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Efficacy of Bisphosphonates in the Treatment of Low Bone Density in the Pediatric Population

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ABSTRACT

Low bone density for age is becoming an increasingly recognized problem in the pediatric world. It can be a very tricky condition to properly diagnose and treat. Current treatment guidelines maintain that bisphosphonates are a last resort therapy and are not currently FDA approved for pediatric use. There is data available that supports the use of these agents in children for the treatment of low bone density, as well as secondary benefits, i.e. decreased incidence of insufficiency fractures. However, the majority of the studies includes small population sizes, they are not randomized, or are not compared to a control group. There is clearly a need for further investigation. METHODS: 36 patients from the Carrie Tingley Bone Health Center were included as treatment subjects (received IV and/or PO bisphosphonates) in this retrospective review of pre and post-treatment Dual-Energy X-Ray Absorptiometry (DXA) scans. They were compared to a control group of 30 patients, also with low bone mineral density. Statistical comparison of the differences of bone mineral density, g/cm^2, of each region scanned was done with the Mann-Whitney test. RESULTS: A statistically significant improvement over the control group was found in the lumbar region of patient's receiving treatment. Mean improvement for the lumbar region of the treatment group was 0.091 g/cm^2, compared to 0.032 g/cm^2 for the control group; P-value of 0.03. Average treatment length is 14.5 months, (range 0.5 to 53). The treatment group also demonstrated an 88% decrease in the occurrence of fractures, as well as an average 17% improvement in the R1 region of the distal femur. CONCLUSIONS: Bisphosphonate therapy led to a statistically significant improvement in BMD in the lumbar region and potentially decreases the rate of fractures.

INTRODUCTION

Low bone density for age is becoming an increasingly recognized problem in the pediatric world. It can be a very tricky condition to properly diagnose and treat. It is generally considered an adult disease, but there is increasing evidence that its roots lie in childhood [3]. As Dr. Laura Bachrach states, "the foundation for lifetime skeletal health is established during childhood and adolescence [4]." Low bone density for age is defined as a DXA scan resulting in a z-score less than -2.0 SD from age and gender matched norms [2,3,15]. Pediatric osteoporosis is not defined the same as adult osteoporosis, it not only includes the definition of low bone density for age but also requires additional evidence of bone fragility such as an insufficiency fracture or fragility fracture. A fragility fracture is a fracture obtained from minimal trauma [15]. Most children, and certainly our study population, who suffer from these problems are suffering from a chronic illness and in many cases are severely debilitated.

The maintenance of bone is a dynamic process between rate of formation and resorption. During childhood and adolescence the process of formation predominates and leads to a net increase in bone mass and size [3]. Our peak bone mass is achieved in early adulthood, sometime during the third decade [2,3,4,10]. After this peak, bone mass (in an otherwise healthy individual) begins to slowly decline over the years. The rate of decline is typically constant for males and females, therefore the more bone mass a person is able to achieve earlier in life will help to lower the risk of future complications [4,8]. A potentially encouraging aspect to low bone density and bone loss in an adult is that it may have started as a failure to achieve optimal peak bone density, and this is a significant and preventable problem. Maintaining a healthy bone density and optimizing

your peak bone density is dependent upon both intrinsic and extrinsic factors. The intrinsic factors are unmodifiable and include genetic background, race and ethnicity, and gender [3]. The extrinsic factors are of particular importance because they are modifiable. The extrinsic factors include the following: physical activity, adiposity, diet/nutritional status, hormonal status, illness, medication exposures, excessive alcohol intake, and smoking [3,4,8,10].

Low bone density for age and pediatric osteoporosis has numerous etiologies. The children presented here are not all suffering low bone density from the same cause. Furthermore, despite the numerous illnesses associated with low bone density, not all etiologies share the same reason for their low bone density. Finding low bone density in a child does not tell you if the bone loss is accelerated or if the density is low due to a failure to gain the expected bone mineral density [14]. This difference in mechanisms has the potential to determine the therapy needed to properly treat the low bone density.

