is not exactly evident what is measured with QUS, making it difficult to separate growth from actual bone mass development in children [8]. Although in our study QUS has shown to be easily applicable and not stressful in persons with ID, only part of the study group (21.9%) had severe neurological impairment and ID. The 95% CI for successfully measuring bone quality using QUS

in these 27 adults and 6 children with severe neurological impairment and ID was 74-94% (additional analysis stata 11.0).

Research on QUS in relation to fracture incidence may improve its status as screening instrument in both adults and children with ID.

Two aspects favour the use of automated radiogrammetry. Firstly, the availability of the method: only a radiograph of the hand is needed to assess the paediatric bone index (PBI), and the software is accessible via internet. Secondly, simultaneous with the PBI, bone age is determined. Comparing the paediatric outcome value to bone age related reference values appears to result in more accurate outcome measures, because skeletal growth and maturation, and bone mineral accrual appear to be closely related [11]. This is most clearly illustrated in pathological conditions. In children with growth hormone deficiency skeletal growth, bone maturation and BMD are initially decreased and improve after growth hormone therapy has been started [16]. In pubertal delay, growth, bone maturation and bone mineral accrual are retarded as they are advanced in precocious puberty [17]. In our study, bone and chronological age diverged more than one year in 64% of the children and in most of them bone age was retarded. Additional analysis was performed and showed that when comparing PBI to reference values related to chronological age, the mean PBI SDS was −2.05, which is significantly ($p=0.001$) lower than the mean PBI SDS related to bone age (−1.85). Although both SDS values are highly correlated (0.975, $p<0.0001$), comparing outcome to chronological age related reference values will overestimate low bone quality prevalence in children with retarded bone maturation. In addition, automated radiogrammetry, having limited radiation, appears to be an ideal method for longitudinal screening of bone quality in severely disabled children. Automated radiogrammetry appears attainable in longitudinal research, since in earlier studies on children treated for acute lymphoblastic leukaemia and growth hormone deficiency, it has shown the ability to detect changes in bone quality during treatment [18].

Further research with automated radiogrammetry is recommended for acquiring longitudinal PBI data in children with severe neurological impairment and ID to provide insight in bone development in this group. In addition, automated radiogrammetry should be further validated in this group of severely disabled children by comparing PBI outcome with fracture incidence.

Prevalence of low bone quality

Earlier studies on bone quality in disabled children mainly consisted of children with moderate to severe CP [19, 20]. However, our study is the first study on bone quality in the most severe handicapped group of children with complex health problems. We observed a prevalence of low bone quality (PBI SDS < -2) of 48% which is lower than the prevalence of low bone density found in other groups of disabled children [19-21]. Since PBI measurements could not be obtained in the children with the most severe motor handicaps, and motor function appeared to be a determinant of PBI, the true prevalence is probably higher. Otherwise, it should be taken into account that the prevalence numbers found in other studies, mostly performed with DXA, might be overestimated. In these studies chronological age related reference values were used, producing a more negative outcome in children with a retarded bone age [8].
Nevertheless, the prevalence numbers of low bone quality in this thesis (48-77%) are disturbingly high.

Routine assessment of bone quality in children with motor disabilities should become clinical practice. In children with low bone quality evaluation for possible fractures must be performed after trauma and distress of unknown cause. If a significant fracture occurs, bisphosphonate therapy must be considered.

Determinants of low bone quality

Another aim of our study was to identify children within this group of severely handicapped children which are most at risk to develop low bone quality and

fractures. Our analyses have shown that the combination of anticonvulsant use and severe motor impairment (GMFCS level V) is associated with poor bone quality. No other determinants were identified. Presumably this occurred since a relatively homogeneous population was studied with little variance in co morbid conditions, due to our inclusion criteria (GMFCS level IV or V) and selection procedure (out-patient paediatric clinics).

Anticonvulsant medication has shown to have a negative effect on BMD in both adults and children [22, 23]. The mechanisms are not quite clear. The older enzyme inductive anticonvulsants, e.g. phenytoin and phenobarbital, increase vitamin D catabolism by inducing liver enzymes, which negatively influences bone quality [24]. However, results concerning other anti-epileptic agents are less conclusive. In some studies carbamazepine, another enzyme inducer, and valproate affect bone mineralization adversely as well [23]. However, it is also stated that the decrease in BMD in children with epilepsy is mainly caused by complicating diseases and comorbidity leading to vitamin D deficiency, for example by a diminished exposure to sunshine [25].

