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# Impact of Bisphosphonates on Survival for Patients With Duchenne Muscular Dystrophy

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# Impact of Bisphosphonates on Survival for Patients With Duchenne Muscular Dystrophy

**WHAT'S KNOWN ON THIS SUBJECT:** The use of steroids as a treatment for patients with Duchenne muscular dystrophy results in a slower progression in weakness. Bisphosphonates often are used in conjunction with steroid therapy to enhance bone health.

**WHAT THIS STUDY ADDS:** The combination of steroids and bisphosphonates seems to be associated with significantly improved survival rates compared with treatment with steroids alone.

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**KEY WORDS**

bisphosphonates, Duchenne muscular dystrophy, prognosis, steroids, survival

**ABBREVIATION**

DMD—Duchenne muscular dystrophy

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## abstract

**OBJECTIVE:** In this article we describe the association of bisphosphonate therapy on survival within a regional cohort of patients with Duchenne muscular dystrophy (DMD) who received steroid therapy and were managed in a single center.

**PATIENTS AND METHODS:** The records of all patients with confirmed DMD who were born between 1963 and 2006 and who had received at least 1 year of steroid therapy were reviewed from birth until they reached the study end points (death, loss to follow-up, or the last follow-up was in 2009). A survival analysis was used to account for the variable follow-up duration within this cohort.

**RESULTS:** Forty-four boys from this cohort with DMD were exposed to continuous steroid use. Bisphosphonate therapy was initiated for 16 patients (36%) between 1997 and 2007 at a median age of 12.5 years (range: 7–23 years). At the time of the last follow-up in 2009, 13 patients had died (30%) at a median age of 16 years (range: 14–27 years). Survival curves demonstrate that the prescription of bisphosphonates was associated with a significant improvement in survival rate ($P = .005$, log-rank test). Furthermore, a possible therapy-duration effect could be shown for bisphosphonate use ($P = .007$, log-rank test).

**CONCLUSIONS:** The treatment of patients with DMD with steroids and bisphosphonates seems to be associated with significantly improved survival compared with treatment with steroids alone. *Pediatrics* 2011; 127:e352–e357

Duchenne muscular dystrophy (DMD) affects ~1 in every 3500 male births and is characterized by relentlessly progressive weakness. In the past, the course of this condition was predicable; loss of ambulation occurs toward the end of the first decade, and death occurs before the age of 20 years.

There has been an increase in life expectancy for those with DMD over the past 15 years. This increase is considered to be related to both the introduction of steroid therapy and early ventilatory support.[1–3] Because the routine use of steroids is associated with an increased risk of vertebral fractures,[4] we monitored bone density in our patients and treated them with bisphosphonates when progressive osteopenia was detected.

Our population of patients with DMD was somewhat unique in 2 regards. Virtually all patients and their families elected to use steroids, and few chose mechanical ventilation as a treatment modality. Therefore, we explored whether bisphosphonates, in combination with steroids, might have played a role in the enhanced longevity that was seen in our patients with DMD.

## PATIENTS AND METHODS

All patients with DMD from the 2 Canadian provinces of Nova Scotia and Prince Edward Island were seen by members of the Pediatric Neurology Division at Dalhousie University in Halifax, Nova Scotia. In addition, some patients from the province of New Brunswick were followed within our clinic. As part of a study describing the incidence and clinical course of DMD,[5,6] the records of all those born between 1963 and 2006 with muscle biopsy or genetically confirmed DMD were retrospectively reviewed, and information about the clinical course for each patient was abstracted. Because this birth cohort spanned both the eras of presteroid and poststeroid management of patients with DMD, we elected to only include patients who received at least 1 year of steroid therapy (either prednisone or deflazacort). These patients were reviewed from birth until they reached 1 of the study end points (death, loss to follow-up, or the last follow-up point in 2009). Time-related information was obtained for year of diagnosis, age at wheelchair use, mechanical ventilation, steroid use, and bisphosphonate therapy.

Data were entered into an Excel (Microsoft, Redmond, WA) spreadsheet, were checked for errors, and the bisphosphonate and survival data were subsequently rechecked against the patients' files. The subsequent analysis was performed by using Systat 9.0.[7] The clinical characteristics of the cohort were described using nonparametric statistics. Survival analysis examined the probability of dying over time according to a univariate log-rank test, given the variable follow-up duration within this cohort. All statistics shown are for nonmissing data. The chart review was approved by the research ethics board at the IWK Health Centre.

