Fracture in Duchenne Muscular Dystrophy: Natural History and Vitamin D Deficiency

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Abstract
The present study examined the natural history of fracture and vitamin D levels in Duchenne muscular dystrophy patients, who are vulnerable to osteoporosis and fractures. Retrospective analysis of a cohort of 48 Duchenne muscular dystrophy patients revealed that 43% of patients experienced ≥1 fracture. Fracture probabilities at ages 6, 9, 12, and 15 years were 4%, 9%, 31%, and 60% respectively, accelerating around the time of ambulation loss (mean age 11.8 ± 2.7 years). Chronic corticosteroid therapy was utilized in 69% of patients and was associated with all vertebral fractures. A history of vitamin D deficiency occurred in 84%, and 35% were currently deficient. Despite chronic vitamin D supplementation, 38% remained deficient. These results demonstrate that osteoporosis and fracture remain major concerns in Duchenne muscular dystrophy. Bone health should be optimized well before loss of ambulation, however current levels of vitamin D supplementation may be inadequate given high levels of deficiency.

Keywords
Duchenne muscular dystrophy, bone health, osteoporosis, fracture, vitamin D

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Duchenne muscular dystrophy is an X-linked recessive neurodegenerative disease affecting approximately 1 in 3600 live male births, caused by a mutation in the dystrophin gene.1,2 Symptoms usually appear in male children before 6 years of age, with progressive muscle weakness, loss of independent ambulation by approximately 13 years of age, and premature death.3,4 While extensive efforts are being undertaken to develop novel treatment strategies, chronic corticosteroid therapy remains the only disease modifying treatment, slowing disease progression, prolonging ambulation and improving respiratory function.5-10 Current treatment focuses on anticipating and preventing complications through multidisciplinary and supportive management.3,4

Fractures occur in 21-44% of Duchenne muscular dystrophy patients and in addition to being painful, can have a detrimental impact on mobility and quality of life.11,12 Significantly, this contrasts to a fracture prevalence of 9% in healthy children,13 and urgently highlights the need to further develop strategies to reduce and treat osteoporosis and fracture in Duchenne muscular dystrophy. Reduced weight-bearing exercise, side effects of long-term corticosteroids, potential for reduced exposure to sunlight and direct pathological effects of the myopathy are among major risk factors for osteoporosis in Duchenne muscular dystrophy.14-17

Optimizing bone mineralization through adequate intake of 25-hydroxyvitamin D and calcium is important in fracture prevention. While the prevalence of vitamin D deficiency in Australian Duchenne muscular dystrophy patients has not yet been established, remarkably only 22% of patients were vitamin D sufficient in a United Kingdom national audit.18 Although there is some evidence for the efficacy of vitamin D supplementation,19 the optimal treatment of vitamin D deficiency in Duchenne muscular dystrophy has not yet been established. The present study was undertaken to develop an understanding of the natural history of and predisposing factors to fracture and vitamin D deficiency and the effectiveness of vitamin D supplementation in a cohort of Australian Duchenne muscular dystrophy patients

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dystrophy patients, such that insights into improving treatment approaches may be gained.

**Methods**

The present study incorporated patients with Duchenne muscular dystrophy who presented to the Sydney Children’s Hospital multidisciplinary neuromuscular clinic for routine clinical care from 1993-2013. The diagnosis of Duchenne muscular dystrophy was confirmed by genetic testing for mutations in the dystrophin gene or the absence of dystrophin staining on muscle biopsy. Data were collected from patient notes and the clinical investigation database. The study was approved by the South Eastern Sydney and Illawarra Area Health Service Human Ethics Committee (ref 09/176).

A retrospective review was undertaken to describe the prevalence and natural history of fracture in Duchenne muscular dystrophy patients. Type of fracture (long bone or vertebral), age at fracture and latency from commencement of corticosteroid therapy to vertebral fracture were recorded. Skeletal characteristics at time of vertebral fracture were obtained using dual-energy x-ray absorptiometry scans (Lunar Prodigy, Madison WI) and analyzed using proprietary software version 10.50. Age, gender, and height adjusted areal bone mineral density Z-scores, as compared to Australian normative data, were calculated for lumbar spine (L2-4).20