More research is needed to clarify the effects of different anti-epileptic drugs on bone quality. This evidence will help us to give a more founded advice on the use and/or selection of anticonvulsants.

Bones will adjust their strength in proportion to the amount of mechanical stress put on them. The largest physiological loads on a bone result from muscle contraction: muscle contractions during every day activities put larger loads on the skeleton compared to gravity [26]. Also, lean body mass, which is used as a surrogate for muscle load, has proven to be a strong predictor for total body and lumbar spine bone mineral content (BMC) [27]. Therefore, severe motor impairment causing limited use of skeletal muscles and insufficient loading of the skeleton, leads to bone fragility. Few studies have investigated the role of physiotherapy and weight bearing activities on BMD in severely disabled children [28]. Those studies have shown that BMD can increase in both spine and femur after weight bearing exercises [29, 30]. However, these were studies with small numbers and different intervention strategies [31].

More research is needed to determine which aspects of weight bearing physiotherapy (e.g. duration, frequency, type of intervention) are necessary to improve bone quality in children with severe neurological impairment and ID.

Appropriate gains in bone mineral content are achieved only when environmental conditions are favourable. Nutritional status, with appropriate calcium and vitamin D levels, are important for bone health. In the North American Growth in Cerebral Palsy project lower nutritional status and low calcium intake were correlated with lower BMD in children with moderate to severe CP [32]. In addition, Jekovec-Vrhovsek et al. found an increase in BMD of the lumbar spine after administrating vitamin D and calcium supplementation for 9 months in children with severe CP [33].

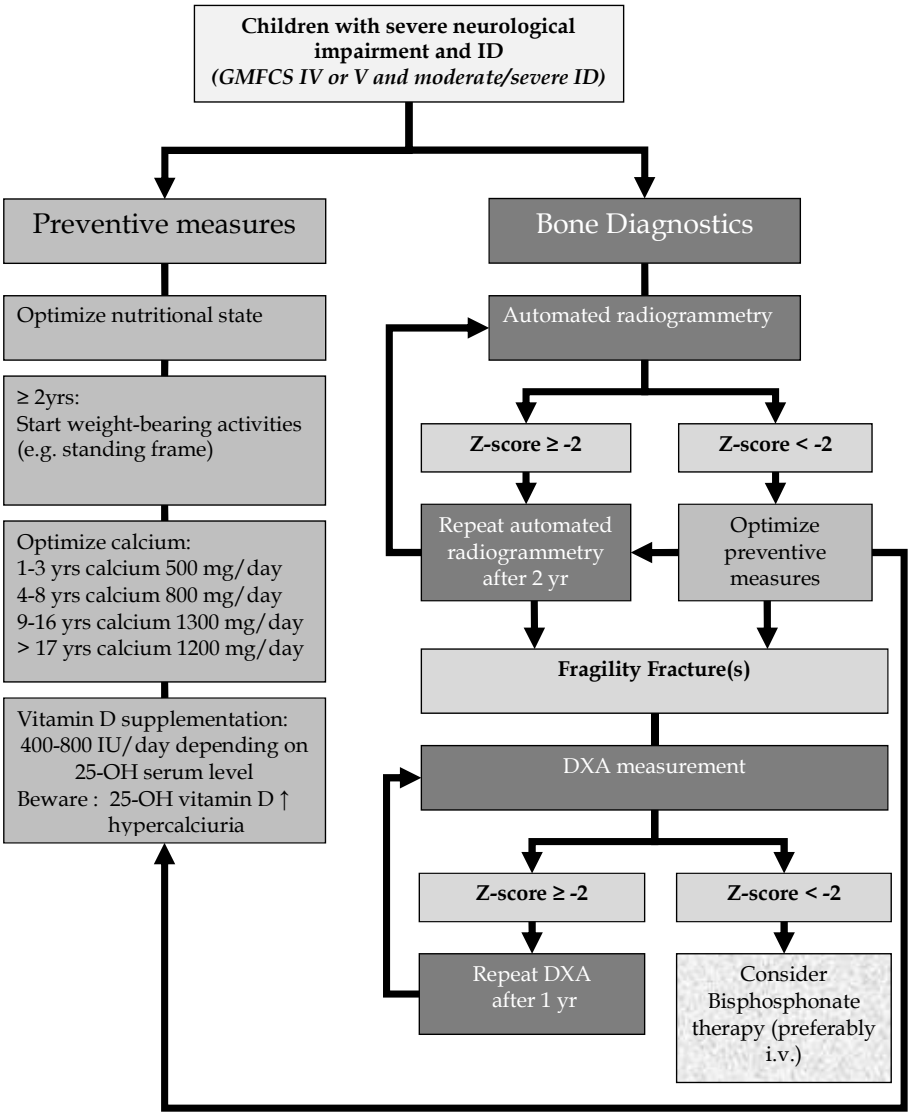
Optimizing nutritional status, especially vitamin D and calcium intake, are important in the prevention and treatment of low bone quality in children with severe neurological impairment and ID.