## RESULTS

Eighty-one boys with DMD were born between 1963 and 2006 in our region. Forty-four boys from this cohort, born between 1977 and 2006, were exposed to continuous steroid use for longer than 1 year.

The data set was complete for all variables, except date of diagnosis (2 missing values), date of wheelchair use (4 missing values), and steroid use at last follow-up (2 missing values). A total of 2 patients, who moved to another Canadian province, were lost to follow-up, and their last available data were used.

The median age at diagnosis for this cohort was 5 years; prenatal diagnosis ranges up to 8 years. A total of 75% of patients were wheelchair users by the end of follow-up; the median age of wheelchair use is 11 years (range: 7–17 years). All patients older than 17 years were wheelchair users. One patient was mechanically ventilated. By the time of follow-up in 2009, 13 patients had died (30%) at a median age of 16 years (range: 14–27 years).

All patients were being treated with steroids, which were started at a median age of 7 years (range: 1–17 years). Steroid therapy used prednisone alone ($n = 5$), prednisone replaced by deflazacort when it became available in 1996 ($n = 13$), and deflazacort alone ($n = 26$). Steroid treatment was started 2 years after diagnosis, and their use preceded wheelchair use by 1 or more years in 86% of patients. At the last follow-up, 39 of 42 (93%) patients remained on steroid therapy ($n = 2$, missing data). Compliance was assessed clinically.

Bisphosphonate therapy had been initiated in 16 patients (36%) between 1997 and 2007, at a median age of 12.5 years (range: 7–23 years) or a median of 9.5 years after diagnosis. Bisphosphonate therapy preceded wheelchair use by 1 or more years in 36% of patients. All patients were treated for a median of 6 years after steroid institution (range: 1–12 years). Bisphosphonate therapy used pamidronate alone ($n = 11$), pamidronate replaced by alendronate ($n = 1$), alendronate alone ($n = 3$), and clodronate alone ($n = 1$). Bisphosphonate use had been discontinued before 2009 in 6 patients who had been treated for a median of 6 years (range: 0.5–10 years). Treatment was discontinued because the patients had matured and their bone density was stable ($n = 3$), because intravenous access was difficult ($n = 2$), and for unknown reasons ($n = 1$). Bisphosphonate use was continuous for the remaining 10 patients who had been

treated for a median of 8 years (range: 2–12 years).

For this cohort of boys with DMD, who have all received at least 1 year of steroid therapy, the prescription of bisphosphonates is remarkable for its association with longevity (Fig 1) ($P = .005$, log-rank test). Approximately 60% of the patients prescribed bisphosphonates were alive at age 24 years, whereas ~60% of the patients who did not receive bisphosphonates lived to the age of 16 years. Equally remarkable is that when the last patient in the "no bisphosphonate" group died at 22 years of age, there still were approximately three-quarters of the patients within the group who received bisphosphonates who survived.

On the basis of the primary finding, 2 supplementary questions were addressed: (1) Was there a dose/time response within the bisphosphonate group? and (2) was there any difference within our data between those who were being treated with bisphosphonates and those who were not?

After a review of the bisphosphonate-treated patients, there was considerable overlap in the duration of treatment between the bisphosphonate-continuous and the bisphosphonate-discontinuous groups (above); therefore, the duration of treatment was reviewed and dichotomized at 6.5 years into 2 equal-sized groups ($n = 8$). Figure 2 demonstrates that there may be a significant therapy-duration effect within this data set ($P = .007$, log-rank test). Shorter durations of bisphosphonate therapy demonstrated intermediary survival between those not exposed to bisphosphonate therapy and those with longer therapy duration. Of 8 patients with at least 6.5 years of bisphosphonate therapy, only 1 patient died at the age of 19 years, whereas the remaining patients continued to thrive at ages 18, 21, 22, 24, 24, 26, and 28 years.