The population used in this study is comprised of children who are suffering from a chronic illness that in many cases is very debilitating. The more common etiologies of low bone density for age in our study population are associated with the following disorders: cerebral palsy, corticosteroid therapy, and anticonvulsant therapy. Each of these etiologies in our population has lead to low bone density by a particular mechanism. For example, cerebral palsy patients tend to suffer from low bone density if they are non-ambulatory. Ambulation is necessary for bone health and strength. It is the bearing of ones body weight on the skeleton that improves bone strength [2]. Children on corticosteroids, for various reasons including autoimmune disorders and immunosuppression, suffer low bone density as a side effect of this therapy and the drugs

overall catabolic effects [2,3]. Patients who take anticonvulsants or require multi-agent therapy for seizure control also suffer low bone density because the anticonvulsants will increase the metabolism of vitamin D [2,10], this in effect hinders its ability to increase intestinal calcium absorption and bone formation as a whole is decreased [7].

Calcium and Vitamin D are of extreme importance in the cause and treatment of patients suffering from low bone density. Calcium and Vitamin D play important roles in bone formation [3,7]. Calcium is necessary to maximize and maintain peak bone mass and to minimize bone loss during aging, therefore optimal intake is necessary [3]. Further increasing the demand for calcium are periods of rapid growth, such as infancy and adolescence [3]. Retrospective studies have shown that adequate calcium intake during childhood and adolescence was associated with a lower incidence of osteoporosis in postmenopausal women [3]. Unfortunately, similar data is unavailable for children and adolescents [2]. Nevertheless, adequate intakes of calcium and vitamin D should be provided [2].   Vitamin D is crucial for the effectiveness of calcium and its deficiency can certainly be a cause of low bone density. It is recommended that patients be treated with both calcium and vitamin D simultaneously [3,10]. Vitamin D supplementation may also be most effective for certain etiologies of low bone density [2]. Studies suggest that calcium and vitamin D supplements are an excellent place to start when treating low bone density, and additional medications should be started only when bone density does not improve on calcium and vitamin D supplementation [5].

Bisphosphonates are anti-resorptive agents used to treat low bone density in adults. Currently they are not FDA approved for pediatric use. Their mechanism of action is not completely elucidated but they reduce bone turnover by decreasing bone

resorption. They directly decrease the recruitment and function of osteoclasts and indirectly inhibit osteoclasts by stimulating osteoblasts to produce an inhibitor of osteoclast formation [2]. There is an unfortunate lack of research involving use of bisphosphonates in pediatric cases [2,13,14], most involved a very small population size and were poorly controlled.   Nonetheless, small studies have shown encouraging results with the use of bisphosphonates in children. Other studies have shown that low-dose pamidronate can result in increased bone mineral density in children with a variety of conditions (including: osteogenesis imperfecta, corticosteroird therapy, idiopathic juvenile osteoporosis) [14]. This data has been considered "pilot data" and the need for additional studies has been emphasized [13,14]. The current treatment for low bone density in the pediatric population is supplementation with calcium, vitamin D and/or bisphosphonates, however sufficient data to prove efficacy is lacking.

One study in particular, by Henderson, et. al., [1], looked at the use of bisphosphonates in children with cerebral palsy. The results of this study are very encouraging as they demonstrate an improvement in bone mineral density (BMD) of 89% in the distal metaphyseal femur. His study group is small, but is randomized to include a control group. A control group is an important feature that needs to be taken into account with the pediatric population. Growing children are moving targets, so evaluating their bone mineral density requires that normal growth be accounted for; unfortunately there is an overall lack of data (other than case studies and small population sizes) that truly show an improvement [3,13]. Against comparison to a control group, we too have demonstrated improved BMD with IV or PO bisphosphonate therapy.

METHODS

Approval was obtained from the University's internal review board to conduct a retrospective review of available data where both a pretreatment bone density scan and a post-treatment, follow up scan is performed. The subject population is the pediatric population at the Carrie Tingley Hospital (CTH) who have undergone Dual-Energy X-Ray Absorptiometry (DXA) scanning for clinical reasons, and whose scans indicated low bone density based on age matched databases used for the DXA scanning. Scans were performed between 2003 and 2008. Those included have had both their pretreatment and follow up scan performed at the Carrie Tingley Bone Health Center. Furthermore, the patients included were only those who consented to have their data used in research. All scans were performed by a certified DXA technologist using a Hologic Delphi W densitometer (Hologic, Inc, Bedford, MA) using pediatric software for the spine, hip (based on publications of Faulkner and Southard) and lateral distal femoral scan. The distal femoral scans include three regions: R1 – cancellous bone, R2 – mixed cancellous and cortical bone, and R3 – cortical bone. To ensure consistency between DXA scans the same machine was used for the pre and post scans.