Although children with more severe motor disabilities and anticonvulsant medication appear to be more at risk, we conclude that distinguishing specific risk groups does not contribute to clinical consequences of primary prevention of low bone quality in all children with mental and motor disabilities, since preventive measures should be applied to every disabled child.

Recommendations for clinical practice

Based on current literature and the presented research a proposal for a guideline is formulated for prevention, diagnosis and treatment of low bone quality in children with severe neurological impairment and ID (see Figure 1) [11, 34]. Although this guideline is formulated for children with a combination of cognitive impairment and motor impairment, it might be useful to monitor bone quality in all children with severe motor disabilities regardless of an intellectual disability.

Figure 1. Flow diagram concerning the prevention, diagnosis and treatment of low bone quality in children with severe neurological impairment and ID



Preventive measures should be stimulated from an early age to optimize peak bone mass. Bone quality assessment should start in young children to be able to monitor bone development. To assess bone quality, automated radiogrammetry is advised every two years following a specialist consultation (e.g. paediatrician, physician for people with intellectual disability, child neurologist or orthopaedic surgeon). Awareness of low bone quality can contribute to early recognition of fractures in severely handicapped children. Fractures may occur after minimal or no apparent trauma in this group and often the lack of history or a trauma causes diagnostic delay. In a pilot study (N=11) we found that the mean delay in diagnosing a non-traumatic fracture was 3.5 days (range 0 – 10 days) in this group [35].
When fragility fractures occur in children with severe neurological impairment and ID, DXA measurement, including distal femur DXA, should be requested to asses BMD. A history of significant fractures in combination with low BMD (a Z-score less than −2.0) measured with DXA demands consideration for treatment with bisphosphonates [34]. Significant fracture history can be defined as a long-bone fracture of the lower extremities, a vertebral compression fracture, or two or more long-bone fractures of the upper extremities (International Society for Clinical Densitometry, 2007, http://www.ISCD.org).
In a recent review by Fehlings et al. therapy with bisphosphonates was found to be probably effective in improving BMD in children with CP and possibly effective in reducing fragility fractures [34]. The five studies used were all concerning non-ambulatory children with CP, with numbers of participants ranging from 14 till 25. In four of these studies intravenous pamidronate was used at a frequency of three to four times per year and the most commonly used dosage was 1mg/kg for three days. Transient flu-like symptoms and occasional hypocalcaemia were reported as possible adverse effects of intravenous bisphosphonate therapy. The duration of the studies did not exceed one year and information on long-term effects of bisphosphonates on growing bones is currently lacking [34].

More research is needed to establish the effect of bisphosphonate therapy on the prevention of fragility fractures in children with low BMD and significant fracture history, to provide more insight in optimal dosage and length of this treatment and to establish safety of long-term bisphosphonate use. Studies on preventive treatment of low bone quality with bisphosphonates before the occurrence of fractures are required as well.

