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Workshop report

274th ENMC international workshop: recommendations for optimizing bone strength in neuromuscular disorders. Hoofddorp, The Netherlands, 19–21 January 2024

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ABSTRACT

The 274th ENMC workshop for optimizing bone strength in neuromuscular disorders (NMDs) was held on January 19–21, 2024. The group of participants included experts in the fields of bone health and neuromuscular medicine along with the patient voice. Bone strength represents a crucial aspect of the management of pediatric and adult patients with NMDs. Bone strength may be compromised due to different pathophysiologic mechanisms, including disrupted bone–muscle "cross-talk", loss of biomechanical loading, nutritional insufficiency, inadequate weight-bearing physical activity, muscle weakness and/or immobility, and drug treatment. While for Duchenne muscular dystrophy recommendations for evaluation and treatment of bone strength have been published, evidence on bone strength in other hereditary and acquired NMDs is scarce. Enhanced knowledge is needed to understand the development and maintenance of bone strength in patients with NMDs. This workshop aimed to develop a strategy to improve bone strength and thus prevent fractures in patients with NMDs.

1. Introduction

The 274th ENMC workshop for optimizing bone strength in neuromuscular disorders (NMDs) was held in Hoofddorp on January 19–21, 2024, The Netherlands. Twenty participants, including three patient representatives, were brought together to discuss different aspects of bone strength in people with NMDs. The group of participants included experts in the fields of bone health and neuromuscular medicine (along with the patient voice).

Bone strength represents a crucial aspect to consider in the management of pediatric and adult patients with NMDs. Fractures, the major complication of osteoporosis, stem from lower bone strength influenced by factors like bone geometry, density, and metabolism. Bone strength can be estimated indirectly through various methods including dual-energy X-ray absorptiometry (DXA) and vertebral fracture assessment (VFA) [1].

In various NMDs, bone strength may be compromised due to different pathophysiologic mechanisms, including disrupted bone–muscle "cross-talk", loss of biomechanical loading, nutritional insufficiency, inadequate weight-bearing physical activity, muscle weakness and/or immobility, and drug treatment (i.e. glucocorticoid therapy). While for Duchenne muscular dystrophy (DMD) consensus recommendations for evaluation and treatment of bone strength have been published [2], evidence on bone strength in other hereditary NMDs, myasthenia gravis, and inflammatory myopathies is scarce [3]. Recently, a scoping review on bone strength in congenital myopathies (CMs) was performed [3], showing that (fragility) long bone fractures (LBFs) are common in pediatric and adult patients with CM.

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Enhanced knowledge is needed to understand the development and maintenance of bone strength in patients with neuromuscular disorders. Addressing persistent gaps is crucial for optimal diagnosis, monitoring, treatment strategies, and developing outcome measures in clinical and therapeutic trial settings. The ultimate aim of this workshop is to develop a strategy to improve bone strength and thus prevent fractures in patients with NMDs by:

- Bringing together experts in bone health, NMDs, and patient advocates to connect and share knowledge about bone strength;
- Conducting a gap analysis to identify which data should be obtained in future research in four main categories:

(1) Characterizing the effects of hereditary and immune-mediated NMDs on bone strength.
(2) Identifying risk factors for compromised bone strength in hereditary and immune-mediated NMDs.
(3) Optimizing screening for compromised bone strength in order to initiate bone protection therapy in a timely fashion.
(4) Defining the optimal therapies and timing of treatment initiation to prevent first-ever fractures and progression of bone fragility.

2. Overview of currently available knowledge on bone strength management in various NMD

In preparation for this workshop, **Madelon Kroneman, Ingrid de Groot** and **Silke Schlüter** (the patient representatives) conducted a survey among patients with NMDs in Europe and presented the results at the workshop. The survey included questions on experience with fractures, medication, mobility, presence of osteoporosis/osteopenia diagnosis, place of diagnosis (hospital/practice), treatment and side effects. Five hundred eighty-one patients with various NMDs from four countries took part in the survey.

The patient representatives shared their medical history and experiences with fractures and bone health. The patients underscored that fragility fractures, at all skeletal sites, can have a huge impact on mobility, self-reliance, and quality of life. Indeed, also wrist fractures might worsen disability particularly limiting the use of walking aids and other indispensable devices.

The survey revealed the following: 30 % experienced fracture following a fall in the past five years, 56 % of them experienced reduced mobility as a result of the fracture, 21 % of the respondents are diagnosed with osteopenia/osteoporosis. Of those 55 % were only diagnosed after the first fracture. Those with osteoporosis/osteopenia were mainly treated with vitamin D (75 %). However, bisphosphonates (BPs, 48 %), and calcium supplementation (53 %) were also reported. Fifty-four percent were prescribed vitamin D by doctors, 21 % take it on their own initiative and 10 % with osteoporosis/osteopenia receive no vitamin D, or calcium supplementation. Twenty percent of BP users reported side effects (muscle pain, weakness, fever, fatigue and intestinal problems), some of which were so severe that treatment was stopped in around a third of the patients. When asked whether patients were currently or had been treated with glucocorticoids (GCs) for more than a year in the past, 18 % agreed and one out of four of the GCs users has been diagnosed with osteoporosis or osteopenia.

Based on this survey, the patient representatives created a list of unmet needs from the patient perspective: screen and prevent osteoporosis in patients with NMD, raise awareness on increased risk of osteoporosis in patients with NMD (due to inactive lifestyle, prednisone use etc.), more information about side effects of medications (diuretics etc.) for bone health and emphasize the importance of exercise.

To investigate the current awareness and practice of bone strength management in NMDs, **Nicol Voermans** and colleagues performed an international online survey among clinicians (health care providers) through the European reference network EURO–NMD. The survey was created by the organizers and the patient representatives of this workshop, based on their widespread (patient) experience in the field of bone strength and on the scoping review [3]. It was sent to all 85 health care providers (HCPs) or their representatives of EURO–NMD on December 22nd 2023.

After 3 weeks (January 15th, 2024), an ad-interim analysis was performed and the preliminary results were presented. In total, 39 HCPs from 13 countries filled out the online survey (response rate 46 %, 65 % neurologist; 28 % pediatric neurologist; 5 % pediatrician and 3 % other). Most respondents considered their medical training on bone strength moderate to poor. Nevertheless, awareness (attention for bone strength) was reasonable to good, both at diagnosis (28/39) and at follow up (17/39). Clinicians performed bone health surveillance mostly in patients with muscular dystrophies, congenital myopathies and spinal muscular atrophy, in addition to DMD and patients with inflammatory neuromuscular disorders who were on steroids. Different screening methods were used, of which DXA was most common. The bone sites which were assessed by DXA were variable. There was a large range of laboratory tests reported. The prescription of vitamin D, calcium and other medical treatments was variable, as were the recommendations on physical exercise. A dedicated bone clinic was reported to be present in 57 % of centres, and local guidelines on bone strength in NMDs in 33 %. Disease specific guidelines with (limited) recommendations on bone strength available in literature were only used by a minority.

Strengths of the study so far were the design of the study by bone experts and patients, and the high response rate in a short time. Limitations were the possible bias caused by inviting only one clinician per centre and the fact that the survey itself already raised awareness. The study remained open online until March 2024, after which the full dataset will be analysed, and compared with the results of the patient study.

Anne Dittrich delivered a presentation concerning terminology in bone fragility. First the process of bone turnover was discussed. Osteocytes play an important role in communication between cells. Osteoclasts instigate the resorption of bone matrix before undergoing apoptosis, while osteoblasts participate in bone formation by synthesizing bone matrix, which subsequently mineralizes [4]. A gradual increase in bone density usually occurs during childhood, with an acceleration during puberty, culminating in peak bone mass attainment in early adulthood. Subsequent to this peak, there is a gradual decline in bone density, with women facing a faster decline post-menopause. Various factors, for example genetic predisposition, nutritional status, and physical activity, influence this process.