Data was extracted from the dictated report and included the patient's past medical history, past surgical history, current medications, supplementation, ambulatory status, fracture history and of course, the bone densities of the various regions scanned. Similarly, data for a control group was established. The control group patients met the same inclusion criteria as the treatment group. Efforts were made to form a control group of patients whose primary medical conditions mirrored those of the treatment group.

Again, patients eligible for inclusion in the control group were those who consented for their data to be used in research.

A comparison of each region scanned was done and the difference in bone mineral density between the pretreatment and post treatment scan was recorded. The difference reflects the changes in bone mineral density, g/cm^2, over the interval. This was done for all regions scanned. It was the difference of each region that underwent statistical analysis.

Summary statistics were calculated using standard methods. Mean bone mineral density values were compared for treatment and non-treatment groups using the Mann-Whitney test. All calculations were performed on an Intel Pentium-based microcomputer with a clock speed of 1.8 GHz. Statistical calculations were made with Statgraphics Centurion XV version 15.2.06 (StatPoint, Inc., Herndon, VA). Data management was carried out using Microsoft Excel 2002 (Microsoft Corporation, Redmond, WA). Two tailed tests and a Type I error rate of 0.05 were employed throughout.

RESULTS

Forty-three patients were identified as candidates for inclusion in the treatment group. At the end of the study period there were 36 patients with data available for analysis. Of the initial 43 identified, 4 patients who received treatment did not have a follow-up scan available. Two patients did not have the correct medical record number recorded and their data was unable to be retrieved. One patient's record was too unclear to determine a treatment period and was thought to be too unreliable for inclusion. The

control group is made up of 30 patients who were identified to have low bone mineral density and similar medical histories as those comprising the treatment group.

The patient's included in the treatment group have the following characteristics. The average age of the patients is 11.9 years old, with a range from 2yrs to 21years old. The average treatment length is 14.5 months, with a range from 0.5 to 53 months. The average interval between DXA scans is 16 months, with a range from 4 to 42 months. The bisphosphonate therapy received was either alendronate (PO) or pamidronate (IV). Twenty-seven patients received solely alendronate therapy, 5 patient's received only pamidronate therapy, 3 patient's began alendronate therapy and were switched to pamidronate therapy and 1 patient was begun on pamidronate therapy and switched to alendronate. The control group has an average age of 9.2 years old, with a range from 1 to 16 years old. The average interval between DXA scans for the control group is 17.9 months, with a range from 6 to 44 months. Please see Table 1 for a more in depth comparison of the treatment and control groups.

The most common medical conditions found in the patients comprising the treatment group are cerebral palsy with a seizure disorder and osteogenesis imperfecta and other dysplastic syndromes. For the control group, the most common medical conditions for these patients are cerebral palsy with seizure disorder and long-term corticosteroid therapy and malignancy. Please see Table 2 for a comparison of the patient's medical histories.

Results of the comparison of the difference in bone mineral density, g/cm^2, of the multiple regions scanned yields the following result. The only region of the treatment group found to have a statistically significant improvement over that of the control group,

was the lumbar region. Mean improvement (difference of BMD in pre/post scan) for the

lumbar region of the treatment group was 0.091 g/cm^2, compared to 0.032 g/cm^2 for the

control group; P-value of 0.03. The remaining regions compared did not demonstrate any

statistically significant improvements in BMD in the treatment group compared to the

improvements made by the control group. Please see Table 3 for a summary of the mean

improvements of each region. Table 3 also presents the average percent change for each

region scanned for both groups. This calculation is a straight average of all the results

available in each group for each region. The percent change was not used in any

statistical analysis.

DISCUSSION

It has been found that the most useful regions for interpretation on pediatric DXA

scans are the distal femora and the lumbar region [15]. As the results to this study would

indicate, there was a statistically significant improvement in the lumbar region of the

treatment group. This would suggest that bisphosphonate treatment was of benefit to

these patients; that the improvement seen was more than expected for bone mineral

density increases related to normal growth. This is established by the comparison to the

control group, a group of children with similar medical histories, but whose increases in

bone mineral density are best explained by growth. An important point of discussion is

necessary for this result. The number of patients in the control group who were receiving

long-term corticosteroid therapy was much greater than that of the treatment group, (4

patients in the treatment group versus 11 in the control group). This is important because

the decreases in bone mineral density associated with corticosteroids are most

pronounced in the spine. This makes true interpretation of the results more difficult, as it is possible the improvement the treatment group demonstrated was confounded by the expected losses in the lumbar regions of a high percentage of the control group.