Factors potentially contributing to osteoporosis and fracture were reviewed and included: age, mobility status (ambulant or nonambulant), age at loss of ambulation, corticosteroid therapy (age at commencement, duration of therapy, current daily dose of prednisolone) and history of vitamin D deficiency. A serum 25-hydroxyvitamin D level >50 nmol/L was defined as sufficient, 25-50 nmol/L as mildly deficient, 12.5-25 nmol/L as moderately deficient, and <12.5 nmol/L as severely deficient.21 Regular measurement of vitamin D had been undertaken routinely from 2005 following a workshop report on bone health in Duchenne muscular dystrophy.21 Body mass index was calculated as weight/height,2 using a stadiometer in ambulant patients and estimated height from ulnar length in nonambulant patients.22 Patients were then categorized into “underweight,” “normal,” “overweight,” or “obese” according to age and gender-matched standards.23,24

Duchenne muscular dystrophy patients were classified into 3 disease stage groups, according to age and motor function. Duchenne muscular dystrophy boys in “early childhood” were younger than 6 years, usually making gross motor progress and not prescribed corticosteroids; “ambulatory” boys had experienced a plateau then decline in motor skills but were able to walk independently; and “nonambulatory” boys were mostly reliant on a wheelchair for mobility. The lowest serum 25-hydroxyvitamin D level recorded at each of the 3 disease stages was documented for longitudinal vitamin D analysis. It was noted whether levels had increased or decreased between each disease stage. Factors related to treatment with vitamin D including dose, duration, compliance and use of stoss therapy, in which the total treatment dose of vitamin D is administered over several large doses, were obtained from patient notes.

Demographic dual-energy x-ray absorptiometry data were expressed as mean ± standard deviation of the mean. Comparisons between groups were made using the Mann-Whitney U test (2-tailed) or Fisher exact test (2-tailed), while relationships between variables were analyzed using Spearman’s correlation coefficient. Fracture probabilities and curves were calculated using the Kaplan-Meier method and differences in curves were compared with the log-rank test.

### Results

A clinical and genetic diagnosis of Duchenne muscular dystrophy was confirmed in 48 patients during the study period, who were followed for a total of 648 patient-years. There were 34 current patients; 13 patients had transitioned to adult medical services following the completion of secondary school and 1 patient had died at age 17 years due to respiratory failure. The characteristics of the Duchenne muscular dystrophy cohort at the time of their last follow-up are summarized in Table 1.

Overall 22 patients (46%) were ambulant and 26 patients (54%) were nonambulant. As expected, ambulant patients were significantly younger than patients who were nonambulant (age ambulant 10.0 ± 4.1 years, nonambulant 17.6 ± 3.0 years, P < .001).

Corticosteroid therapy (daily prednisolone) was initiated at a mean age of 6.7 years. This typically occurred once the “plateau phase” was identified (ie, when ambulant patients no longer made gross motor progress). Corticosteroid therapy was continued throughout the disease course if tolerated; 11 patients (23%) were not prescribed chronic corticosteroids, 5 of whom were younger than 6 years and were continuing to demonstrate gross motor progress. 33 patients (69%) received chronic corticosteroid therapy, while 4 (8%) had short-term therapy but ceased due to related side effects. Ambulation was preserved for significantly longer in Duchenne muscular dystrophy patients prescribed chronic corticosteroids (chronic corticosteroids loss of ambulation 13.0 ± 2.4 years, no corticosteroids loss of ambulation 9.2 ± 1.6 years, P < .005).

### Evaluation of anthropometry

33% patients were in the normal body mass index category, 33% were overweight and 33% obese. Body mass index had a significant positive correlation with age, with older and nonambulant patients having a significantly greater body mass index than younger, ambulant ones (age and body mass index, R = 0.6, P < .01; ambulant patients 52.6% overweight/obese, nonambulant patients 100% overweight/obese, P < .05). Among only the patients on chronic corticosteroid therapy, the relationship between ambulation status and body mass index remained significant (ambulant patients 50% overweight/obese, nonambulant 100% overweight/obese, P < .05).

### Table 1. Characteristics of the Duchenne Muscular Dystrophy Cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
<th>Mean (± 1 SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, months)</td>
<td>48</td>
<td>13.6 ± 4.7</td>
<td>2.0-18.5</td>
</tr>
<tr>
<td>Age at commencement of corticosteroids (years, months)</td>
<td>37</td>
<td>6.8 ± 1.0</td>
<td>4.0-9.6</td>
</tr>
<tr>
<td>Age at loss of ambulation (years, months)</td>
<td>26</td>
<td>11.0 ± 2.8</td>
<td>7.0-17.7</td>
</tr>
<tr>
<td>Current body mass index (kg/m²)</td>
<td>34</td>
<td>23.4 ± 7.3</td>
<td>14.8-42.8</td>
</tr>
<tr>
<td>Current dose of corticosteroids (mg/kg/day)</td>
<td>33</td>
<td>0.53 ± 0.2</td>
<td>0.21-0.9</td>
</tr>
</tbody>
</table>
Fractures