The terms bone mineral density, bone strength, and bone quality are often used interchangeably, although they denote distinct aspects of bone health. BMD is quantifiable through DXA. Bone strength encompasses a broader spectrum of parameters, including bone geometry, cortical thickness, porosity, trabecular bone morphology, and microarchitecture, which collectively contribute to bone resilience. Bone quality extends beyond BMD, encapsulating diverse facets of bone composition and structure, such as turnover dynamics, microdamage, mineralization, and matrix composition [1,5].

Osteoporosis can ensue when bone resorption is increased and/or bone formation processes falter. It manifests as either

primary osteoporosis, stemming from menopause or aging, or secondary osteoporosis, precipitated by underlying medical conditions or external factors like medication usage or hormonal imbalances. Chronic glucocorticoid use, inflammatory disorders, and compromised mobility are prominent contributors to secondary osteoporosis, exacerbating fracture risk and compromising quality of life.

Diagnostic criteria for osteoporosis encompass specific thresholds of BMD, with the World Health Organization (WHO) defining osteoporosis as a T-score of −2.5 or lower at the femoral neck in post-menopausal women. The International Society of Clinical Densitometry (ISCD) has extended diagnostic parameters to men aged 50 and above, with a T-score of −2.5 or lower at the lumbar spine, total hip, or femoral neck indicative of osteoporosis. Pediatric osteoporosis diagnosis poses unique challenges due to fluctuating bone mass during growth and puberty, with fracture incidence rising during growth spurts [6]. In 2014, the ISCD outlined pediatric osteoporosis criteria to prevent overdiagnosis in healthy children, emphasizing the significance of combining low BMD with fracture history for diagnosis. However, for children with chronic illnesses predisposing them to fragility fractures, even a solitary fracture warrants consideration for osteoporosis diagnosis and intervention, as underscored by recent research by Leanne Ward and colleagues [7,8].

Strict adherence to diagnostic criteria may inadvertently delay diagnosis and intervention for patients with congenital bone disorders or medication-induced bone fragility. The potential repercussions of delaying treatment, particularly in pediatric patients, underscore the importance of proactive management strategies to mitigate fracture risk and safeguard long-term skeletal health.

Marianne de Visser provided an overview on the current state of knowledge on bone strength in NMDs. The mechanism for developing osteoporosis in NMDs is multifactorial (e.g. progressive muscle weakness causing loss of weight-bearing activity, malnourishment as a result of dysphagia, osteotoxicity from GC therapy, endocrine and metabolic impairment (e.g., hypogonadism in myotonic dystrophy (DM 1, DM2) [9] and Kennedy's syndrome [10]), systemic inflammation (e.g., in myositis, myasthenia gravis [11], chronic inflammatory neuropathies [12]), impaired calcium/vitamin D homeostasis, other medical conditions [13], e.g., renal or liver dysfunction in mitochondrial myopathies [14] .

With the exception of DMD [15], there are sparse data from studies on bone strength in NMD. Numerous studies have been performed on amyotrophic lateral sclerosis [16], spinal muscular atrophy [17], Kennedy's disease [10], immune-mediated neuropathies [12] and myopathies [13], myasthenia gravis [11], hereditary neuropathies [18] and myopathies [3,9,19,20], and mitochondrial myopathies

[14], respectively. However, these studies suffer from the following shortcomings: haphazard selection of NMDs, small sample sizes, reviews are sparse and mainly narrative, mostly retrospective studies, variety of bone density assessments, different age groups, and limited number of pediatric studies. There are no studies on safety, tolerability, and efficacy of anti-osteoporotic therapies across age and disease subtypes in NMDs.

Sze Choong (Jarod) Wong discussed key issues to consider in assessments of bone strength in people with neuromuscular conditions. As previously discussed by Anne Dittrich, there are numerous surrogate measures of bone strength used in clinical practice and research.

Assessment of bone density as a surrogate measure of bone strength through DXA is widely adopted due to its minimal radiation exposure and widespread availability. Comprehensive guidelines for acquiring and interpreting DXA scans in both growing youths and adults are readily available. The ISCD recommends the posterior-anterior (PA) spine and total body less head (TBLH) as the primary skeletal sites for DXA scanning in children and adolescents [6]. Alternative scanning sites for youths include the proximal femur, 33 % radius, and lateral distal femur [21]. Notably, the association between bone density at the lateral distal femur and fractures in immobile young individuals, particularly those with neuromuscular conditions like DMD, has been established [22]. However, normative data for the lateral distal femur site remains limited. For adults, the ISCD recommends the PA spine and the hip (proximal femur or neck of femur) as the preferred scanning sites [23]. When interpreting DXA bone density in growing youth, especially those with short stature and delayed maturation, adjustment for size is crucial [6]. Height adjustment is recommended for interpreting bone density at the total body site, while volumetric adjustment is recommended for the spine [6]. Consensus regarding the necessity of size adjustment in adults with considerable short stature, and the most effective method for such adjustment, is still needed.

Although information on the relationship between DXA, bone density and fractures in people with neuromuscular conditions is still limited, recent evidence establishes a relationship between DXA areal bone density at the spine and both prevalent and incident vertebral fractures in young people with DMD [24] and spinal muscular atrophy (SMA) [25].

DXA bone density assessment might be challenging for non-ambulant individuals with advanced muscle disorders. Transporting them to scanners is difficult, especially without suitable hoists. Positioning is tough for those with spinal deformities or contractures, affecting accurate results, particularly at the hips. Spinal metal instrumentation for scoliosis may also lead to falsely elevated DXA bone density readings.

Alternative assessment modalities, such as peripheral quantitative computed tomography (pQCT) [26], high-resolution pQCT [27], and high-resolution MRI [28], offer promising prospects by providing more detailed information on bone geometry and microstructure. However, their widespread use is hindered by factors such as limited availability, high costs, absence of standardized scanning protocols, and a lack of normative data. These enhanced imaging modalities are currently mostly used as research tools. To gain a deeper understanding of osteoporosis and the impact of novel therapies in individuals with neuromuscular conditions, there may be a need to explore newer and high-resolution imaging modalities, albeit in a limited participant pool.

Additionally, the Bone Health Index, derived from automated computerized programs and based on a composite score of metacarpal thickness, width, and length obtained from hand radiographs, emerges as an attractive tool for assessing surrogate measures of bone strength in this specific population. Notably, this index has demonstrated associations with DXA and pQCT measures of bone [29], further highlighting its potential utility in clinical assessments. Currently, there are no published studies of this method of assessing bone strength in people with neuromuscular conditions.

The landscape of bone health assessment in pediatric and adult patients with NMDs is evolving, and **Antimo Moretti** guided the fellow participants. Key elements, such as DXA taxonomy, Trabecular Bone Score (TBS), body composition evaluation, and practical considerations have been considered in the presentation. DXA, the gold standard in the instrumental diagnosis of primary and secondary osteoporosis, is recommended when interventions to mitigate the risk of fragility fractures are deemed beneficial. Diagnosis usually relies on a combination of clinical history of fragility fractures and/or low BMD (Z-scores in children, T-score in patients over 50 years and after menopause in

women). In DXA reporting, attention must be paid to aBMD measurement adjustments (height-adjusted Z-score and/or Bone Mineral Apparent Density, BMAD) in children with growth delay, as well as DXA manufacturer, model, and software to allow diagnostic accuracy, particularly for follow-ups [6,21].

Various NMDs, such as DMD, SMA, and congenital myopathies, exhibit distinct patterns of BMD loss [30]; notably, DXA helps identify lower aBMD in non-ambulatory patients and those with severe SMA.

Trabecular Bone Score (TBS), a measure derived from lumbar spine DXA scan, assesses bone microarchitecture. Despite its potential to predict fragility fractures that foster international recommendations to use TBS in the management of secondary osteoporosis, including glucocorticoid-induced osteoporosis (GIO) [31], evidence in NMDs remains limited.

