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ORIGINAL ARTICLE

Vertebral fractures and muscle function in glucocorticoid-treated individuals with Duchenne muscular dystrophy: a cohort study

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Abstract

Summary **Brief rationale:** To investigate vertebral fracture and risk factors in DMD.
Main results: Vertebral fractures were found in 42% of subjects with an increased risk associated with low TB BMD, early steroid exposure and low BMI.
Significance of the paper: Bone health monitoring should start early, regardless of functional status.

Purpose To describe the prevalence of vertebral fractures (VFs) in Duchenne Muscular Dystrophy (DMD) and to establish the role of several risk factors, focusing on ambulatory status and functional motor scores (Performance Upper Limb, North Star Ambulatory Assessment) not previously assessed.

Methods We recorded the number and site of fractures together with anthropometric, radiological (total body bone mineral density (TB BMD) Z-scores measured by Dual Energy X-ray Absorptiometry (DXA)), and functional scales. Logistic and linear regression analyses were conducted to identify factors associated with prevalent VFs and predictors of Spinal Deformity Index (SDI).

Results Of the 149 individuals (7–26 years) studied, 62 (42%) had VFs. These were equally present in ambulant and non-ambulant individuals (41 vs 42%) and were not associated with functional scores. The TB BMD Z-score was a protective factor both in non-ambulant and ambulant subgroups. Lower TB BMD Z-scores were also predictive of a greater SDI. In the ambulant subgroup a lower BMI reduced the risk of VF. In the overall cohort, each one-year delay in starting glucocorticoids reduced the risk of VFs by 27% ($p=0.007$), and each additional unit in TB BMD Z-score reduced the risk of VFs by 54% ($p=0.0007$).

Conclusion Our results suggest that ambulatory status and functional scores alone may not be reliable predictors for developing VFs and confirm the association with known risk factors, such as early initiation of glucocorticoid therapy and low BMD Z-scores, highlighting the need to guarantee a careful surveillance of possible VFs from the time of glucocorticoid initiation.

Keywords Bone fragility · DMD · Fractures · Functional status

Introduction

Duchenne Muscular Dystrophy (DMD) is a progressive genetic disorder characterized by muscle degeneration due to dystrophin deficiency [1, 2].

Beyond the well-documented muscle impairment, individuals living with DMD also face increased bone fragility and high risk of osteoporosis related to several factors. Bone fragility is a recognized complication across various neuromuscular disorders (NMDs) due to shared mechanisms including progressive muscle weakness, reduced mobility, muscular inflammation, and vitamin D deficiency [3, 4]. In DMD this risk is further exacerbated by long-term systemic use of glucocorticoids (GCs) [3–5], that are the gold standard treatment for this disease as reported by the most recent care recommendations [2]. GCs are generally administered since the age of 4–5 years and contribute to bone fragility by inhibiting bone formation and reducing bone mineral density (BMD) [6, 7].

A few papers have already reported an increased risk of bone fragility and a markedly higher incidence of both vertebral and

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long bone fractures in boys affected by DMD compared to the general population [8–11]. Most papers report the risk for long bone fractures, particularly in the lower limbs [8, 12, 13] while over the last decade there has been increasing attention to the possible presence of vertebral fractures (VFs) [9, 14–20] and on their early detection [13, 21] The 2018 standards of care strongly suggest that performing regular lateral spine X-ray can facilitate the early identification of the first signs of VFs [2] often occurring without pain or other clinical signs [9].

Several papers have reported the association between a number of variables such as age, BMD, evaluated by Dual Energy X-ray Absorptiometry (DXA), BMI and, not surprisingly, GCs duration, and the risk of VFs in individuals with DMD [11]

While several studies have reported that BMD dramatically decreases after loss of ambulation [11, 12, 22], little attempt has been made to establish the correlation between fractures and functional status.

Purpose

This cross-sectional study aims to describe the frequency of VFs in a large cohort of GC-treated individuals with DMD, and to establish the potential role of several factors, including GCs therapy, age, functional status and the degree of functional impairment, measured by standardized scales.