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Summary

In clinical practice, children with severe motor handicaps regularly develop fragility fractures. These fractures are generally the result of low bone quality. In the first chapter of this thesis the subject of low bone quality is introduced and illustrated with a case report concerning a severely disabled boy with fragility fractures.
The introductory part of this thesis proceeds with the results of a systematic review on incidence of fractures and on prevalence of low bone quality and its determinants in severely handicapped children (chapter 2). Only a limited amount of high quality data was found and this concerned children with moderate to severe cerebral palsy (CP). The incidence of fractures was 4% per year in this group and the prevalence of low bone mineral density (BMD) was 77% with dual energy X-ray absorptiometry (DXA) of the distal femur. Determinants associated with low BMD were limited ambulation, anticonvulsant use, lower body fat mass, feeding difficulties and a history of fractures.
The second part of this thesis consists of studies into the applicability of three diagnostic methods for assessing bone quality in children with severe neurological impairment and ID.
At first, the applicability of DXA of the total body and lumbar spine was studied in 34 children (chapter 3). Using a standardized checklist, it was found that disrupting factors that may influence the accuracy of the DXA outcome, are frequently present in this group. The children had a mean of five disrupting factors, of which movement during measurement (82%), aberrant body composition (67%), small height for age (56%), and scoliosis (37%) were most frequent.
Chapter 4 describes a study into the feasibility of quantitative ultrasound (QUS) of the heel bone in a broader group of people with different levels of ID (n=151). In this group 27 adults and 6 children with severe neurological impairment and ID were included. This method appeared feasible, with a successful measurement in at least one foot in 95% and without observable stress in 90% of the studied population. However, although measurement was technically possible, the results of the measurement could not be interpreted in 24% of the persons with severe neurological impairment and ID.
The third method studied was automated radiogrammetry, a method which determines bone quality and bone age of a regular hand radiograph (chapter 5). The feasibility of this method was investigated in 95 children with severe neurological impairment and ID. Bone quality could be obtained successfully in 63% of the children. Unsuccessful measurement was mostly caused by severe contractures of the hands. In addition to bone quality, bone age was determined as

well. In 64% of the children chronological age diverged more than a year from bone age. In most of these children bone age was retarded as compared to chronological age.
The last part of this thesis is dedicated to a clinical study on prevalence of low bone quality and its determinants in 60 severely disabled children (chapter 6). With automated radiogrammetry, low bone quality was diagnosed in 48% of the children. A severe motor handicap (GMFCS level V) in combination with using anticonvulsant medication was associated with low bone quality ($p=0.007$).
In chapter 7, the findings of all studies are discussed in the context of recent literature and clinical practice. Recommendations for future research are given and a proposal is made for a guideline concerning prevention and treatment of low bone quality in children with severe neurological impairment and ID in clinical practice.

Samenvatting

Spontaan fracturen zijn botbreuken die na een minimaal trauma kunnen optreden. Deze fracturen komen in de praktijk regelmatig voor bij kinderen met ernstige meervoudige beperkingen. Het ontstaan van deze fracturen hangt samen met een lage kwaliteit van de botten bij deze kwetsbare kinderen.
In het eerste hoofdstuk van dit proefschrift wordt het onderwerp lage botkwaliteit geïntroduceerd en geïllustreerd aan de hand van een casus van een ernstig meervoudige gehandicapte jongen met spontaan fracturen.
Het tweede hoofdstuk van dit proefschrift beschrijft een systematische review waarin gekeken is naar het optreden van fracturen, het voorkomen van lage botkwaliteit en de samenhang met determinanten van lage botkwaliteit bij ernstig gehandicapte kinderen. In de literatuur zijn maar een beperkte hoeveelheid studies gevonden van voldoende kwaliteit en de meeste van deze studies onderzochten kinderen met matige tot ernstige cerebrale parese. Bij deze kinderen was de incidentie van fracturen 4% per jaar. Bij 77% van de kinderen werd een lage botmineraal dichtheid vastgesteld na meten van het distale bovenbeen met een DEXA scan. Factoren die samenhingen met lage botmineraal dichtheid waren beperkte mobiliteit, gebruik van medicijnen tegen epilepsie, een laag lichaamsvetgehalte, voedingsproblemen en een voorgeschiedenis van fracturen.
In het tweede gedeelte van dit proefschrift worden drie studies beschreven waarin de toepasbaarheid van drie verschillende methoden voor het vaststellen van botkwaliteit is onderzocht.
Om te beginnen is de toepasbaarheid van DEXA onderzocht bij 34 kinderen met ernstige meervoudige beperkingen (hoofdstuk 3). Met behulp van een checklist is gekeken naar het voorkomen van factoren die de DEXA meting zouden kunnen verstoren. Het bleek dat bij deze kinderen gemiddeld vijf van dergelijke factoren aanwezig waren. Bewegen tijdens het onderzoek (82%), een afwijkende lichaamssamenstelling (67%), een kleine gestalte (56%) en scoliose van de wervelkolom (37%) kwamen het meest voor.
Hoofdstuk 4 beschrijft een studie naar de toepasbaarheid van echometingen van het hielbot bij 151 mensen met een verstandelijke beperking. Een subgroup hiervan waren mensen met ernstige meervoudige beperkingen (27 volwassenen en 6 kinderen). De methode bleek goed toepasbaar en leverde bij 95% van de onderzochte personen een succesvolle meting op in tenminste één voet. De methode veroorzaakte nauwelijks stress en gaf slechts bij 10% van de deelnemers enige spanning. De resultaten van de meting bleken, ondanks dat het onderzoek