DXA extends beyond aBMD assessment to evaluate body composition, in terms of both total and regional skeletal muscle and fat tissue content, especially in chronic conditions linked to malnutrition or muscle wasting. Lean body mass emerges as a potential biomarker for disease progression, particularly in DMD [32].

DXA remains pivotal in bone health assessment for NMD patients, despite ongoing debates regarding measurement site selection and adjustment methods in children. Challenges, including technical difficulties in non-ambulatory patients and constant bone remodelling changes, underscore the complexity of BMD evaluation through DXA. TBS shows promise in enhancing bone health assessment and monitoring anti-osteoporosis therapy in NMDs, despite current evidence limitations. The lack of fracture risk algorithm (e.g., FRAX) to define the drug intervention threshold in children with NMDs highlights a huge research gap in this population.

Kristl Claeys presented bone strength data about Pompe disease (PD). It is caused by two pathogenic variants in the acid alfa-glucosidase gene (GAA), resulting in decreased or absent GAA enzyme, corresponding to late-onset (LOPD) or infantile-onset Pompe disease (IOPD). In PD, GAA is unable to metabolize glycogen into glucose resulting in an excessive amount of glycogen in the muscles. PD is characterized by axial and proximal muscle weakness and respiratory failure. Enzyme replacement therapy (ERT) has a positive effect on motor and respiratory function.

In a cross-sectional study including 46 patients (42 LOPD and 4 IOPD), BMD was determined using DXA scans of total body, lumbar spine (L2-L4) and femoral neck, and was significantly lower in PD patients with 26 % being osteoporotic and 76 % osteopenic. Osteoporosis occurred more frequently in wheelchair-bound patients. A significant correlation between proximal muscle strength and total body aBMD was identified, but not with femoral neck or lumbar spine aBMD [33]. In another study including 8 ambulatory LOPD patients (4 receiving ERT), the initial DXA total body was normal in all, DXA L2-L4 was reduced in 3 patients and DXA femoral neck was reduced in 2, all in the osteopenic range. After ERT, 2 patients had an improvement in L2-L4 aBMD and 1 in femoral neck aBMD [34]. The prevalence of vertebral fractures was studied in 22 adult ambulatory LOPD patients, of which 19 were symptomatic and treated with ERT [35]. In 77 % of the patients, at least one vertebral fracture was present, all asymptomatic and atraumatic, and all except one were located in the thoracic spine. They occurred independently of muscular and respiratory parameters, ERT or genotype. aBMD was in the osteoporotic range in 27 % and normal in 36.5 % [35]. In a DXA study including only four LOPD patients, three patients had osteoporosis prior to ERT. After ERT, all patients showed improvement in aBMD [36]. It was concluded that 1) data on bone involvement in PD is very scarce, 2) across the studies different definitions and methods to measure BMD were used, 3) small and heterogeneous patient groups were studied in cross-sectional designs only. Better definitions, standardization of methodology, longitudinal studies involving larger patient populations are needed to conclude on bone involvement in PD.

Corrie Erasmus presented the data of the scoping review on bone quality in patients with CMs [3]. Thirty-five papers were included describing 244 cases of CM, of whom more than 90 cases had a decreased bone quality with a mean age at diagnosis of 2.6 years (range 0–34 years). In 64 patients, one or more congenital fractures were described. Twenty-eight patients were reported to have multiple congenital fractures. In 17 patients, the number of congenital fractures was not described. Low BMD was found in 11 patients (4.5 %) (mean age: 10.9 ± 9.7 years). Four patients were reported to receive Vitamin D and/or calcium supplementation or intravenous diphosphonate administration, which were started after low bone mineral density and/or fragility LBFs were noticed. Congenital fractures of the humerus (n=19) and femur (n=32) were most frequently reported. She discussed that due to a reporting bias, there could be an overestimation of the congenital fractures [3].

She also reported on the one-year prospective natural history study on bone health in LAMA-2-related muscular dystrophy and SELENON-related congenital myopathy [37]. The used definition of low bone quality is based on the internationally accepted definitions for osteoporosis and osteopenia in adults and children. All patients were asked about the occurrence of fractures and treatment given and underwent a DEXA-scan and/or bone health index (BHI). In the case of low bone quality, a VFA was performed. At baseline, 8 LAMA-2 patients (38 %) and 5 patients with SELENON (50 %) had retrospectively experienced one or more fragility LBFs. No congenital LBFs or vertebral fractures were found in any of these patients. In none of the patients was a routine assessment of bone quality done, nor was treatment to optimize bone quality initiated before study participation. On DEXA low aBMD in the femoral and lumbar regions was found. In this one-year follow-up, no differences in bone health were noticed and the study period will be extended to 5-year follow-up. The findings showed that bone health does need attention in patients with CMs [37].

3. Overview of currently available knowledge on bone strength management in various NMDs

Andrea Del Fattore introduced the second session by discussing bone physiopathology in NMDs. Skeletal health in NMD patients is usually compromised as a consequence of modified bone-muscle cross-talk, resulting in an increased risk of bone fragility. Since this relationship is often underestimated until a fracture occurs, the bone-muscle crosstalk must be investigated across the different phase of bone development, from embryonic to adult life.

The alteration of the bone remodelling activity in NMD is due to several factors [38]: alterations of osteokines, muscle-derived myokines and inflammatory cytokines, including RANK-L [Receptor activator of NF-κB (RANK) ligand], osteoprotegerin, sclerostin, irisin, myostatin and IL-6; changes of the number of circulating extracellular vesicles and of their content; low level of physical activity or immobility; nutritional issues as over- and undernutrition; vitamin D deficiency; drugs (GCs) with adverse effects on bone tissue (Fig. 1). GCs adversely affect bone strength/quality leading to GIO which represents the most common form of secondary osteoporosis [39]. GCs exert their activity in bone mainly by binding to the beta isoform of cytoplasmic GC receptor (GR). GCs alter bone remodelling activity, leading to a reduction of bone mass after a few weeks from the start of the treatment [40]. GC treatment has a biphasic effect on bone cell. At the early phase GCs stimulate osteoclast survival