Methods

Definition of the cohort and inclusion criteria

This study is part of a large Italian natural history prospective study in DMD. Here we present a sub study with a retrospective analysis based on routinely collected clinical data of prevalent VFs. The sub study was performed in two Centres (Fondazione Policlinico A. Gemelli IRCCS (Rome) and IRCCS Istituto Giannina Gaslini (Genova)) sharing a similar protocol for bone health. In the sub study patients were included if they were 7 years of age or older and had an available lateral spine X-ray plus a total body BMD by DXA (carried out within a six-month period of each other). The age of 7 years was chosen as until recently normative data for DXA were not available for boys younger than 7 years.

The study was approved by the Ethical Committees of both institutions. Written informed consent was obtained from all participants (or guardians) in the study.

Demographic and anthropometric parameters

Demographic and anthropometric parameters including age, height, weight, BMI (as absolute values and standard deviation score (SDS) calculated based on the national growth chart for BMI [23] were noted. In ambulant patients, height was assessed in the standing position, while in non-ambulant subjects it was measured by arm span, than converted to height. Medical history including concomitant vitamin D supplementation, osteoporosis treatment, and non- VFs history was also recorded at the time of the bone health assessment. Serum 25OHD blood levels were available, with levels below 20 ng/mL classified as insufficient [24, 25].

Radiological parameters

Lateral spine X-rays were evaluated to assess the prevalence of VFs. In each Centre, all the X-rays were reviewed by one expert reader after a training session involving both readers from the two Centers. Readers were certified radiologists in active clinical practice with specific expertise in musculoskeletal radiology. X-rays were taken as part of our clinical routine for bone surveillance which in recent years includes annual lateral X-rays performed in all boys with DMD on GCs, in keeping with the 2018 Care Considerations [2]. In patients with multiple X-rays showing VFs, we included the first X-ray in which they were observed. On the other hand, if no VFs were detected, we included the latest X-ray available. VFs quantification was obtained using the Genant semi-quantitative method, which classifies vertebral deformities based on proportional reductions in vertebral height from T4 to L4 [26]. The severity of each fracture was graded as follows: grade 0, ≤ 20% (normal); grade 1, > 20%—25% (mild VF); grade 2, > 25%—40% (moderate VF); grade 3, > 40% (severe VF). In addition, the Spinal Deformity Index (SDI) was calculated as the sum of the Genant grades from T4 to L4 for all VFs [14]. VFs detected in other vertebrae (T3 and T5) were noted as present or absent.

Total body less head (TBLH) DXA scans (Lunar Prodigy, GE Healthcare, Madison, WI, USA) were also performed in both centres to provide the BMD (g/cm2) and Z-score. Normal bone density was defined as Z-scores > −2 and low bone density as Z-scores ≤ −2. Both centers used the same scanner, the same protocol and the same definitions. In consideration of the age of the cohort, a bone density "within the expected range for age" was defined as Z-scores > −2 and "below the expected range for age" bone density as Z-scores ≤ −2, according to official position of International Society for Clinical Densitometry (ISCD) [27].

Functional data

Details of the functional measures were collected identifying the assessments performed on the day of the selected X-ray. These included ambulatory status, functional scores on North Star Ambulatory Assessment (NSAA) and six-minute

walking test (6MWT) in the ambulant cohort, Performance of Upper Limb 2.0 (PUL) in the non-ambulant cohort [28–30]. Subject were defined "ambulant" if they were able to walk for 10 m independently; those who had lost this ability were classified as "non-ambulant".

Statistical analysis

Descriptive statistics were calculated to summarize the demographic and clinical characteristics of the study population. Continuous variables were reported as means and standard deviations (SD). Categorical variables were summarized as frequencies and percentages.

To identify factors associated with VFs, a logistic regression analysis was performed. The model included the following independent variables: BMI standard deviation score (BMI Z-score), height standard deviation score (height Z-score), motor function status (ambulant vs. non-ambulant), age at GCs initiation, duration of GCs treatment (in years), and TB BMD Z-score. The dependent variable was the presence of VFs, coded as a binary outcome (0 = no fracture, 1 = one or more vertebral fracture(s)). The model was fitted using the glm function in R with a binomial family specification appropriate for binary outcomes. Results were expressed as odds ratios (OR) with 95% confidence intervals (CI), and statistical significance was defined as $p < 0.05$.

In addition, a linear regression analysis was conducted to explore predictors of the SDI within a pediatric population affected by neuromuscular disorders. The primary variable of interest was BMD Z-score, with BMI Z-score, height Z-score, motor function status, age at GCs initiation, and years since starting GCs therapy included as covariates.