technisch goed uitvoerbaar was, in 24% van de mensen met ernstige meervoudige beperkingen niet goed te interpreteren.
De derde methode die we hebben bekeken is een methode waarbij de botkwaliteit en de skeletleeftijd bepaald worden met behulp van een röntgenfoto van de hand (hoofdstuk 5). De toepasbaarheid van deze methode is onderzocht bij 95 kinderen met ernstige meervoudige beperkingen. Bij 63% van de kinderen kon de botkwaliteit succesvol gemeten worden. Het aanwezig zijn van ernstige contracturen van de handen was de meest voorkomende reden voor het niet slagen van de meting. Naast botkwaliteit werd ook skeletleeftijd gemeten bij deze kinderen en bij 64% werd er een verschil van meer dan één jaar gevonden tussen de skeletleeftijd en kalenderleeftijd. In de meeste gevallen liep de skeletleeftijd achter op de kalenderleeftijd.
Het laatste gedeelte van dit proefschrift beschrijft een klinische studie naar voorkomen van lage botkwaliteit bij 60 kinderen met ernstige meervoudige beperkingen en de factoren die hiermee samenhangen (hoofdstuk 6). Met behulp van röntgenfoto's van de handen (via de methode zoals beschreven in hoofdstuk 5) werd bij 48% van de kinderen een lage botkwaliteit vastgesteld. Een ernstige motorische beperking (omschreven als GMFSC nivo V) in combinatie met het gebruik van medicatie tegen epilepsie was geassocieerd met een lage botkwaliteit ($p=0.007$).
In het laatste hoofdstuk (algemene discussie) worden de bevindingen van bovenstaande studies bediscussieerd in het licht van recente literatuur en de klinische praktijk. Er worden suggesties gedaan voor toekomstig onderzoek en er wordt een eerste voorstel gegeven voor een richtlijn op het gebied van preventie en behandeling van lage botkwaliteit bij kinderen met ernstige meervoudige beperkingen.

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Curriculum Vitae

Sandra Mergler werd op 14 november 1970 geboren te Delft. In 1990 behaalde zij haar gymnasiumdiploma aan het Stanislas College te Delft.
In eerste instantie werd zij uitgeloot voor de studie geneeskunde en begon ze aan een studie technische wiskunde aan de Technische Universiteit te Delft. Na drie maanden werd ze echter nageplaatst en kon zij alsnog beginnen aan de studie geneeskunde aan de Rijksuniversiteit Limburg te Maastricht. Hier heeft ze in 1991 haar propedeuse geneeskunde gehaald en in 1994 haar doctoraal examen (cum laude). Tijdens haar studie heeft ze gewerkt als verpleeghulp in diverse verpleeghuizen, bij de thuiszorg en bij Maasveld, een zorgorganisatie voor mensen met een verstandelijke beperking.
Na het behalen van haar artsexamen in 1997 wilde Sandra graag verder in de zorg voor mensen met een verstandelijke beperking en is ze gaan werken bij de ASVZ, een organisatie voor zorg- en dienstverlening aan mensen met verstandelijke beperkingen in Sliedrecht.
In 1998 heeft ze de opleiding voor artsen werkzaam in de zorg voor mensen met een verstandelijke handicap aan de NSPH (Netherland School of Public Health) te Utrecht afgerond. In 2000 werd Sandra geregistreerd als AVG (arts verstandelijk gehandicapten). Van 2002 tot 2008 is ze AVG-opleider geweest aan de Erasmus Universiteit te Rotterdam.
Naast haar werk bij ASVZ, is Sandra vanaf 2008 als arts onderzoeker in deeltijd verbonden aan de leerstoel geneeskunde voor verstandelijk gehandicapten, onderdeel van de afdeling huisartsgeneeskunde, aan de Eramus Universiteit te Rotterdam. Hier heeft ze haar in dit proefschrift beschreven onderzoek afgerond.
Sinds September 2010 is zij één dagdeel per maand werkzaam op de AVG polikliniek van het Maasstadziekenhuis te Rotterdam, alwaar ze een transitie polikliniek doet voor 18 plussers met een motorische en/of verstandelijke beperking.
Sandra woont samen met Andries Troost en hun zoon Jasper in Gorinchem.