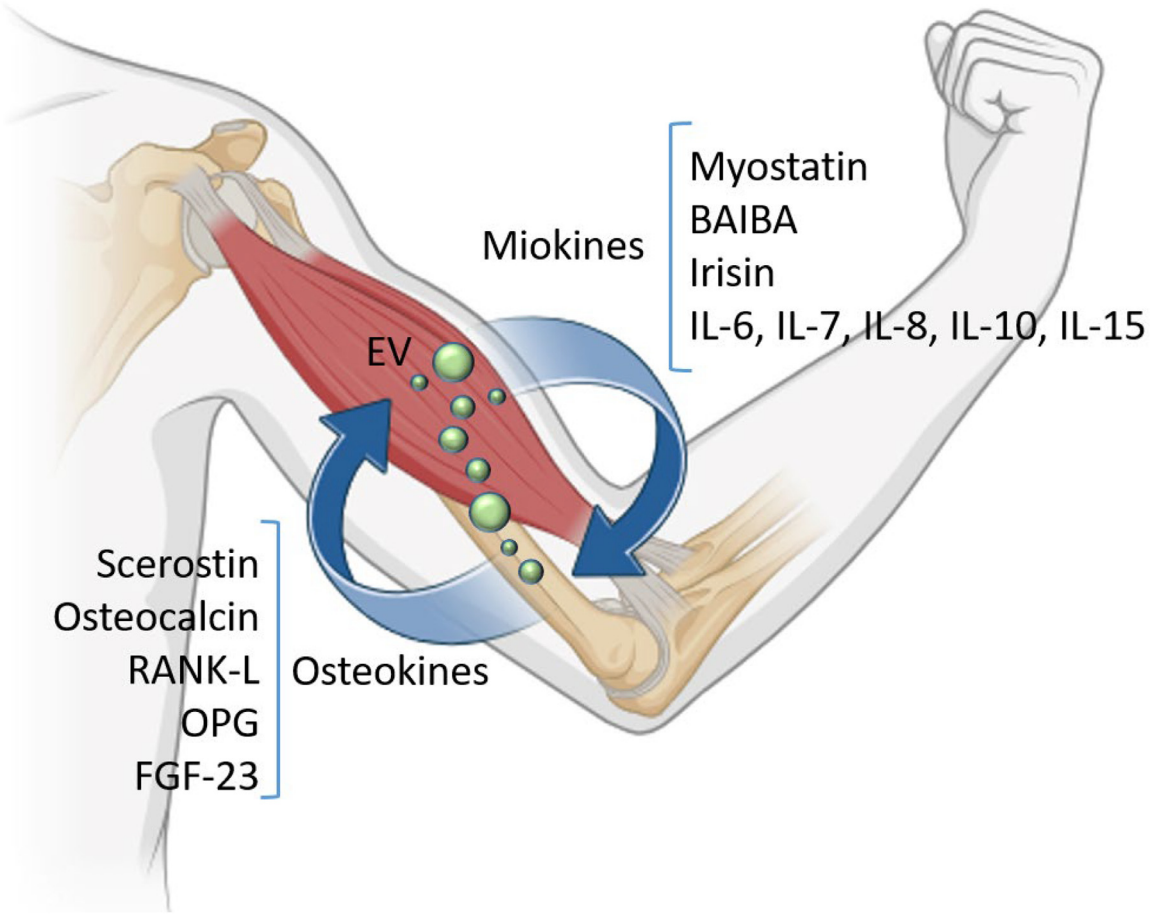

Fig. 1. Bone-Muscle crosstalk. Bone and Muscle communicate each other by soluble factors (osteokines and miokines) and extracellular vesicles (EV). Bone tissue releases Sclerostin, Osteocalcin, Receptor Activator of Nuclear Factor Kappa B Ligand (RANK-L), Osteoprotegerin (OPG) and Fibroblast Growth Factor 23 (FGF-23) that influence muscle function. Muscle is able to affect the bone remodelling activity by secretion of Myostatin, Beta-Aminoisobutyric Acid (BAIBA), Irisin and several interleukines (IL-6, IL-7, IL-8, IL-10 and IL-15).

and bone resorption activity, then they decrease osteoblastogenesis and induce apoptosis of osteoblasts and osteocytes, resulting in decreased bone formation [41]. Interestingly, dexamethasone induces cytoskeleton rearrangement and decreases Cx43 protein expression in osteocytes, shortening the dendritic processes [42].

Bone health data in SMA both for children and adults were presented by **Anna Kostera-Pruszczyk.** It has been recognized that fractures in SMA patients may lead to permanent functional deterioration, including loss of ambulation. Authors of the current standard of care (SoC) in SMA acknowledge that fragility fractures are common in children with SMA1 and 2 and recommend yearly DXA studies and monitoring of vitamin D levels, with an appropriate supplementation in case of its deficiency or low BMD values. They also indicate that in the case of recurrent fractures, BPs may be considered [43]. A potential role of SMN protein in skeletal development has been suggested by studying murine models of SMA, and a decrease in total bone area and poorly developed caudal vertebra have been observed on DXA exams in mice [44]. Studies conducted in SMA patients demonstrated that low BMD is more frequent in non-ambulatory than ambulatory patients [45]. In a retrospective study of annual fracture history and BMD follow-up on 85 children with SMA, the probability of remaining fracture-free resulted higher for SMA3 than for SMA2 and 1 patient [46]. SMA patients often had femoral fragility fractures, even if clinically silent vertebral fractures were also diagnosed [46,47]. In a study of 32 SMA children low BMD was observed in 16/17 patients, of which four showed a history of long bone fractures and one fulfilled the 2019 (ISCD) pediatric definition of osteoporosis [47]. An optimal treatment approach for SMA patients with low BMD should be carried out, regardless of the history of low-impact fractures.

Giovanni Iolascon described the pharmacological pillars of the management of bone fragility in adults with osteoporosis, considering the biological plausibility and mechanism of action, efficacy, safety, and cost-effectiveness of available drugs. Antiresorptive drugs include BPs and denosumab (a monoclonal antibody against RANKL). BPs are used for primary and secondary osteoporosis, including those related to NMDs. Neridronate is a nitrogen-containing BP approved in Italy for the prevention and treatment of fragility fractures in the pediatric population affected by osteogenesis imperfecta. A recent study demonstrated that this drug may counteract bone loss in patients with DMD receiving GCs [48]. Denosumab markedly reduces bone resorption by blocking osteoclast maturation, function, and survival. Antiresorptive drugs significantly increase BMD and reduce the risk of vertebral (60–70 %) and non-vertebral fragility fractures (20–30 %), including hip fractures (40 %). Teriparatide, a recombinant fragment of human parathyroid hormone, is effective in reducing vertebral fragility fractures due to bone anabolic effect by modulating the pathways involved in the survival and function of osteoblast/osteocyte lineage. Despite biological plausibility, no clinical evidence supports the use of this intervention in children with bone fragility. Romosozumab is a humanized monoclonal antibody against sclerostin, with a dual effect on bone, increasing bone formation and decreasing bone resorption, by modulating Wnt-beta-catenin and OPG/RANK/RANKL pathways, respectively. Once-

a-month subcutaneous injection for 12 months is effective in reducing the risk of vertebral, hip, and non-vertebral fragility fractures (81 %, 55 %, and 25 %, respectively) [49]. International recommendations suggest that oral BPs or intravenous zoledronate should be considered as first-line therapy for postmenopausal women and men with osteoporosis. Denosumab and anabolic therapies are second-line options. This approach does not fit the biological plausibility of an appropriate sequential pharmacological intervention that consists of anabolic followed by antiresorptive agents. This sequence should be the gold standard for the secondary prevention of fragility fracture according to the available evidence [50]. For patients affected by NMDs, only BPs are supported by evidence of efficacy in the treatment of bone fragility. Further studies are needed to explore the effectiveness of other anti-osteoporotic drugs, including anabolics (e.g., teriparatide and abaloparatide) or dual-action (i.e., romosozumab).

Claire Wood set the scene by reminding workshop participants that GCs not only have a detrimental effect on bone development and therefore cause growth failure but also pubertal delay in almost all young people with DMD on daily GC therapy. This in turn exacerbates the adverse effects of GC therapy on the skeleton. Short stature is prevalent in DMD even before GCs are initiated, which further exacerbate the problem. GC-induced growth failure is ranked as particularly problematic by patients when considering steroid side effects [51]. The current standards of care recommend routine assessment of height velocity and investigations to rule out other causes of growth failure but only recommend the consideration of GH stimulation testing under individual circumstances [52]. Two studies examined the effects of recombinant human growth hormone (rhGH) and recombinant human insulin-like growth factor 1 (rhIGF-I) on patients with DMD, showing improvements in growth velocity and stability in height z-score without negative effects on cardiac or neuromuscular function. Additionally, GH was found to reduce the risk of vertebral fractures when used alone or in combination with zoledronic acid [53,54]. Regarding the use of testosterone for the induction of puberty in DMD, the 2018 Care Considerations recommend that testosterone should be used for those with delayed puberty by 14 years of age [47,55]. Lee et al. found that pubertal induction with testosterone undecanoate in individuals with DMD led to an increase in BMD at the lumbar spine and no progression in vertebral fractures (VF) in most participants [56]. Wood's study using a 2-year regimen of intramuscular testosterone showed an increase in contractile surface area, an unchanged fat fraction and stable BMD in boys with DMD [57]. The Loscalzo study showed a reduction in VF risk in 27 patients receiving four-weekly regimens IM testosterone [50]. Finally, longer-term data from the recently published study by Wood et al. did not demonstrate a sustained improvement in muscle mass in the 3 years after testosterone treatment was stopped and a significant decrease in BMD was observed during the follow-up period. Claire Wood recommended prompt induction of puberty in DMD provided that the young person is psychologically ready, ideally around 12 to 13 years of age [58].