Separate regression models were fitted for the overall sample and for subgroups based on ambulatory status (ambulant and non-ambulant). For the total sample, a standard multiple linear regression was used to estimate the effect of predictors on SDI. Subgroup analyses employed the same model structure to evaluate potential differences in associations by mobility status. Model assumptions were assessed for both analyses. For linear regression, normality of residuals was evaluated using Shapiro–Wilk tests and Q-Q plots, and homoscedasticity was assessed via residual plots.

For logistic regression, linearity of continuous predictors with the log-odds was checked using Box-Tidwell tests, and model fit was evaluated using the Hosmer–Lemeshow test. Multicollinearity was examined using variance inflation factors (VIF < 5) for all models. All statistical tests were two-tailed, with significance set at $p < 0.05$. Model estimates were reported as standardized beta coefficients (β) along with standard errors (SE), t-values, and p-values. Overall model fit was evaluated using the F-statistic and its associated p-value.

Results

Of the 188 male subjects with genetically confirmed diagnosis of DMD treated with GCs, 174 had at least one lateral spine X-ray, with 152 also having a TB DXA scan within six months before or after the X-ray acquisition. In three of the 152 patients with a spine X-ray plus TB BMD DXA, the X-rays were difficult to assess due to difficulties in acquiring a reliable view of the vertebrae and were therefore excluded from the analysis. All patients agreed to had their data in the study.

The final cohort included 149 individuals with DMD aged between 7–26 years (mean 14.76 years). Table 1 and Supplementary Table 1 report details of the whole cohort.

Serum 25OHD blood levels were available in all 149 participants, with 58/149 (38.92%) having 25OHD levels below the normal range. One-hundred-forty-three of the 149 (96.6%) was on vitamin D supplementation, with 14/143 (9.79%) remaining below the normal range despite supplementation. Forty-eight of the 149 (32.2%) were on bisphosphonate treatment at the time of the assessment, i.e. for individuals with VF the time of the first fracture and for those who never had a VF, the last assessment available.

The decision to use bisphosphonate was mainly based according to low bone density [31].

Seventy-six of the 149 (51%) were ambulant and the remaining 73/149 (49%) were non-ambulant (Supplementary Fig. 1), with a mean of years from loss of ambulation (LOA) of 4.5 y (range 0–13.5 y).

In the ambulant cohort the NSAA scores were available in 72/76 ranged between 2 and 34 (mean 16.29), and the 6MWT was available in 64/74 ranging between 54 and 615 m (mean 326.6). In the non-ambulant cohort, the PUL score were available in 67/76 ranging between 0 and 38 (mean 20.4).

Sixty-four of the 149 (43%) did not have any fracture (mean age 14.3), 36 (24%) had VFs only (mean age 14.0), 26 (17.5%) had VFs plus a history of at least one long bone fracture (mean age 15.6); the remaining 23 (15.5%) had long bone fractures only (mean age 16.7).

Vertebral fractures cohort

Sixty-two of the 149 patients (41.6%) presented with vertebral fracture. Thirty-one of the 62 (50%) were ambulant, and 31 (50%) were non-ambulant. Thirteen (21%) had a single VF; 49 (79%) had multiple VFs (range 2–13; mean 4.32). Figure 1 shows details of the VFs and ambulatory status.

Stratifying the VFs according to Genant classification, we considered 207/224 VFs between T4 and L4 65/207 (31.4%) were grade 1, 106/207 (51.2%) were grade 2 and 36/207 (17.4%) were grade 3 (Fig. 2).

Table 1 Characteristics of the cohort; anthropometric data are referred to the time of the X-ray