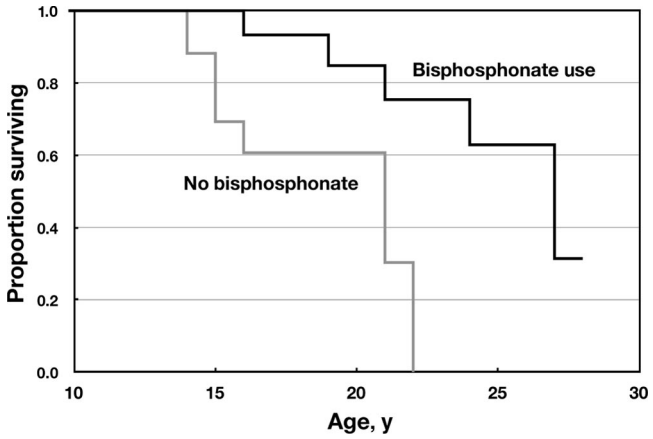


**FIGURE 1**
Survival analysis of a regional cohort of patients with DMD treated with steroids, stratified according to whether bisphosphonates were used ($P = .005$).

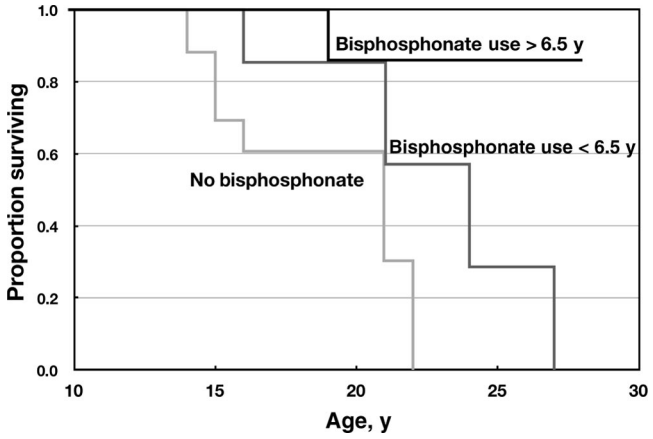


**FIGURE 2**
Survival analysis of a regional cohort of patients with DMD treated with steroids, stratified according to the duration of bisphosphonate use ($P = .018$).

We reviewed the age at diagnosis and age at steroid use in our posthoc analysis and found no difference between those who were and those who were not treated with bisphosphonates. Bisphosphonate users seemed to use a wheelchair at a later age (median 11.5 years [$n = 14$]) than nonusers (median: 10 years [$n = 15$]). If bisphosphonate use preceded wheelchair use, the median age at wheelchair use was 13 years ($n = 5$); if bisphosphonate use followed the wheelchair use, the median age was 11 years ($n = 9$).

We also reviewed what effect the performance of spinal surgery might have had on our results. Only 7 patients from the cohort had spinal surgery. Those with spinal surgery were more likely to have been treated with bisphosphonates (odds ratio: 5.9; $P = .08$, Fisher's exact test). The survivorship of this group did not differ from the group who did not undergo spinal surgery ($P = .69$).

A single patient who was continuously treated with steroids from the age of 7 years, and who had received clodronate from the ages of 12 through 19 years, was electively mechanically ventilated at the age of 22 years and currently is alive at 24 years of age. We repeated our analysis with both terminal and edited data at the age of 22

years without any substantive differences in the results of our survival analysis.

## DISCUSSION

Over the past 25 years, the promise of putative therapies for DMD has resulted in cycles of hope and despair for patients and their families. Currently, the major focus is on strategies that would allow gene replacement, exon skipping, and mutation suppression. Other proposals have included interventions to enhance muscle size and strength without having a specific effect on the pathogenesis of the disease.[8]

Steroid therapy generally is accepted as the only presently available beneficial intervention for DMD. There is agreement that steroid therapy improves strength and slows the progression of weakness, thus delaying the loss of ambulation and reducing the need for major spinal surgery.[6,9] Since its introduction, the natural history of DMD has evolved and most patients have an enhanced life expectancy and quality of life. The improvements that have been ascribed to steroid therapy remain incompletely explained because their method of benefit remains unclear.

Our population is unique because although they seldom chose assisted ventilation, data from this group still showed a trend to healthy survival late into their third decade. We therefore questioned whether steroid therapy alone, or along with some other intervention, might account for this alteration in the clinical course of DMD.

Our data has shown a remarkable association between enhanced longevity and treatment with the combination of both steroids and bisphosphonates compared with steroid treatment alone. This effect is further associated with the duration of bisphosphonate therapy; those treated for longer fared better that those treated for a shorter duration.