The benefits of exercise as a rehabilitation intervention for bone health in individuals with NMDs were discussed by **Sara Liguori**. Exercise exerts forces on the bone at multiple levels and activates signalling pathways that improve bone health [59]. It also counteracts oxidative stress and other consequences of disuse frequently observed in NMDs [59]. In addition, exercise promotes cross-talk between bone, muscle, and fat, which helps maintain homeostasis and improves organ function. Therapeutic exercise is a structured activity prescribed by a specialist, defined by frequency, intensity, time, and type. It can be divided into strength-resistance training and weight-bearing aerobic training. Strength and resistance exercises, including loaded and unloaded exercises, can increase muscle mass and bone mineral density in specific body regions. Eccentric contractions in strengthening exercises provide an anabolic bone stimulus with lower cardiovascular demands, representing a potential safe training for people with NMDs. Low-intensity eccentric training demonstrated to improve muscle functionality in dystrophic soleus muscle of mdx mice [60]. Weight-bearing aerobic exercises like walking and stair climbing also benefit bone health. Walking alone is not enough to modify bone mineral density loss, but it is recommended as part of a general health maintenance program. For individuals with NMDs experiencing loss of ambulation, the use of bodyweight support treadmills is encouraged. Finally, multicomponent exercises that combine different methods can help increase or preserve bone mass, especially in deteriorating patients with NMDs who may not be able to perform pure reinforcement exercises. Whole-body vibration has shown a potential to stimulate bone formation and protect the skeleton in individuals with NMDs [61]. However, more research is needed due to small sample sizes and heterogeneous interventions [62]. Personalizing comprehensive exercise protocols for individuals with NMDs is crucial, considering factors such as age of onset, disease genotype, concomitant diseases, ambulant status, and specific outcome measures. Healthcare professionals should be aware of warning signs of over-weakness and tailor the exercise program accordingly.

Finally, **David Weber** began by summarizing the factors underlying skeletal fragility in NMD. For childhood-onset conditions, this includes insufficient bone accrual due to muscle weakness and diminished weight bearing, and a failure to achieve peak bone mass (Fig. 2). Other factors that adversely affect bone strength are hypothesized to include aberrant muscle-bone cross-talk and possibly a primary negative effect of the genetic deficiency on bone in some conditions, such as SMA [63]. Individuals with NMD have additional bone health risk factors including bone-toxic medication use, malnutrition, hormonal deficiency and a high risk of falls with subsequent fragility fractures. Fracture risk is greatest in people with DMD where most individuals will have at least one fracture before reaching adulthood [64]. The risk varies widely across other NMDs. The impact of NMDs on bone density is also variable and in many cases associated with disease severity. Often, aBMD likely underestimates fracture risk when standard thresholds (e.g., "low bone density" defined by an aBMD Z-score of < -2) are applied. Failure to accrue bone at a typical rate (children) or frank bone loss (all ages) are potentially actionable findings that may warrant clinical intervention. Emerging techniques for evaluating bone quality in NMDs include the BHI from hand radiographs and TBS from lumbar spine DXA scans. TBS is approved for use in adults, though not yet in children. Pediatric TBS reference data are in the process of being updated for the newest software version [65]. Standard and high-resolution peripheral quantitative computed tomography (pQCT) are highly specialized imaging modalities that provide detailed information on bone geometry, microarchitecture and allow for estimation of bone strength. Bone biopsy with tetracycline labelling is another method of assessing bone quality that has the benefit of providing a dynamic assessment of bone formation. Due to the highly specialized nature of pQCT techniques and bone biopsy, these tests have limited utility for routine clinical monitoring of bone health in NMDs, but should be considered in select clinical and/or research investigations of new therapeutic interventions.

4. Lessons to be learnt from management in Duchenne muscular dystrophy

Nicola Crabtree focused on the identification of vertebral fractures in children as a critical component of the assessment of bone health, not least as the diagnosis of osteoporosis is

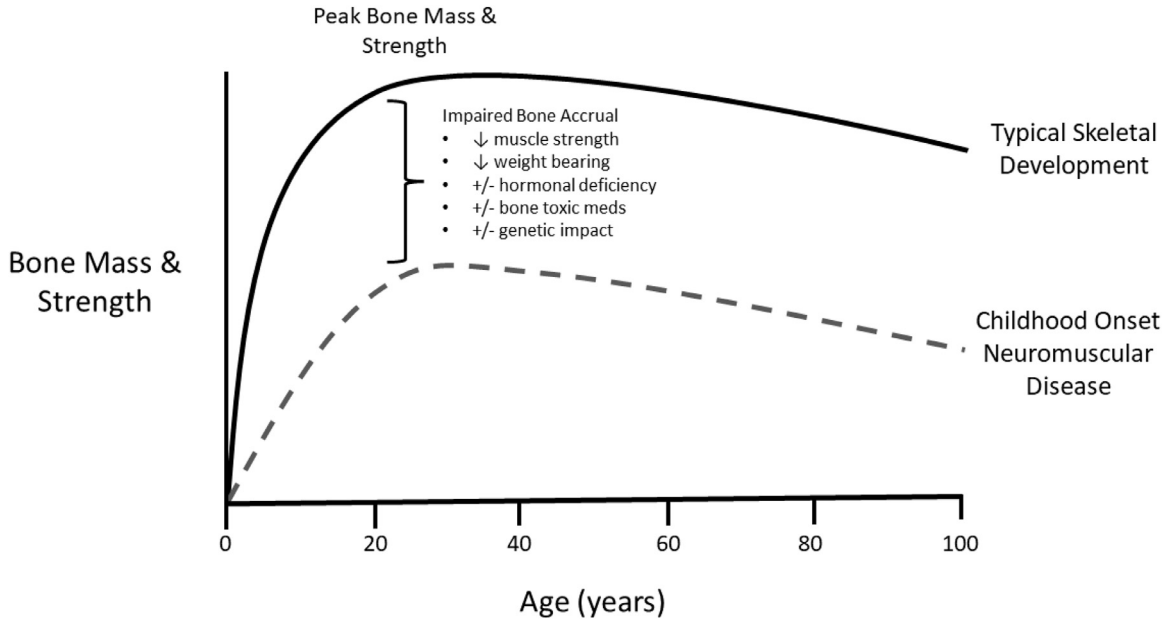

Fig. 2. Impact of a childhood-onset neuromuscular disorders on bone mass and bone strength. This figure shows the impact of Childhood onset NMD on growth of bone mass and strength.

underpinned by the identification of such fractures. Despite their rarity in healthy children, low trauma vertebral fractures are common manifestations in boys with DMD due to significant exposure to GCs [66]. As such, in boys with DMD routine surveillance is advised since fractures, especially mild vertebral fractures, are often asymptomatic, can occur despite normal bone density and importantly are predictive of future fracture or in severe cases complete vertebral fracture cascade [24].

Vertebral fractures are diagnosed as a disruption of the endplate or cortex with or without vertebral height loss. Several different approaches have been used to help with the diagnosis of vertebral fractures as it is often difficult to distinguish between normal variants and fracture. The most frequently used methods are clinical algorithms based on a visual assessment, such as the Genant semi-quantitative method [67] and the Algorithm-Based Qualitative (ABQ) method [68]. Reassuringly, for moderate and severe vertebral fractures there is good agreement between all available techniques. However, the diagnosis of mild vertebral fractures remains a clinical challenge. The main difficulty lies in reliably distinguishing normal physiological, developmental, and morphological variability from fracture, which is further complicated by the lack of normative vertebral morphological data.