Clinical characteristics	Whole cohort ($N=149$)	VFs naïve cohort ($N=87$)	VFs cohort ($N=62$)
Age (years), mean (SD)	14.76 (4.28)	14.89 (4.70)	14.58 (3.64)
Height (m), mean (SD)	1.40 (0.15)	1.42 (0.17)	1.38 (0.12)
Weight (kg), mean (SD)	44.23 g (15.2)	44.71 (15.99)	43.56 (14.10)
BMI Z-score	0.0	−0.1	0.2
Glucocorticoids exposure			
Age at starting GCs (years), mean (SD)	6.03 (1.97)	6.34 (2.24)	5.59(1.40)
Duration of GCs exposure(years), mean (SD)	8.73 (4.15)	8.50 (4.40)	8.90 (3.60)
Type *- Deflazacort n (%)* *- Prednisolone, n (%)*	*143/149 (99.3%)* *6/149 (4.0%)*	*84/87 (96.5%)* *3/87 (3.4%)*	*59/62 (95.2%)* *3/62 (4.8%)*
Regimen *- Daily, n (%)* *- Intermittent, n (%)*	*137/149 (91.9%)* *12/149 (8.0%)*	*80/87 (91.9%)* *7/87 (8.0%)*	*57/62 (91.9%)* *5/62 (8.1%)*
Bone mineral density			
TB BMD (SD)	0.742 g/cm^2 (0.15)	0.754 g/cm^2 (0.15)	0.722 g/cm^2 (0.14)
TB BMD Z-score mean (SD)	−2.6 (1.05)	−2.4 (1.03)	−2.9 (1.03)
- Normal bone density, n (%)	*32 (21.5%)*	*24 (27.58%)*	*8 (12.9%)*
- Low bone density, n (%)	*117 (78.5%)*	*63 (72.42%)*	*54 (87.1%)*
Bisphosphonate Treatment			
Age at starting, mean (SD)	15.64 y (2.94)	16.56 y (2.81)	14.94 y (2.89)
Bisphosphonate Treatment n (%)	49 (32.9%)	21 (24.1%)	28 (45.2%)
Type			
- Alendronate, n (%)	*19/49 (38.8%)*	*11/21 (52.4%)*	*8/28 (28.6%)*
- Ibandronate, n (%)	*5/49 (10.2%)*	*1/21 (4.8%)*	*4/28 (14.3%)*
- Neridronate, n (%)	*21/49 (42.9%)*	*6/21 (25.6%)*	*15/28 (53.6%)*
- Risedronate, n (%)	*4/49 (8.2%)*	*3/21 (12.3%)*	*1/28 (3.6%)*

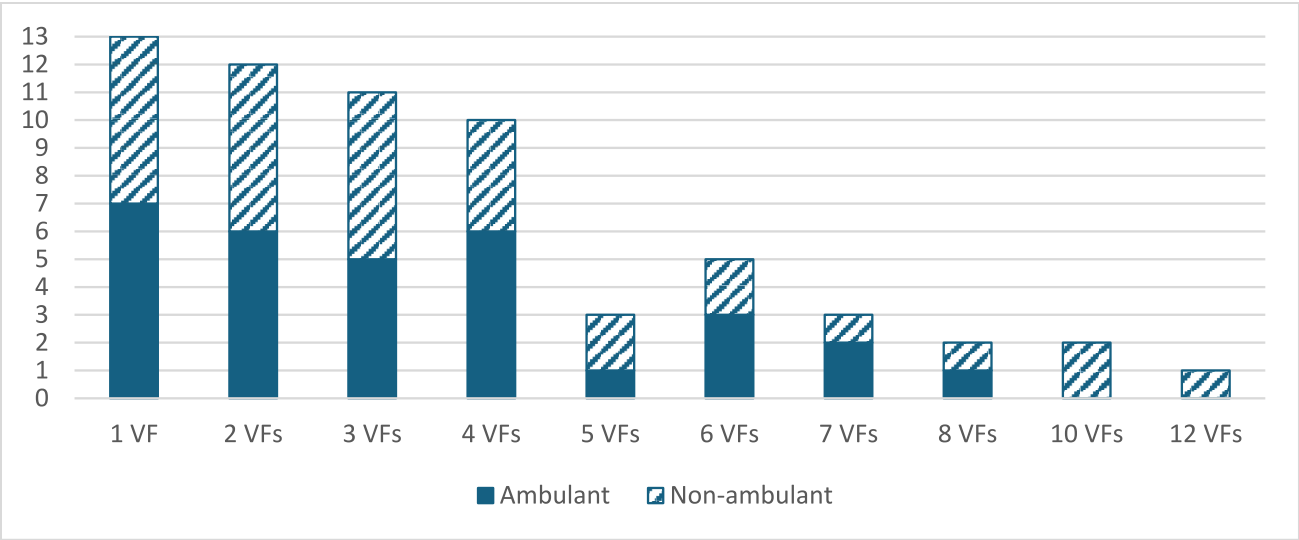

Fig. 1 Number of vertebral fractures (VFs) and ambulatory status

Of the remaining 17 VFs, localized outside of the scoring region for the Genant VF evaluation method, 1 was localized in T3 and 16 in L5.