Phd Portfolio

Courses

2004 Tweedaagse cursus Wetenschappelijke methoden voor de AVG, Erasmus MC, Rotterdam.

2004/2005 Masterclass Wetenschappelijk onderzoek, 's Heerenloo Zorggroep, Amersfoort.

2005 Erasmus Summer programme, courses Principles of Research in Medicine and Epidemiology and Introduction to Data-analysis, Eramus Universiteit, Rotterdam.

2009 SPSS basis training, Learnit training, Rotterdam.

2008/2009 Erasmus MC Graduate School, course "Biomedical English Writing and Communication, Rotterdam.

2011 Basismodule Evidence-bassed richtlijnontwikkeling (EBRO), CBO, Amsterdam.

Oral presentations

1999 Tweetal avonden deskundigheidsbevordering aan artsen voor verstandelijk gehandicapten in de regio Zuid-Holland over het onderwerp osteoporose, Nootdorp.

2000 Presentatie "Osteoporose en risicofactoren voor osteoporose bij mensen met een verstandelijke handicap", themamiddag NVAZ, Apeldoorn.

2004 Presentatie "Spontaan fracturen bij kinderen met een gegeneraliseerde cerebrale parese, congres kindergeneeskunde NVK te Veldhoven.

2005 Workshop "AVG en wetenschappelijk onderzoek in de praktijk", samen met dhr. H. de Waal, AVG lustrumsymposium, Rotterdam.

2006 Voordracht Kinderartsenweek Erasmus MC Sophia "Zorg voor een kind met een beperking", Rotterdam.

2006 Presentatie "Digital X-ray Radiogrammetry (DXR) in diagnosing low bone mineral density in children with severe generalized cerebral palsy" 2nd European Congress of the International Association for the Scientific Study of Intellectual Disabilities (IASSID), Maastricht.

2006 Avond deskundigheidsbevordering AVG's regio Utrecht over osteoporose bij verstandelijk gehandicapten.

2006 Themaochtend Osteoporose bij mensen met een verstandelijke beperking voor AVG opleiding 3e jaars AIOS, Rotterdam.

2008 Avond deskundigheidsbevordering AVG's regio Zuid Holland over osteoporose, Nootdorp.

2008 Twee presentaties "Low bone mineral density in children with generalized cerebral palsy" en "Feasibility and outcome of ultrasound bone measurement of the heel bone in people with intellectual disabilities"; 13th World Congress of the International Association for the Scientific Study of Intellectual Disabilities (IASSID), Kaapstad (Zuid-Afrika).

2009 Voordracht studiedag sectie erfelijke en aangeboren aandoeningen NVK. Voordracht: "Osteoporose: een (on)bekende aandoening bij meervoudig gehandicapte kinderen", Nieuwegein.

2010 Twee presentaties "Feasibility of DXA bone density measurement in children with profound intellectual and multiple disabilities" en "Measuring bone quality in children with profound intellectual and multiple disabilities (PIMD) with a hand radiograph"; 3rd European Congress of the International Association for the Scientific Study of Intellectual Disabilities (IASSID), Rome (Italië).

2010 Presentatie "Prevalentie van lage botdichtheid bij kinderen met ernstige meervoudige beperkingen" congres kindergeneeskunde NVK, Veldhoven.

2011 Bijeenkomst sectie kinderrevalidatie, voordracht "Osteopenie bij kinderen met ernstige CP", Utrecht.

Poster presentations

2006 'Measurement of bone density in children with profound intellectual and multiple disabilities (PIMD) by using an X-ray of the hand', Annual meeting of the European Society for Paediatric Endocrinology (ESPE), Rotterdam.

2007 'Measuring bone mineral density in children with severe generalized cerebral palsy', Annual meeting of the European Academy of Childhood Disability (EACD), Groningen.

2007 'Measuring bone mineral density in children with severe generalized cerebral palsy', Annual meeting of the Dutch Academy of Childhood Disability (DACD), Utrecht.

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