All recorded fractures were symptomatic, presenting with pain, as asymptomatic fractures were not screened for. Twenty-one of 48 boys (43%) had sustained at least 1 fracture, and 9 had multiple incidents of fracture. In total, there were 34 incidents of fracture within the cohort: 19 with long bone and 15 with vertebral fracture (Table 2). Of the 21 patients with fracture(s), 11 (52%) sustained a fracture while nonambulant, 6/11 (55%) of these experiencing vertebral fractures. The probability of sustaining at least 1 fracture for all Duchenne muscular dystrophy patients was 4% at age 6 years, 9% at age 9 years, 31% at age 12 years, 60% at age 15 years (Figure 1).

Comparing patients receiving chronic corticosteroid therapy and patients without long-term corticosteroids, there was also no significant difference between overall fracture probability rates (Figure 3, \( P = .635 \)); however, chronic corticosteroid therapy was related to fracture type. All patients with vertebral fractures were on chronic corticosteroid therapy, and the latency to vertebral fracture following commencement of corticosteroids was 6.6 ± 1.2 years (range 3.8-8 years). Evaluating long bone fractures revealed the probability of sustaining at least 1 long bone fracture was 34% at age 18 years in patients on chronic corticosteroids and 53% at age 18 years in patients without chronic corticosteroids (\( P = .33 \)).

Bone mineral density data were available for 7 patients who presented with symptomatic vertebral fracture (mean age 12.4 years, range 11.4-14.9 years). The mean age, gender and height adjusted lumbar spine areal bone mineral density \( Z \)-score was –2.9 ± 1.1 (range –1.4 to –4.5). The majority (5/7, 71%) of these patients met the pediatric criterion for low bone mineral density (\( Z \)-score < –2) at the lumbar spine.25

Vitamin D Deficiency

Critically, 38 (84%) patients had a history of vitamin D deficiency at some time throughout the disease course: 82% (14/17) of assessed patients were deficient in the “early childhood” disease stage, 84% (21/25) in the “ambulatory” stage and 82% (18/22) in the “nonambulatory” stage. There was a decline in vitamin D levels between disease stages in 54% of cases, with individual chart review revealing nonadherence to supplementation (15%), inadequacy of the prescribed 1000 IU daily older age and over a more limited time span than long bone fractures, although there was not a statistically significant difference between separated Kaplan-Meier analyses (\( P = .089 \), Figure 2).

Figure 1. Probability of a fracture in patients with Duchenne muscular dystrophy over disease course. Shaded box indicates the range of ages at loss of ambulation ± 1 standard deviation from the mean.

<table>
<thead>
<tr>
<th>Number of patients (n, %)</th>
<th>Long bone</th>
<th>Vertebral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of incidents (n)</td>
<td>13 (27)(^a)</td>
<td>11 (23)(^a)</td>
</tr>
<tr>
<td>Mean age at time of fracture (years, months ± 1 SD)</td>
<td>11.0 ± 3.10</td>
<td>13.1 ± 1.1, 8(^**)</td>
</tr>
<tr>
<td>Range of ages at time of fracture (years, months)</td>
<td>4, 0-17, 6</td>
<td>9, 8-15, 10</td>
</tr>
<tr>
<td>Length of time on corticosteroids (years, months ± 1 SD)</td>
<td>4, 10 ± 3.10</td>
<td>6, 7 ± 1.2</td>
</tr>
</tbody>
</table>

\(^a\)3 patients had both long bone and vertebral fractures.

\(^**\)\( P < .05 \).

Table 2. Incidents and Age at Time of Long Bone and Vertebral Fractures.

Figure 2. Probability of a fracture in patients with Duchenne muscular dystrophy over time according to type of fracture.

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supplementation dose (23%) and not receiving chronic supplementation (54%) as possible reasons for this. Conversely, of the 25% of cases that demonstrated an increase in vitamin D levels, 33% had received high dose cholecalciferol (stoss) therapy, 33% were prescribed 1000 IU vitamin D supplementation and in 33% ≥2000 IU vitamin D supplementation was prescribed.