When calculating the SDI, that takes into account both number of fractures and severity, for each subject, the values ranged between 1 and 23, with a mean SDI of 6.13 and a SD 5.49 (Supplementary Table 2; Fig. 3; Supplementary Fig. 2).

The total number of the VFs in the whole cohort was 224 and they occurred between T3 and L5. One-hundred-forty-one of the 224 VFs (63%) were thoracic and 83/224 (37%) were lumbar. Ninety-two of 224 (41.1%) occurred in the ambulant cohort, with 68/92 (74%) thoracic and 24/92 (26%) lumbar; 132/224 (58.9%) occurred in the non-ambulant cohort, with 73/132 (55%) thoracic and 59/132 (45%) lumbar.

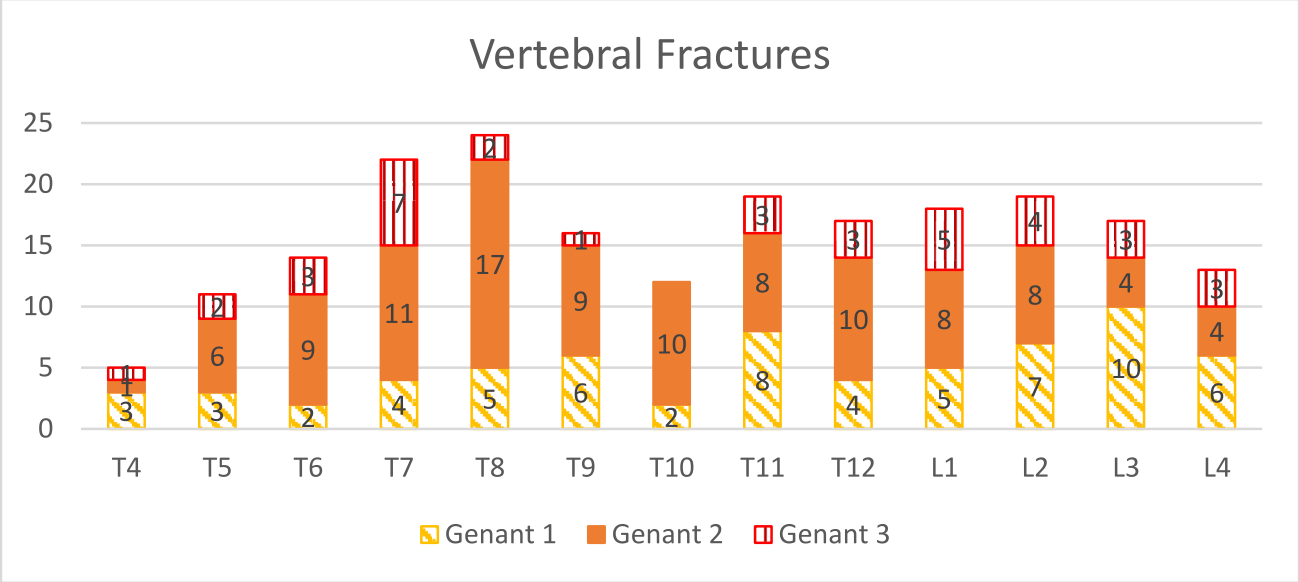

Fig. 2 Vertebral fracture distribution according to Genant classification

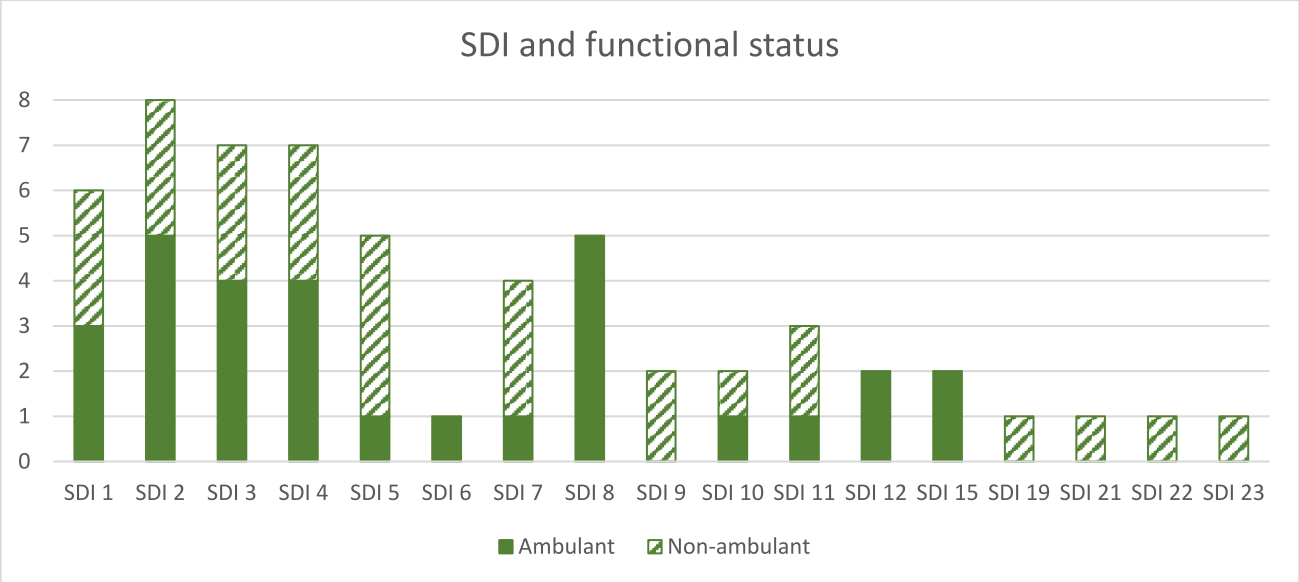

Fig. 3 Spinal Deformity Index (SDI) and functional status in the Vertebral Fractures (VFs) cohort

Risk factors for vertebral fractures

In the overall cohort, each unit increase in height Z-score was associated with a 26% reduction in the odds of VFs (OR = 0.74, 95% CI [0.57, 0.95], $p = 0.022$). Similarly, each additional year in age at GCs initiation was associated with a 29% reduction in odds (OR = 0.71, 95% CI [0.54, 0.88], $p = 0.005$). Finally, higher total body BMD Z-score was associated with a 51% reduction in the odds of VFs (OR = 0.49, 95% CI [0.30, 0.77], $p = 0.003$). (Table 2A).

Among non-ambulant individuals, each additional year in age at GCs start was associated with a 30% reduction in the odds of vertebral fracture (OR = 0.70, 95% CI [0.48, 0.94], $p = 0.033$). (Table 2B).