Although none of the other regions studied may have shown statistically significant improvements, that might suggest more BMD was gained than expected for growth, there is evidence that would still support the use of these agents in the pediatric population. If the average percent changes were looked at for each region, with specific focus on the distal femora, the treatment group experienced greater changes almost across the board. This too is hard to definitively say if normal growth or intervention is the primary cause of improvement. When bisphosphonates are used it is evidenced by the presence of a "bisphosphonate stripe" in the DXA scan [15]. Most commonly seen in the R1 region of the distal femur[15]. The scans of the vast majority of the patient's did comment on the presence of this strip. This is also seen by the large percent improvement of the R1 region alone, combined left and right of 17.4% versus 1.1% in the control. The R2 and R3 regions also show higher percent changes, but not to the same significance. This leads me to believe that the improvements seen in the patients who received therapy were not due to normal growth alone, but are a direct effect of bisphosphonate therapy.

In the treatment group, review of the patient's record demonstrated that the two main indications for initiation of bisphosphonate therapy are, (1) the history of insufficiency fractures or (2) the patient has had serial scans demonstrating a loss of bone mineral density. Generally, the loss was significant enough to place the patient at great risk of fragility fractures. This history suggests that many of the patients were not staying

with a normal growth curve, demonstrated in the reports by worsening z-scores. With the results indicating overall improvement in the BMD of the patients on therapy, it would be favored that the bisphosphonates were in part responsible.

Another important variable in the characteristics of the treatment versus the control group is the ambulatory status of the patients. The majority, 56%, of the treatment group is non-ambulatory. This has profound influence on a person's BMD, as weight-bearing activity promotes increased BMD. The control group is 63% ambulatory, almost double that of the treatment group (36.1% ambulatory). This important difference could potentially minimize the observed effect of bisphosphonate therapy in a larger non-ambulatory population.

Limitations to the study include a restricted patient population available for study, the retrospective chart review format, and the reliance on patient recall, mainly patient caregiver recall, for some of the data obtained. The limited study population for both groups stems from the inclusion of only "Blue Star" patients, again that is those who consented to have their data used in research. A larger treatment group certainly exists at Carrie Tingley Hospital. The retrospective nature of the study did not allow active pursuit of patient compliance with treatment and follow-up DXA scanning. The patient's caregiver recall of medications and supplementations is another area were inherent limitations exist. For example, the data on those receiving calcium and/or vitamin D supplementation was recorded from the DXA report, which reflects the patient survey done prior to the scan. The majority of patients simply stated, "yes/no" or left the section blank. This made it impossible to know frequency and dosing of these supplements. If the section was left blank, it was assumed that no supplementation was being given. Best

efforts were made to identify true treatment intervals by reviewing the patient's medication histories and review of primary care physician notes.

Furthermore, there was no randomization to who received treatment or at what dosing. The dose of the bisphosphonate was determined by the treating physician and was generally weight based and different for all subjects. The only consistency was the use of a 1ml/kg dosing of the IV pamidronate therapy.

One important result discovered that could be a result of the bisphosphonate therapy was the incidence of fractures in the treatment patients, both before and after receiving therapy. There is a study done by Sholas, et al., [17] that also supports this conclusion, as his data demonstrates that those who received oral alendronate therapy displayed a decrease rate of fractures after receiving the therapy. Twenty-nine of 36 patients had a fracture history prior to starting bisphosphonate therapy. Of these 29 patients, 25 of them were classified as pathologic, insufficiency fractures. This was obtained also from the patient's DXA report and other clinic notes. After receiving therapy, 3 patients were noted to have experienced further fractures over the interval studied. One of the patients was then changed from PO to IV therapy, but it is unknown if any further fractures were suffered. This demonstrates that 88% of patients who received treatment did not suffer further pathologic fractures. This is important, as it would lead to an improved quality of life for the patient.