Cross-sectional analysis of biochemical variables measured over the past 12 months demonstrated that mean 25-hydroxyvitamin D levels were 54.3 ± 14.5 nmol/L (sufficient >50 nmol/L), however 11/31 (35%) patients were vitamin D deficient. Only 4/20 (20%) vitamin D sufficient patients had not received any form of supplementation. Chronic vitamin D supplementation was prescribed in 21 (60%) of patients and 5 of these had also received high dose vitamin D stoss therapy in the last year. Importantly, despite being on regular supplementation, 8/21 (38%) patients were vitamin D deficient. No significant relationship was found between fracture and current vitamin D levels (patients with history of fracture mean vitamin D level 59.7 nmol/L, patients with no history of fracture 50.3 nmol/L, \( P = .09 \)), or between fracture and the presence of deficiency at any disease stage (patients with history of vitamin D deficiency fracture rate 43%, patients with no history of deficiency fracture rate 60%, \( P = .6 \)).

**Discussion**

The present study has established the bone health outcomes of an Australian cohort of Duchenne muscular dystrophy patients. As the first study regarding this issue to be conducted in the southern hemisphere, it has shown that geography does not play a significant role in bone health, and that bone health remains a substantial concern in Duchenne muscular dystrophy. In total, 43% of the present cohort of Duchenne muscular dystrophy patients had at least 1 fracture, confirming the high rates of fracture experienced by Duchenne muscular dystrophy patients.\(^{11,12,26}\) In this cohort, the incidence of fracture was approximately 5 times that of healthy children in Australia\(^{13,27}\) with an alarmingly high 60% of patients predicted to sustain a fracture by the age of 15 years. In addition, this study demonstrated that the highest risk period corresponded to the time at which young men with Duchenne muscular dystrophy lose the ability to ambulate independently, confirming loss of ambulation as a major risk factor for fracture in neuromuscular disease.\(^{26}\) Most notable was that virtually all vertebral compression fractures occurred within 1 standard deviation to either side of the mean age at loss of ambulation. This may represent a causal relationship or indeed an inflection point with the culmination of a number of risk factors.

A major factor is likely the accelerated decline of bone mineral density which occurs following the loss of weight-bearing activity, particularly in the lower limbs.\(^{11,17}\) The detrimental impact of muscle weakness on bone health is also supported by comparable rates of fracture in the present cohort to those found in Rett syndrome, a disease which similarly leads to limited weight-bearing activity.\(^{28}\) It was also found, however, that a substantial proportion of patients (48%) experienced fractures before losing ambulation. This highlights the declines in bone mineral density which occur even prior to loss of mobility in Duchenne muscular dystrophy patients, again related to progressive muscle weakness in patients, as well as exposure to other risk factors, including corticosteroid use.\(^{11,29-31}\)
The present study highlights that vitamin D deficiency is a very common problem in any stage of Duchenne muscular dystrophy, with 35% of the current cohort deficient and the vast majority (82%) of the authors’ patients possessing a history of past deficiency. Despite this, the prevalence of vitamin D deficiency was lower than expected given the very high levels of deficiency found in previous Duchenne muscular dystrophy studies, and is encouraging evidence for the utility of vitamin D supplementation in Duchenne muscular dystrophy. However, persisting deficiencies indicate an issue either with adherence to treatment or inadequate dosage. Both factors may play a role, given that 38% of patients prescribed chronic supplementation of 1000 IU daily remained deficient. Increased body mass and fat may also reduce vitamin D absorption. Previous studies have demonstrated vitamin D supplementation of 0.8mcg/kg/day (equivalent to 1000 IU in a 31 kg boy) along with calcium supplementation produced substantial improvements in 25-hydroxyvitamin D and bone mineral density over a 2-year period. Hence, both ongoing monitoring for adherence and increased doses may be required to reduce vitamin D deficiency and improve fracture outcomes.

This study demonstrated several important findings regarding the natural history of fracture in Duchenne muscular dystrophy patients. Significantly, the authors found all 15 incidents of vertebral fracture in the present study occurred in patients who had been treated with chronic corticosteroids, with an average latency of 6.6 years from commencing corticosteroids to fracture. There was also a trend toward vertebral fractures occurring later and being clustered around the time of loss of ambulation, and long bone fractures occurring throughout the entire span of disease. These observations support the notion that vertebral fractures are a direct side effect of long-term corticosteroid use, whereas long-bone fractures are a consequence of general decreases in bone health with Duchenne muscular dystrophy and its risk factors. Although there was not a significant difference between overall fracture probability related to chronic corticosteroid therapy, this could possibly be demonstrated in studies with larger numbers. Of further relevance, a collinear relationship in which steroids slow growth and are also associated with increased fracture may be present and valuable to assess in future studies. As this study only identified symptomatic vertebral fractures, and another study found that 22% of vertebral fractures in Duchenne muscular dystrophy were asymptomatic, the present study is likely underestimating the prevalence of vertebral fractures and the actual latency to fracture might lie closer to Bothwell et al’s finding of 3.3 years.