Among ambulant patients, higher BMI Z-scores was associated with a 62% increase in the odds of vertebral fracture (OR = 1.62, 95% CI [1.08, 2.64]) and higher total body BMD Z-score was linked to a 60% reduction in odds of vertebral fracture (OR = 0.40, 95% CI [0.17, 0.83]). ($p = 0.02$) (Table 2B).

Predictors for increased spinal deformity index (SDI)

In a linear regression analysis predicting spinal deformity index (SDI), only height Z-score was significantly associated with SDI, such that greater height was related to a lower spinal deformity index (b = –0.57, SE = 0.25, t = –2.28, $p = 0.024$). None of the other variables—BMI Z-score, motor function status, GCs start age, years since GCs, or bone DEXA Z-score—were significant predictors ($p > 0.10$).

In the *non-ambulant population*, only height Z-score was significantly associated with SDI, with greater height Z-score related to a lower spinal deformity index (b = –0.92, SE = 0.40, t = –2.28, $p = 0.026$). None of the other variables—BMI Z-score, GCs start age, years since GCs, or bone DEXA Z-score—significantly predicted SDI ($p > 0.25$).

In the *ambulant population*, BMI Z-score was a significant positive predictor of SDI, indicating that higher BMI was associated with greater spinal deformity (b = 0.78, SE = 0.26, t = 2.99, $p = 0.004$). Bone DEXA Z-score (b = –0.93, SE = 0.49, t = –1.88, $p = 0.064$) and NSSA (b = 0.10, SE = 0.05, t = 1.94, $p = 0.057$) were marginally associated with SDI. Height Z-score, GCs start age, and years since GCs were not significantly related to SDI ($p > 0.45$).

