Changes in Bone Turnover Markers During Bisphosphonate Treatment in Puberty

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Introduction

Bisphosphonates have become used routinely to treat children with osteopenia due to chronic disease or glucocorticoid treatment. This class of drugs has been approved for use in adult osteoporosis, hypercalcemia of malignancy, and glucocorticoid-induced osteoporosis where demonstrated beneficial effects on bone density and subsequent fracture rate have been noted. In the pediatric population, in contrast, definitive benefit for fracture reduction from chronic illness-induced osteopenia is less well established. Fracture activity persists even after treatment -- a reduction in fracture rate can be difficult to convincingly demonstrate (1).

To avoid the need to demonstrate changes in fracture rate, alternative markers of benefit of bisphosphonate treatment have been examined. Bone density through DXA scanning and bone metabolic turnover markers such as alkaline phosphatase, procollagen type 1 N-terminal propeptide (P1NP), N-telopeptide (NTX) have been monitored in various reports. In many pediatric patients, bone density is difficult to assess due to skeletal deformity or contractures, or due to placement of orthopedic metallic rods which alter DXA results. Measurement of bone metabolic markers may be an alternative option for monitoring bisphosphonate treatment (2).

Whether the metabolic turnover markers are of benefit for monitoring progress of bisphosphonate treatment is uncertain from previous studies with some describing interpretable effects (3,4), but others suggesting alternative explanations for changes such as the entrance into puberty. NTX is most suppressed during the initial treatment year, with less effect noted subsequently (5).

References

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Methods

Clinical cases were selected for those with an extended duration of pamidronate treatment. The patients represent different underlying diagnoses, including osteogenesis imperfecta of differing severity, idiopathic osteopenia associated with chromosomal anomalies (unbalanced translocation of 9P with extra material on chromosome 20), and both male and female patients.

Results

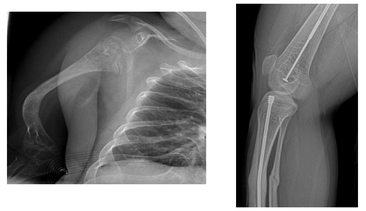
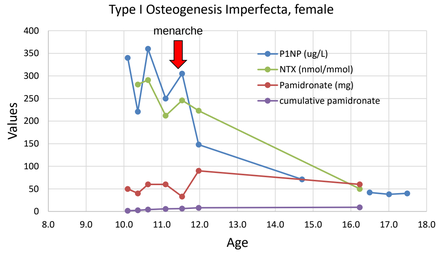
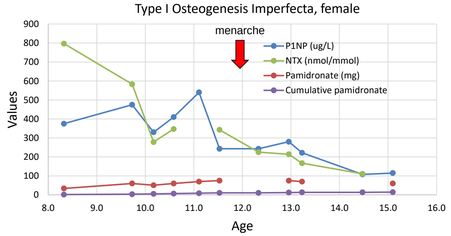
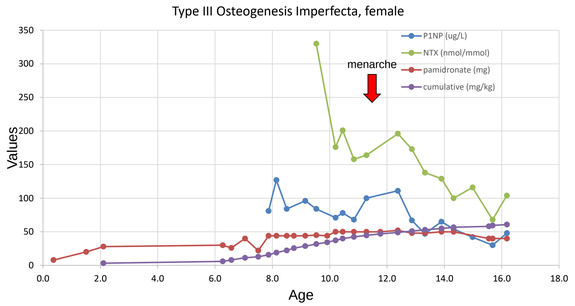
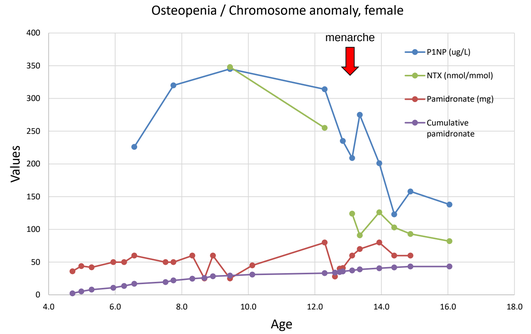


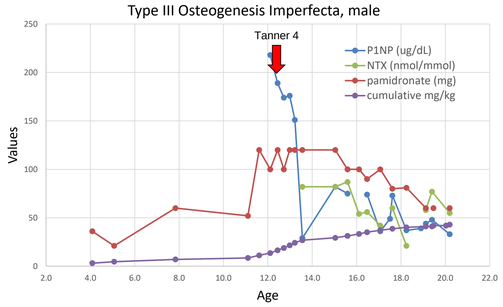
Figure: Type III OI with deforming bone curvature (left). Type III OI showing rod placement and hyperdense lines following many courses of pamidronate (right).











Discussion

The bisphosphonates pamidronate and zoledronate have been used for treatment of pediatric osteopenia or bone fragility in our practice for greater than 10 years. As have others, we have struggled to define parameters that can help us assess effectiveness of bisphosphonate treatment. Most frequently, we have used P1NP, an anabolic marker, and NTX, a resorptive marker, as measures of bone metabolic activity. This case series review of 5 patients was performed in attempt to better define the clinical utility of those bone turnover markers.

Sequential measurement of P1NP and NTX was recorded during the time of bisphosphonate treatment, which ranged up to 16 years. P1NP and NTX levels remained relatively stable up until the time of puberty (menarche in adolescent girls) at which point levels visibly declined.

Outside of the pubertal transition, the bone turnover markers P1NP and NTX did not show a clear long-term response to sequential years of pamidronate infusion. This result differs from the observed suppression of bone markers suggested by other studies. Importantly, the duration of observation of the clinical cases reviewed here was approximately 4 to 10 years while previous reports of changes in bone markers typically have been limited to a few years of observation.

The use of bone markers to assess bone metabolic activity as affected by bisphosphonate can be limited by other factors which affect bone turnover such as puberty, intercurrent fractures, or orthopedic surgical intervention. Additionally, there is a circadian rhythm as well as a feeding effect on marker levels. Bone markers in this study were obtained as "convenience" samples, at the time of scheduled bisphosphonate infusion. Although preferred to be drawn fasting and in the AM, practical scheduling issues prevented consistent timing of sample collection. Differences in the timing of blood or urine sampling may have increased variability in bone marker values. However, the decrease in markers appearing after the onset of puberty appears qualitatively much more significant than fluctuation prior to the pubertal changes.

Summary

Sequential measurements of P1NP and NTX were recorded during an extended duration of bisphosphonate treatment which crossed the entrance into puberty. P1NP and NTX levels remained relatively stable up until the time of puberty (menarche in adolescent girls) at which point levels declined greatly. In retrospect, the P1NP and NTX levels contributed very little to monitoring efficacy of bisphosphonate treatment. Instead, the bone turnover markers indicated a transition point in bone metabolism at puberty. Reliance on bone turnover markers as a measure of bisphosphonate action near the time of pubertal maturation may be misleading.