Virtually all of our patients chose treatment with steroids. To reduce the risk of steroid-induced osteopenia, we routinely prescribed supplemental calcium and vitamin D. We also monitored bone density with dual-energy radiograph absorptiometry scans. When there was evidence of progressive osteopenia, we offered therapy with bisphosphonates, which are recognized as effective in the treatment of patients with metabolic bone disease.[10]

Bisphosphonates are analogues of endogenous pyrophosphates with a high affinity for the hydroxyapetite of bone. They generally are well tolerated, although adverse effects can involve all major systems, including osteonecrosis of the jaw.[11] The complete mechanism of action of bisphosphonates remains unclear, but as a class they seem to impair osteoclast structure, function, and viability.[12–14] Nonamino bisphosphonates (eg, clodronate and etidronate) act in part by forming nonhydrolyzable adenosine triphosphate analogues within osteoclasts and thus inhibiting key metabolic enzymes involved in cellular growth, differentiation, and activation.[15,16] In comparison, the aminobisphosphonates (eg, alendronate, pamidronate, and zoledronic acid) affect bone resorption through the inhibition of the mevalonate pathway, thereby affecting small signaling proteins (GTPases) that regulate cellular processes.[17–19]

The benefits of the aminobisphosphonates, however, extend beyond their effect on bone, and there is recognized value in other disease states such as metastatic cancer. The effect on the cancer cells may be by directly inhibiting key intracellular signaling pathways, altering growth factor and cytokine levels, and by facilitating apoptosis and antiangiogenesis.[20,21] The majority of the antineoplastic effects have been observed with aminobisphosphonates, which were used in all but 1 of our patients.

In the context of muscular dystrophy, there are several ways that aminobisphosphonates could affect the disease course, but a full analysis of possibilities is beyond the scope of this article. In addition, all the patients in this study also were taking steroids, which raises the possibility of an additive or synergistic effect between agents. Nonetheless, 1 important effect of the aminobisphosphonates is their influence on calcium metabolism. In DMD, the absence of dystrophin leads to a loss of membrane stabilization and increased intracellular calcium concentrations.[22,23] This increased intracellular calcium causes sustained localized contraction, contributing to myofibril pathology[14] and the activation of proteases, such as calpain, which have been implicated in the pathology of muscular dystrophy.[17] Thus, by lowering extracellular calcium levels, the bisphosphonates may increase muscle cell viability.

Aminobisphosphonates also can effect normal apoptosis through several pathways. Prenylation of small GTP-binding proteins (eg, Ras, Rho, Rab) is important for their function in cellular regulation,[18–21,24,25] and inhibition of this pathway by the aminobisphosphonate has been shown to induce apoptosis.[19,20] They also can modify apoptosis by inhibiting the antiapoptotic and pro–proliferative protein kinase C,[26] suppressing urokinase type plasminogen activator uPA,[27] accumulating p21 and p27, and the reducing the bcl-2/bax ratio.[28–30] It is therefore intriguing to speculate that the disease-modifying effect of the aminobisphosphonates in DMD may result from inhibition of pathologic cellular activity such as fibrosis.[31] This possibility is somewhat supported by a recent

study[32] demonstrating that aminobisphosphonates inhibit fibroblast viability in vitro. However, the selectivity of this effect for pathologic tissue remains to be demonstrated.

The indication for prescribing bisphosphonates for our patients with DMD was primarily for their role in bone protection. The added benefit to life expectancy was serendipitous. Although we cannot assign a causative effect to the combination of bisphosphonates and steroids on pronged life expectancy, the association is remarkable.

Our findings represent the experiences of a regional cohort and reflect our regional practice. Patients were selected to receive bisphosphonate therapy on the basis of declining bone density or fractures. It remains possible that there was an unidentified selection bias in choosing patients for bisphosphonate therapy that was independently associated with improved survival. Our demonstration of an apparent therapy-duration effect is only relevant if bisphosphonates are causal in the prolonged survival of our patients.

## CONCLUSIONS

Quasi-experimental data such as this study have the potential to uncover important modifications in the clinical course of patients with DMD. We are unaware of any other data on the effect of bisphosphonate therapy when added to steroids in the treatment of DMD. The improvement in the clinical course of most patients with DMD over the past 15 years has been attributed to the introduction of steroids and early ventilation. Our data would suggest that the addition of bisphosphonates to a patient's steroid regime might have significant beneficial disease-modifying effects. Because this is a retrospective study from a regional cohort, we encourage others to analyze their data in other patient populations. Our findings provide hope to families that treatment with bisphosphonates and steroids may alter the course of DMD as we await more definitive interventions.

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