Discussion

The revised care recommendations in 2018 and other recent papers have increased the attention on the risk of VFs across the spectrum of DMD [2, 11, 14, 32], increasing awareness and a more systematic surveillance of these aspects. These studies report the possible risk factors for fractures suggesting a multifactorial ethology and the need for a multidisciplinary approach. While the role of GCs use, bone density, bone metabolites has been thoroughly investigated, less has been reported on possible associations with motor function across the whole spectrum of age and severity in DMD. In our cohort including both boys and young adults with DMD, approximately 40% (62/149) had at least one

Table 2 **A** Odds Ratios (OR) and 95% Confidence Intervals (CI) for Factors Associated with Vertebral Fractures. Key to table: Statistically significant results ($p < 0.05$) are marked in bold. **B** Odds Ratios (OR) and 95% Confidence Intervals (CI) for Factors Associated with Vertebral Fractures divided by non-ambulant and ambulant patients. Key to table: Statistically significant results ($p < 0.05$) are marked in bold

A)

Variable	OR	95% CI	*p*-value
BMI (Z-score)	1.23	0.97, 1.60	0.10
Height (Z-score)	**0.74**	**0.57, 0.95**	**0.022**
Motor Function (Ambulant vs Non-ambulant)	0.97	0.40, 2.36	> 0.9
GCs Start Age	**0.71**	**0.54, 0.88**	**0.005**
Years Since GCs	0.90	0.79, 1.02	0.12
TB BMD Z-score	**0.49**	**0.30, 0.77**	**0.003**

B)

Non-ambulant				**Ambulant**			
Variable	**OR**	**95% CI**	***p*-value**	**Variable**	**OR**	**95% CI**	***p*-value**
BMI (Z-score)	1.07	0.76, 1.53	0.7	**BMI (Z-score)**	**1.62**	**1.08, 2.64**	**0.033**
Height (Z-score)	0.78	0.54, 1.11	0.2	Height (Z-score)	0.63	0.38, 0.98	0.053
GCs Start Age	**0.70**	**0.48, 0.94**	**0.033**	GCs Start Age	0.69	0.42, 1.04	0.10
Years Since GCs	0.99	0.81, 1.18	0.9	Years Since GCs	0.83	0.61, 1.06	0.2
TB BMD Z-score	0.52	0.24, 1.00	0.065	**TB BMD Z-score**	**0.40**	**0.17, 0.83**	**0.021**
PUL	1.03	0.97, 1.11	0.3	NSAA	1.04	0.98, 1.11	0.2

CI confidence interval, *OR* odds ratio, *GCs* glucocorticoids

VF, with the large majority of them (79%) having multiple prevalent VFs. When stratifying the VFs according to severity, most of them (51%) were moderate (Genant 2) and only 17% of VFs were severe (Genant 3). SDI, calculated as the sum of the Genant grades from T4 to L4 for all VFs for each subject, ranged between 0–23, with scores between 1 and 4 in more than half of those with VFs. Interestingly, as already reported [14], we also found that the largest number of fractures in the overall cohort was in T8 and T7, followed by T11, L2, T12 and L3, with the ambulant cohort showing over 70% limited to the thoracic VFs, and the non-ambulant ones having a wider localization (55% thoracic vs 45% lumbar). As previously reported, in the ambulatory phase, compensatory lumbar hyperlordosis, is more evident, whereas in the non-ambulatory phase these features are reduced, and are associated with relatively greater thoracic loading [14]. These findings suggest spinal biomechanics may play a role in VFs distribution in DMD.

It has previously been postulated that fractures (both VFs and non-VFs) are more likely to occur in older non-ambulant patients [10, 22, 33] for a combination of concomitant concurring predisposing factors such as reduced mobility, increased time on GCs, and reduced BMD. In our cohort, when focusing on VFs only, a nearly identical proportion of prevalent fractures were found in ambulant (31/76) and non-ambulant (31/73) patients.

As both ambulant and non-ambulant cohorts were very heterogeneous, we assessed whether the possibility to detect VFs could be related in different levels of activity within each sub-cohort, but we could not find any specific association with the NSAA scores in the ambulant subgroups or with the PUL scores in the non-ambulant ones, this confirming a non-consistent effect of function on the occurrence of VFs. A multivariate analysis, taking into account other variables such as TB BMD Z-scores, age at starting GCs treatment and height Z-score and BMI Z-scores, showed that in the overall cohort, each unit increase in height Z-score was associated with a 26% reduction in the odds of VFs and similarly, each additional year in age at GCs initiation was associated with a 29% and each additional unit in TB BMD Z-score by 51% reduction in odds. Stratifying the cohort according to functional status, the TB BMD Z-score was a protective only in the ambulant subgroups, while in the non-ambulant subgroups GCs start age was significantly protective.