The results to this study are not without clinical implications. Despite the fact that a statistically significant improvement was not seen in all regions studied, secondary measures would suggest usefulness in this population. The results demonstrate a benefit on reduction of the rate of fractures these patients are experiencing. As stated previously,

one of the current reasons to begin bisphosphonate therapy is a history of insufficiency

fractures. Bisphosphonate therapy appears to work to prevent future fractures. However,

further investigation on the efficacy is needed, especially with larger study populations.

Studying these agents in a more controlled environment, i.e. one where compliance and

medication administration is optimized and reliable, as well as optimization of calcium

and vitamin D administration. Comparatively, a low percentage of the treatment group

was receiving calcium and vitamin D supplementation. Calcium supplementation was

reported in 56% of the treatment group versus 70% of control group. Vitamin D

supplementation was reported in 3% of the treatment group versus 27% of the control.

The magnitude of the affect this difference has made on the results of this study is

uncertain. Nevertheless, bisphosphonate use in the pediatric population can provide

important quality of life outcomes, with demonstrated improvements in bone mineral

density.

ACKNOWLEDGMENTS

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TABLES

Table 1. Comparison of Treatment and Control Groups

	Treatment Group	Control Group
Avg Age, yrs (range)	11.9, (2-21)	9.2, (1-16)
Gender	Male: 56%, (20/36) Female: 44%, (16/36)	Male: 57%, (17/30) Female: 43%, (13/30)
Avg Treatment Length, months (range)	14.5, (0.5-53)	N/A
Avg Interval between DXA scan, months (range)	16, (4-42)	17.9, (6-44)
Ambulatory Status	Yes: 36.1%, (13/36) No: 55.6%, (20/36) Minimal: 8.3%, (3/36)	Yes: 63.3%, (19/30) No: 33.3%, (10/30) Minimal: 3.3%, (1/30)
% With Pathologic Fracture, (#)	69.4%, (25/36)	13.3%, (4/30)
% With Gastric Tube, (#)	41.7%, (15/36)	20%, (6/30)
% With Calcium supplementation, (#)	55.6%, (20/36)	70%, (21/30)
% With Vit. D supplementation, (#)	2.8%, (8/36)	26.7%, (8/30)
% Taking Multivitamin supplementation, (#)	63.9%, (23/36)	53.3%, (16/30)
% Taking other dietary supplementation, (#)	36.1%, (13/36)	53.3%, (16/30)

Table 2. Included Patient's Medical Histories, # of patients

	Treatment Group*	Control Group**
Cerebral Palsy	3	3
Seizure Disorder	3	3
Cerebral Palsy with Seizure Disorder	8	6
Osteogenesis Imperfecta and other Dysplastic syndromes	7	7
Paralysis	6	2
Corticosteroid therapy or Malignant Processes	4	11
Other	6	2

*Sum of patients is 37; one patient was included in both the CP and paralysis group
**Sum of patients is 34; 1 patient is both seizure and autoimmune, 1 patient is seizure and other, 1 patient is CP and paralysis, and 1 is both autoimmune and dysplasia.

Table 3. Results

DXA Region	Mean Pre BMD	Mean Post BMD	Treatment Group*, g/cm²	Avg % Change - Treatment	Mean Pre BMD	Mean Post BMD	Control Group*, g/cm²	Avg % Change-Control	P-value
Lumbar	0.533	0.625	0.091	18.9%	0.495	0.527	0.032	6.7%	***0.03***
L Hip	0.574	0.603	0.029	4.3%	0.529	0.550	0.020	4.6%	0.75
R Hip	0.618	0.697	0.079	12.8%	0.541	0.579	0.038	7.5%	0.15
L Femur - R1	0.478	0.525	0.047	13.5%	0.520	0.546	0.026	4.8%	0.46
L Femur– R2	0.482	0.515	0.033	9.0%	0.575	0.604	0.028	7.6%	0.77
L Femur – R3	0.566	0.622	0.056	10.7%	0.632	0.713	0.080	22.6%	0.56
R Femur – R1	0.428	0.495	0.067	21.3%	0.522	0.515	-0.007	-2.6%	0.09
R Femur – R2	0.472	0.505	0.034	8.8%	0.577	0.604	0.027	6.2%	0.50
R Femur – R3	0.569	0.599	0.030	5.3%	0.699	0.733	0.034	5.2%	0.92

*Values presented are the mean values of the difference of BMD in each group.