Traditionally, plain lateral radiographs were used to identify vertebral fractures. However, more recently due to the improvement in image resolution, lower radiation dose and the availability at the point of care, VFA is increasingly being performed using the DXA-acquired image of the spine [69].

The most recent pediatric position statement from the ISCD (2019) has endorsed the use of VFA as a substitute for the identification of vertebral fractures providing the reader has experience of pediatric vertebral fractures [70]. With the caveat that further imaging is required in cases where vertebral visualisation is limited, where a single Genant Grade 1 fracture is identified, and that identification would change management or where the radiographic findings are not typical for an osteoporotic vertebral fracture. In such cases, either plain lateral radiography or whole spine MRI is recommended.

The common clinical scenarios prompting a bone health assessment for individuals with NMDs were reviewed by **David Weber**: 1) As a part of routine screening, 2) Following a finding of low aBMD on a DXA scan, 3) For optimization of bone health prior to major orthopedic surgery, and 4) Following a fragility fracture. These scenarios encompass both proactive and reactive care and provide valuable context as the approach to bone health in people with NMDs shifts from secondary to primary fracture prevention.

Clinical recommendations for preventing and treating skeletal fragility are most advanced for DMD, potentially serving as a model for other NMDs. The 2018 DMD Care Considerations introduced routine screening for vertebral fractures in individuals treated with GCs and recommended considering bisphosphonate therapy for symptomatic mild or asymptomatic moderate or severe vertebral fractures [71]. These advancements have deepened the understanding of skeletal fragility's natural history and led many clinicians to begin bisphosphonate therapy at earlier stages of vertebral compression. The 2017 Care Considerations for SMA briefly discussed bone health, recommending annual DXA scans and laboratory monitoring of vitamin D [43]. Bisphosphonates were mentioned as a possible treatment for individuals with multiple fractures. Children with SMA are commonly referred for bisphosphonate therapy ahead of scoliosis surgery, despite a lack of published protocols. Children with SMA who underwent growth-friendly spinal implants for scoliosis were found to have lower vertebral volumetric BMD, highlighting the need for further study into perioperative bisphosphonate therapy in this population [72].

The usefulness of DXA for screening individuals at risk for fracture was then discussed, considering the most recent ISCD guidelines for the use of DXA in children and adults, with a focus on lateral distal femur in and proximal tibia [6], non-standard scans assessing a clinically relevant fracture site in people with NMDs, yet challenging to obtain in the presence of contractures. Currently, there is no validated model for predicting fracture risk in people with NMDs from DXA or clinical characteristics. FRAX is commonly used to predict the 10-year probability of hip and major osteoporotic fracture and inform treatment decisions for older adults. It is not known if the current FRAX calculator can be applied to people with NMDs, as there are only small studies describing its use in this population [73]. Developing a fracture prediction calculator for NMDs would be desirable, but this would

require a large sample of patients which will be challenging to obtain for this rare disease group.

Chiara Panicucci underscored the importance of addressing bone fragility in the adult DMD population, emphasizing the significant lack of data dedicated to osteoporosis management in this age group. Despite substantial advancements in the standard of care (SoC) over the past decade [52,71,74], resulting in an increase in DMD life expectancy [75], there remains a lack of research on bone health status in adult DMDs. In this demographic, bone fragility is further worsened by reduced muscle function and immobility. Fragility fractures prevalence by the age of 18 can reach 83 % [76], though it remains unknown if this prevalence increases in older patients, and no bone mineral density natural history data are known in this group.

Monitoring bone quality in non-ambulant DMD patients can pose challenges due to logistical difficulties during DXA scans (i.e. transferring patients to DXA scanners, or suboptimal positioning due to contractures or metal instrumentation), thus affecting accurate interpretation of bone density results. Although alternative assessment modalities were discussed in this ENMC workshop, their widespread adoption is hindered by limited availability, high costs, absence of standardized scanning protocols, and a lack of normative data.

The lack of clear indication for long-term bisphosphonate treatment in adults with DMD was also outlined. After a fragility fracture, bisphosphonate treatment is recommended until stability is achieved (defined by absence of new fractures, back and bone pain, and attainment of appropriate aBMD Z-score for height or an aBMD > -2 SDs) [2]. However, once stability is reached, there is no standardized approach for further management, and in adult patients with ongoing risk factors for bone fragility (i.e. the underlying myopathy and steroid treatment), it remains unclear whether bisphosphonate therapy should be discontinued, reduced in dose, or if patients should undergo drug holidays.

Considering the lack of clear guidance for bone health management in adult DMDs, and the burden caused by osteoporosis in DMD patients and caregivers (pain, complications of daily care, limitation of physical therapy), a deeper understanding of mineral density trajectories, together with the development of more accessible bone monitoring methods and the optimization of long-term BP treatment protocols are mandatory for this population.

An introduction on the use of GCs in Duchenne Muscular Dystrophy (DMD) was provided by **Michela Guglieri**, who presented the current evidence on different GC types and regimens, and introduced the newly approved dissociative steroid vamorolone. GCs improve muscle strength and function over a certain period of time, and postpone the onset of respiratory and cardiac complications, leading to prolongation of survival [52,77]. The results from the FOR DMD study (clinicaltrials.gov NCT01603407), a large, international, multi-centre study comparing the three most commonly prescribed GC regimens in DMD (0.75 mg/kg of daily prednisone, 0.90 mg/kg of daily deflazacort, or 0.75 mg/kg of intermittent prednisone for 10 days on and then 10 days off) were discussed [77]. The study showed that daily regimens are associated with better efficacy on motor outcome measures compared to intermittent, 10 days on/10 days off prednisone, with no significant differences between daily prednisone and daily deflazacort. The study also showed that prednisone, administered either daily or intermittently, causes more weight gain compared to daily deflazacort. All GC regimens led to slowing of growth which was significantly less severe with intermittent prednisone than with the daily regimens, being daily deflazacort associated with the worse effect on growth. These findings are overall consistent with other natural history and observational studies. Vamorolone is a newly developed GC that has been recently approved by the FDA, EMA and MHRA for children with DMD. It has a similar effect on muscle function efficacy compared to traditional GC while showing a less detrimental side effect profile on growth and bone health (details are presented below) [78,79].

Learning from the FOR DMD study experience, Dr Guglieri presented challenges in monitoring bone health parameters in large international clinical trials that do not have bone health as primary study outcomes. The lack of international consensus on bone treatments could affect interpretation of study results. Standardization of clinical investigations and procedures (e.g. DEXA scan, spine X-Ray etc.) can be difficult in multi-centre studies, and can be costly and time-consuming to be set up [80]. The FOR DMD study has shown discrepancies in the interpretation of the results of Spine X-ray, with possible lack of specialized knowledge on vertebral fracture grading across different centres and different countries. The provision of written guidance as part of the study protocol might not be sufficient when the methodology used to interpret the results is not part of the clinical practice. Funding and time restrictions can affect the possibility of set up appropriate training, especially for academic studies.

Increasing awareness of these challenges is critical; implementation of standardization of bone health monitoring procedures, as well as interpretation of results in clinical trial settings would have a significant impact on the robustness of bone health data in DMD.

Leanne Ward discussed the results of skeletal health evaluations in young, ambulatory boys with DMD who participated in the vamorolone (VBP15) 003LTE longitudinal observational study (clinicaltrials.gov NCT03038399). Vamorolone-treated boys showed improved growth compared with a daily gGC-treated natural history cohort over 30 months of observation, but with weight gain that was comparable to the natural history cohort [81]. The improved growth but persistent weight gain on vamorolone was recapitulated in a randomized, double-blind, placebo-controlled trial of vamorolone 2 and 6 mg/kg/day versus prednisone 0.75 mg/kg/day and placebo over 24 weeks [79]. In this randomized trial, there was a significant decline in serum bone turnover markers on prednisone, but not with vamorolone [79], suggesting preservation of metabolic bone activity on the novel dissociative steroid.