These findings confirm that the identification of low TB BMD values increases the risk for occurrence of VFs. This did not always hold true in individual cases, as in a number of boys/young adults, fractures were associated with non-pathological Z-scores and, conversely, several patients with pathological Z-scores had no evidence of fractures. These discrepancies could be partly explained by recent suggestions that the BMD Z-scores could be overestimated by calculating the scores according to chronological age rather than by bone age [34]. Because of the retrospective nature of our study, wrist X-ray had not been systematically performed in our cohort at the time when TB DXA were performed and this could therefore not be calculated. In the ambulant cohort, each one-unit increase in BMI Z-score was associated with a 62% increase in the risk of VFs, even after adjusting for TB BMD Z-score. This suggests that body composition influences fracture risk through mechanisms independent of bone mineral density alone. These findings are consistent with recent evidence showing that increased fat mass, particularly FMI, was inversely correlated with total body BMD Z-scores and associated with a higher incidence of fragility fractures in ambulant prepubertal boys with DMD [35]. Together, these results suggest that, beyond BMD alone, body composition may play an important role in skeletal fragility within this population.

Although longer GCs exposure is generally considered a risk factor for VFs, our findings highlight substantial individual variability. While some boys appeared to be overall more affected by the known steroid side effects, with reduced height more often associated with vertebral fractures, it was difficult to establish a causality effect or to establish a consistent association with duration of GCs therapy. The risk of fractures was only relatively higher in older patients with a longer duration of GCs therapy. Indeed, VFs and relatively high SDI could be observed in a number of young ambulant patients as young as 7 years who had been on GCs for a limited time, while some non-ambulant patients older than 25 years who had been on GCs for a long time did not develop any vertebral fracture, thus underscoring the multifactorial and complex nature of skeletal fragility in DMD. As over 95% of our patients were on daily regimen of GCs, we were unable to perform any meaningful analysis between different regimes. The lack of a consistent association between VFs and duration of GCs or increasing age, is somehow different with previous studies [11, 14] and can be only partly explained by the retrospective, cross-sectional nature of the study that does not allow going further on possible cause-effect relation between all analyzed data and the fractures occurrence. These findings suggests a possible multifactorial etiology where other factors may contribute to accelerate or mitigate the occurrence of VFs.

Conclusion

Our results add with new information on the role of function on VFs and, more generally on the frequency and distribution of VFs in a large cohort of males with DMD including both pediatric and adult patients. The relatively large

number of VFs in young ambulant boys highlights the need to perform a careful clinical and radiological surveillance of possible VFs since the time GCs therapy has started. While we were able to confirm the association of established risk factors, such as early initiation of GCs therapy and low BMD Z-scores, on the risk of developing VFs in the overall cohort, we did not identify consistent associations with functional parameters suggesting that functional status alone may not reliably reflect fracture risk. Because of the retrospective nature of our study, the study has also other limitations. First of all, wrist X-ray had not been systematically performed in our cohort at the time when TB DXA were performed and this could therefore not be calculated. Another potential limitation of this study is that the height of the non-ambulant cohort was estimated using predictive equations derived from healthy individuals. These equations may overestimate true stature in glucocorticoid-treated boys with DMD due to their abnormal growth pattern [36], and possibly affect analyses including height or BMI as independent variables. Even with these limitations, the study expands the literature on the topic and provides new insight on the correlation between VFs, steroids and motor function.

These findings should be further investigated in larger longitudinal studies taking into account several aspects of standards of care prospectively collected. These studies would also help to better understand the link between functional status and fracture risk investigating whether a higher incidence of VFs correlates with a more severe functional decline.

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Data Availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethical approval The study was approved by the Ethics committee (Protocol 600014186/17).

Consent to participate Written informed consent was obtained in all cases.

Conflicts of interests GC participated to Advisory Board for Italfarmaco, ROCHE and Sarepta; CB, participated to Advisory Board for ROCHE; EM participated to Advisory Board for ROCHE, Sarepta, PTC, Italfarmaco, Pfizer, Dyne, NS Pharma, Santhera, Avidity, Entrada, Edgewise and Solid. MP participated to Advisory Board for ROCHE, Sarepta, PTC, Italfarmaco, Pfizer and Dyne; The remaining authors have nothing to disclose.

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