Excessive weight gain throughout the course of disease was confirmed in the cohort. Excessive weight has previously been established as a significant side effect of corticosteroid use, particularly during the first few years of corticosteroid therapy. The present study demonstrated that body mass index was highest in boys between 10 and 15 years of age, the period of time during which most boys stop ambulating, highlighting the detrimental impact of loss of ambulation on body mass. Interestingly, since bone mineral density is associated with body weight and skeletal load, it has been suggested and shown in several studies in non–Duchenne muscular dystrophy cohorts that increased body weight may have a protective role in bone health. Given that an association was found between being overweight and experiencing a fracture, these protective effects might be counteracted by reduced muscle strength and corticosteroid use in Duchenne muscular dystrophy, or increased body weight might occur too late (that is, in patients who no longer bear their increased weight) to substantially improve bone mineral density. Nevertheless, increased body mass index has significant implications for the quality of life of Duchenne muscular dystrophy patients, with excessive weight and body fat not only detrimental due to its association with diabetes, decreased pulmonary and cardiac function, but also through its effect on motor function and mobility.

Clinical Implications and Future Therapeutic Directions

The study cohort is representative of contemporary care practices and recommendations in Duchenne muscular dystrophy, with the majority of patients receiving chronic corticosteroid therapy (69%) and chronic vitamin D supplementation (60%). As such, the results are relevant and applicable to many other Duchenne muscular dystrophy clinics. The findings from the present study suggest that daily vitamin D supplementation should be commenced in all Duchenne muscular dystrophy patients from diagnosis to maximize bone mineralization throughout development. In response to adherence and dose issues identified in the present study, clinical recommendations include increasing supplementation from 1000 IU daily to 2000 IU daily (particularly in heavier boys), increased monitoring of compliance, 25-hydroxyvitamin D levels and titration of dosage, education about bone health and its importance, and the increased use of stoss therapy in patients with adherence issues. Furthermore, it is vital that multidisciplinary care incorporates the early and continued involvement of a nutritionist to ensure adequate intake of vitamin D and calcium and to manage body mass index throughout disease course, particularly given body mass index and fracture significantly affect quality of life. In addition, an exercise physiologist is critical in advocating weight-bearing activity to maximize bone mineralization during the critical period of bone development, with the role of exercise therapy an important area for future studies.

Although consensus guidelines currently recommend performing an annual dual-energy x-ray absorptiometry scan for high risk patients, prophylactic measures to prevent fracture in low bone mineral density patients remain a controversial issue in Duchenne muscular dystrophy. As such, dual-energy x-ray absorptiometry scans were only performed in the study clinic upon suspicion of fracture, as intravenous bisphosphonates are currently utilized following vertebral fracture to reduce pain and to improve bone mineral density and vertebral height. Prophylactic bisphosphonates are used in adults suffering from osteoporosis, and a preliminary study in Duchenne muscular dystrophy patients has shown it to be beneficial in improving
bone mineral density Z-scores. Data to demonstrate the effects of bisphosphonates are lacking in Duchenne muscular dystrophy, however, and future studies are needed to explore its safety and efficacy in reducing fractures such that prophylactic measures, together with dual-energy x-ray absorptiometry monitoring, may become routine clinical care. Until then, the present study demonstrates the need for increased suspicion of vertebral fractures several years after commencing corticosteroid therapy, particularly around the time ambulation is lost.

Conclusion

The results of the present study highlight that adverse bone health and osteoporosis remain significant factors causing morbidity and fractures in Duchenne muscular dystrophy. Fracture rates accelerate around the time of loss of ambulation, demonstrating the importance of instituting a multidisciplinary approach optimizing bone mineralization as early as possible. Vitamin D deficiency is a modifiable contributor to bone health which is still prevalent in Duchenne muscular dystrophy cohorts, requiring greater surveillance and more rigorous treatment.

Authors’ Note

All data used in this article are contained within an Excel spreadsheet that can be accessed on request.

Author Contributions

NP carried out data collection and analysis, and drafted the initial manuscript. MF conceptualized and designed the study, supervised data collection and manuscript writing and reviewed and revised the manuscript. HS’ and HW’s contributions include data analysis, data interpretation and revision of the manuscript. All authors approved the final manuscript as submitted.

Declaration of Conflicting Interests

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Ethical Approval

This study was approved by the South Eastern Sydney and Illawarra Area Health Service Human Research Ethics Committee (ref 09/176).

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