Vertebral fractures prevalence on vamorolone after 30 months of drug exposure was benchmarked to an external comparator, the FOR-DMD study [82]. Although the data arose from two different studies, the same central imaging radiologists read the lateral spine radiographs according to the Genant semi-quantitative method, over similar time periods (2019–2022). This analysis (currently in preparation for peer-review submission) showed that the prevalence of vertebral fractures after 30 months of vamorolone was about 40 % that of the vertebral fracture prevalence on daily deflazacort or prednisone. In addition, the Spinal Deformity Index (SDI) on vamorolone was about 1/3 that of daily deflazacort, and about 2/3 that of daily prednisone. After 3 years of drug exposure, there were no vertebral fractures identified on intermittent prednisone 10 days on/off. While intermittent GC therapy appears bone-protective [66], saltatory GC exposure is associated with reduced muscle strength relative to daily therapy [66,82].

Overall, vamorolone is a novel and distinct dissociative steroidal anti-inflammatory drug, with efficacy parity at 6 mg/kg/day to that of daily prednisone (0.75 mg/kg/day) and preservation of linear growth up to 3 years [79,81]. Preliminary analyses suggest that vamorolone preserves bone turnover and may carry a reduced risk of vertebral fractures compared with daily GC therapy. Dr. Ward noted that vamorolone is associated with adrenal suppression [79], and that the long-term impact of vamorolone on non-vertebral

fractures, puberty, muscle strength and cardiorespiratory outcomes remains unknown.

Dr. Ward also reviewed preliminary results of a single-blind, randomized controlled trial *pilot* study of intravenous (IV) zoledronic acid versus sub-cutaneous denosumab in boys with DMD (NCT 02,632,916). The first-infusion side effects of intravenous bisphosphonate, and the inconvenience of the IV route, have generated interest in denosumab (given sub-cutaneously, every six months). The off-label prescription of denosumab on compassionate grounds has been reported in a few children with OI [83], giant cell tumours [84], aneurysmal bone cysts [85], and fibrous dysplasia [86]. However, its use has been challenging in children with normal or high bone turnover due to the "rebound phenomenon". Dr. Ward hypothesized that in GC-treated DMD, where bone turnover is low on trabecular surfaces [87], the rebound may be less of a concern. The fact that RANKL is also implicated in the DMD muscle inflammatory pathway [88] and that anti-RANKL antibody given to the mdx mouse improved muscular histological and functional outcomes [89,90], provided further rationale for the study of denosumab in DMDs.

Pilot data in eight GC-treated DMDs with a history of at least one fragility fracture were presented. Boys were randomized to intravenous zoledronic acid 0.025 mg/kg or denosumab 1 mg/kg every six months for two years. In both groups, BMD trajectories and Z-score trajectories were in a positive direction, and back pain declined. There were no serious adverse events; however, the four boys on zoledronic acid had a total of 17 drug-related adverse events, whereas only one drug-related adverse event was reported on denosumab. Serum bone turnover markers remained suppressed in both groups, and there was no evidence of hypercalcemia or nephrocalcinosis.

All four boys remained on denosumab in the four years following completion of the two-year study. One boy presented with asymptomatic hypercalcemia-hypercalciuria and a rise in serum c-telopeptide of type I collagen six years after starting denosumab (i.e. *while on active denosumab therapy* and a few months after starting testosterone for delayed puberty). Eucalcemia was restored with hydration and IV pamidronate. Given the potential seriousness of denosumab-induced hypercalcemia, Dr. Ward concluded that the low bone turnover of GC-treated DMD was ultimately not protective against the rebound phenomenon, and that the longer-term safety of denosumab was not sufficiently robust to proceed with further study of this agent for routine use in DMD.

5. Management and implementation

David Weber and **Antimo Moretti** concluded the workshop with an open-table discussion of the critical bone health research questions facing the neuromuscular community. Important areas of need that were discussed included natural history studies to better understand fracture risk across the entire age range and spectrum of people affected by neuromuscular disorders, observational studies to define the optimal imaging or other clinical assessments to identify the whole body or regional skeletal weakness specific to different neuromuscular phenotypes, the integration of these findings into a fracture prediction tool similar to FRAX, and ultimately the development of clinical trials to determine the efficacy of pharmacologic and non-pharmacologic interventions to improve bone strength in people affected by neuromuscular disorders.

As a next step to build on the momentum of the workshop and to begin to address these knowledge gaps, Leanne Ward laid out a proposal for two additional manuscripts to follow this workshop report. The first is to be a narrative review of the key principles and disease-specific considerations to guide the management of bone health and osteoporosis among individuals with neuromuscular disorders. This manuscript will summarize existing data, propose practical bone health monitoring and treatment considerations, identify potential barriers to implementation and outline future directions. The expectation is that providing clinicians with a standard way of approaching bone health in patients with NMDs will not only increase awareness of this aspect of NMDs, but also spur clinical and research initiatives – similar to what has occurred following the inclusion of a bone health section in the most recent Care Consideration for people with DMD [71]. The second manuscript will present the findings of the patient and health-care provider surveys discussed above. This work is expected to additionally help guide future research directions by detailing the unmet needs as perceived by both the people with NMDs and the medical providers caring for them.

6. Discussion

At the end of the workshop, the participants defined the main challenges and discussed the potential solutions and strategies to move on. A set of suggestions to improve the diagnostic and therapeutic management of bone fragility in people with NMDs was proposed (Fig. 3).

- Although it is recognized that muscle and bone strength are closely interconnected within a single functional system, and that all NMDs characterized by muscle weakness are potentially associated with bone fragility, there is a lack of comprehensive understanding regarding bone health in NMDs and its management. Consensus has been reached that awareness of osteoporotic risk needs to be heightened, both within patients and health care providers, and that integrating bone fragility assessment into the comprehensive health evaluation of patients with NMDs should be mandatory.
- Participants reached consensus on the importance of considering the patient's clinical context and disease milestones, particularly ambulatory status, as primary factors in understanding the risk of bone fragility and guiding its management, rather than relying on a single diagnostic test. Additionally, they highlighted the absence of a validated fracture risk calculator specifically tailored for patients with NMDs and expressed the need to develop such a tool.
- While solid literature exists for DMD concerning bone fragility, and its management during the pediatric and adolescent stages, a noticeable lack of systematic studies has been highlighted for other NMDs. Prioritizing longitudinal studies over cross-sectional ones and conducting large cohort analyses is crucial. The attendees agreed that this could be facilitated by educational initiatives aimed at harmonizing nomenclature regarding bone health, the assessments across different countries and centres and their interpretation.
- There is no consensus about the instrumental techniques available to evaluate bone health in patients with NMDs. Sites to be addressed specifically for this population are not defined, and classical DXA scans can pose some acquisition challenges in non-ambulant patients. Therefore, new methods serving as surrogates of bone quality and strength should be developed and normative data generated. In this context, bone health index (BHI) from hand radiographs, and trabecular bone score (TBS) from lumbar spine DXA scans might be included in the radiology workflow.

  Longitudinal skeletal phenotyping is key to understand the individual's bone health trajectory and thereby there is a need for progressive intensification of bone health management in patients with NMD. The consensus of the group was that DXA is pivotal in bone health assessment and for longitudinal

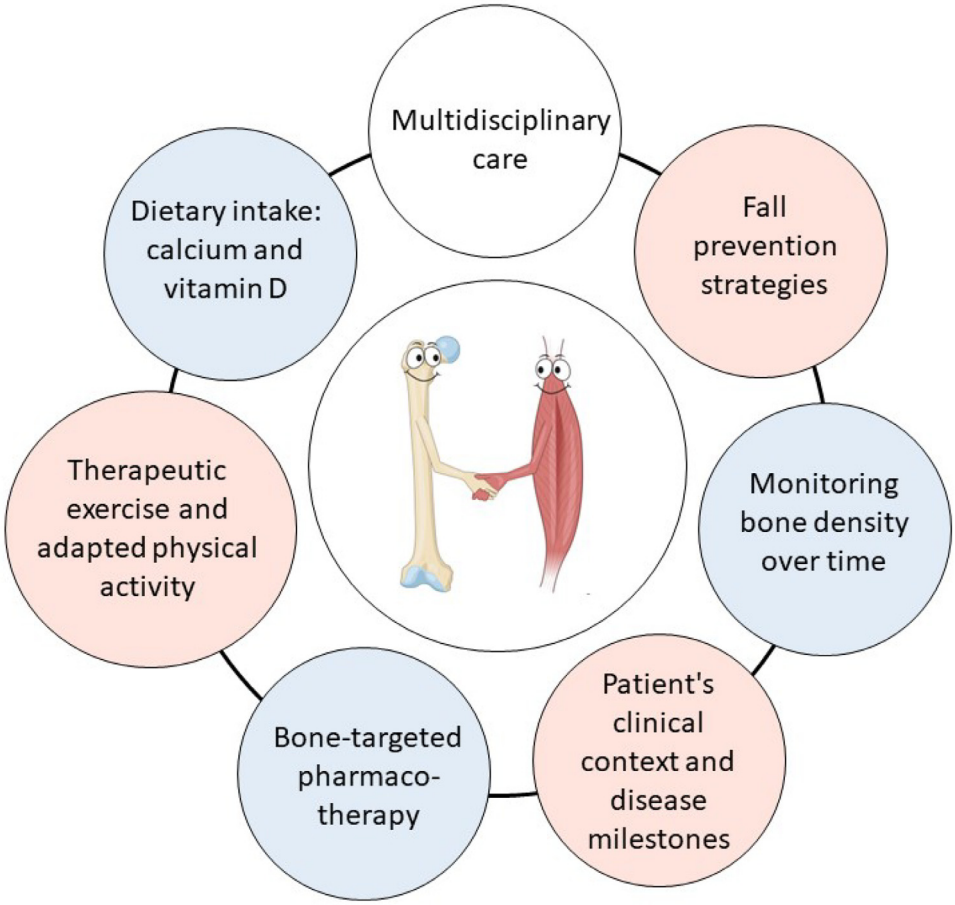

Fig. 3. Multi-disciplinary bone loss prevention and treatment should be considered the cornerstone of timely and effective bone health management to be included in the clinical routine. Physical activity includes weightbearing aerobic and strengthening exercises.

monitoring of changes in bone density over time for NMD patients.

- Recommendations on bone health management available are mainly related to DMD. However, bone strength is impaired in most NMDs; data on bone health in IOPD, LOPD, CM, and SMA showed a lack of robust evidence about the techniques of assessment of poor BMD and its treatment. Improving the knowledge about the natural history of BMD in people with NMDs according to the age of onset and the functional status of patients is mandatory.
  The timing of start assessment, therapies and follow-ups are not defined in most NMDs. The participants discussed when to start and repeat the monitoring of bone health based on the disease milestones, the conservative measures to adopt to enhance bone density and when to consider bone-targeted therapy in primary prevention. All participants agreed that the switch to the non-ambulant phase represents a crucial moment for the loss of BMD, stressing the need to strictly evaluate bone health in this phase.
  Focusing on what we learned about bone health in DMD, several aspects have been addressed. GC therapy in DMD has been largely investigated, highlighting its adverse effect on the skeleton. Both a detrimental effect on bone quality as well as a GC-induced growth failure that further exacerbates the loss of BMD in DMD have been reported. Vamorolone, a newly developed GC, showed improved growth compared with a daily GC-treated natural history cohort over 30 months of observation in DMD. At the same time, vamorolone seems to preserve metabolic bone activity without a significant decline in serum bone turnover markers compared to prednisone. The group agreed that long-term data about the impact of vamorolone on bone, puberty, muscle strength and cardiorespiratory outcomes need to be achieved to encourage its use in clinical practice for this population.
- Another complication related to exposure to GCs is the occurrence of vertebral fragility fractures. Diagnosis of mild VFs remains a clinical challenge in DMD with a lack of normative vertebral morphological data at DXA scans. The VFA is considered a DXA-acquired image of the spine useful as a substitute for the identification of vertebral fractures also in pediatric populations. The attendees suggested implementing this tool in clinical practice and using further imaging in atypical cases.
- Regarding multicentric trials on DMD, several discrepancies in the study protocols adopted occurred: methodologies, funding and resources widely vary across the diverse centres involved. The implementation of standardized procedures as well as univocal interpretation of the data in clinical practice could strengthen bone health findings in DMD. All participants propose to increase awareness of these critical issues.
- Bisphosphonates seem efficacious as first-line therapy in the treatment of bone fragility in patients with NMDs. According to the biological plausibility, an appropriate sequential pharmacological intervention might consist of anabolic (e.g., teriparatide and abaloparatide) followed by antiresorptive agents, particularly as secondary prevention of fragility fractures. However, anabolic drugs should not be used in pediatric patients or young adults with open epiphyses,

limiting their use in NMDs. Regarding denosumab, limits related to the long-term safety of this drug due to the high risk of hypercalcemia were observed. Participants underscored that these drugs should be further studied in terms of efficacy and safety for the different phenotypes of NMD disease and they agreed on the need to identify proper pharmacological management considering the most acceptable benefit-risk profile in NMDs.

Besides pharmacological therapy, non-pharmacological management based on rehabilitative strategies should be implemented in the life-long process of care of patients with NMDs. Therapeutic exercises (including strength and resistance exercises) should be prescribed with specific FITT characteristics. New insights about the use of whole-body vibration in NMDs to promote bone density are encouraged.

7. Conclusion

Bone strength needs to be addressed and treated in NMDs. This workshop highlighted the persistent gaps in knowledge on this topic providing the opportunity to discuss the issues and critical challenges faced in clinical practice. Multi-disciplinary bone loss prevention and treatment should be considered the cornerstone of timely and effective bone health management to be included in the clinical routine. The participants agreed to enhance knowledge about the natural history of bone fragility, optimal timing for diagnosis and monitoring, and the most proper pharmacological and non-pharmacological approaches to suggest in this population. Finally, they aim to provide a standardized diagnostic and therapeutic approach tailored to bone health in NMDs to harmonize the discrepancies existing among different centres and countries.

8. Workshop participants

Ingrid de Groot (The Netherlands), Michela Guglieri (UK), Claire Wood (UK), Sara Liguori (Italy), Giovanni Iolascon (Italy), Anna Kostera-Pruszczyk (Poland), Corrie E. Erasmus (The Netherlands), Marianne de Visser (The Netherlands), Leanne Ward (Canada), David Weber (USA), Chiara Panicucci (Italy), Silke Schlüter (Germany), Nicola Crabtree (UK), Andrea Del Fattore (Italy), Kristl G. Claeys (Belgium), Anne T.M. Dittrich (The Netherlands), Madelon Kroneman (The Netherlands), Sze Choong Wong (UK), Nicol Voermans (The Netherlands), Antimo Moretti (Italy).

Declaration of competing interest

Leanne Ward: none.
Antimo Moretti: none.
David Weber: none.
Nicol Voermans: none.

CRediT authorship contribution statement

Nicol C. Voermans: Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Anne T.M. Dittrich:** Writing – review & editing, Writing – original draft. **Sara Liguori:** Writing – review & editing, Writing – original draft. **Chiara Panicucci:** Writing – review & editing, Writing – original draft. **Antimo Moretti:** Writing – review & editing, Writing – original draft, Conceptualization. **David R. Weber:** Writing – review & editing, Writing – original draft, Conceptualization. **Leanne M. Ward:** Writing – review & editing, Writing – original draft, Conceptualization.

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