Narrative Review

Bisphosphonate Treatment for Children With Disabling Conditions

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Fractures are a frequent source of morbidity in children with disabling conditions. The assessment of bone density in this population is challenging, because densitometry is influenced by dynamic forces affecting the growing skeleton and may be further confounded by positioning difficulties and surgical hardware. First-line treatment for pediatric osteoporosis involves conservative measures, including optimizing the management of underlying conditions, maintaining appropriate calcium and vitamin D intake, encouraging weight-bearing physical activity, and monitoring measurements of bone mineral density. Bisphosphonates are a class of medications that increase bone mineral density by inhibiting bone resorption. Although bisphosphonates are commonly prescribed for treatment of adult osteoporosis, their use in pediatric patients is controversial because of the lack of long-term safety and efficacy data.

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INTRODUCTION

Growing awareness of bone health in pediatric patients has increasingly led practitioners to evaluate and treat children for low bone mineral density (BMD), including children with either primary bone conditions or other disabling conditions that lead to secondary osteoporosis. Bisphosphonates are a staple of osteoporosis treatment and have been used extensively in adults for conditions associated with bone fragility [1]. The literature pertaining to adults supports improvement in clinical outcomes with the use of bisphosphonates [2,3]; however, because of differences in pediatric skeletal metabolism, caution is required when attempting to extrapolate adult data to children. This review will apprise practitioners of the current literature regarding bisphosphonate treatment in children with disabilities, address controversies regarding safety and efficacy, and discuss future directions for improving the knowledge gap in treatment of children with skeleton-related conditions.

BONE MODELING AND REMODELING

Bone remodeling is a continuous, lifelong process in which mature bone is broken down by osteoclasts and new bone is formed by osteoblasts. This process underlies BMD changes in adults, as well as fracture healing and repair of skeletal microdamage. Tight coupling of bone formation and resorption is required to maintain skeletal homeostasis. In childhood, skeletal growth occurs as the result of strictly regulated uncoupling of bone formation and resorption at specific sites, termed "bone modeling" [4]. On the outer periosteal surface, the formation of bone leads to an increase in bone size, driven by genetic factors and mechanical loading forces [5,6]. Bone resorption expands the marrow cavity on the inner periosteum and sculpts the bone on the outer surface, establishing the widened, funnel-like shape of the metaphyses [7,8]. The net result of bone modeling is an overall increase in bone size and mass.

In many skeletal disorders the bone remodeling cycle is disrupted, leading to a net loss of BMD. Treatment strategies include altering the cycle to either inhibit osteoclast activity

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or promote osteoblast activity, with the goal of shifting the balance in favor of bone formation.

BISPHOSPHONATES

Bisphosphonates are a class of drugs that increase BMD by inhibiting osteoclast activity. They are synthetic analogs of pyrophosphate, an endogenous regulator of bone metabolism. In bisphosphonates, the central oxygen atom in pyrophosphate is replaced with a carbon atom (Figure 1). All bisphosphonates share a common phosphorus-carbon-phosphorus motif with 2 side chains (R1 and R2 in Figure 1). The R2 side chain determines the chemical properties of the drug and distinguishes individual types of bisphosphonates. This chemical structure affords a high affinity for calcium hydroxyapatite, permitting rapid and specific targeting of the skeleton.

Bisphosphonates have 2 classes with distinct mechanisms of action [9]. The early compounds that do not contain nitrogen (ie, clodronate, tiludronate, and etidronate) are incorporated into the terminal pyrophosphate moiety of adenosine triphosphate, forming a nonfunctional molecule that disrupts osteoclast metabolism and apoptosis. Newer, more potent bisphosphonates that contain nitrogen (ie, pamidronate, alendronate, ibandronate, risedronate, and zoledronate) inhibit a key enzyme, farnesyl pyrophosphate synthase, in the mevalonic acid pathway. Inhibition of this enzyme blocks posttranslational modification of small guanosine triphosphatases such as Ras, Rho, and Rac, which act as signaling molecules for key components of osteoclast function. These effects disrupt osteoclast activity, reduce osteoclast recruitment, and induce apoptosis [10].

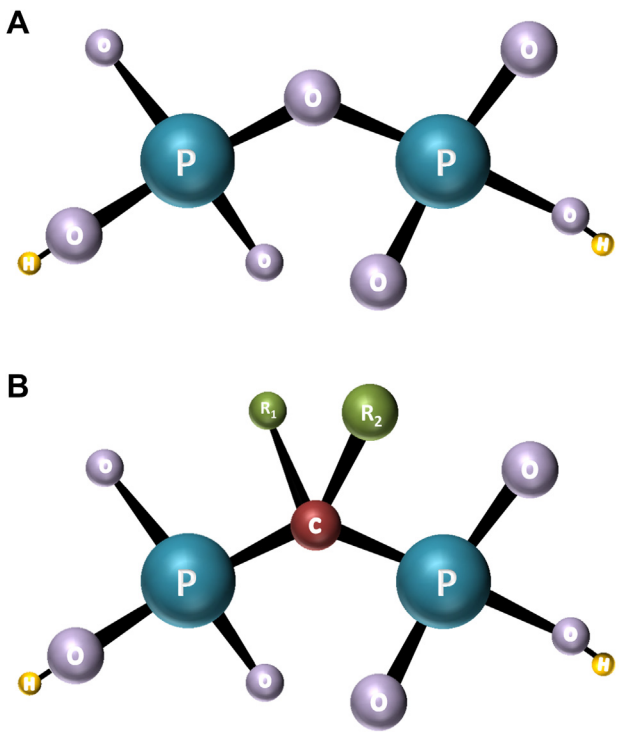

Figure 1. Chemical structure of pyrophosphate (A) and bisphosphonates (B). P = phosphorus, O = oxygen, H = hydrogen, C = carbon, R = side chain.

The bioavailability of oral bisphosphonates is low, with an estimated absorption rate of 0.6%−2.5% [11]. Approximately 40%−60% of each dose is incorporated into bone, and the remainder is excreted unchanged in the urine [11]. The terminal half-life of bisphosphonates in bone is estimated to exceed 10 years, reflecting release from the skeleton with bone remodeling [12]. Bisphosphonates have been detected in the urine of children up to 8 years after use of the drug is discontinued, consistent with prolonged skeletal release after the completion of treatment [13].

LOW BMD IN CHILDREN

Assessment of BMD in Children

As in adults, the most commonly used method to asses BMD in children is dual x-ray absorptiometry (DXA). This modality offers practical advantages, including wide availability, rapid scanning time, and low use of radiation. In children the posteroanterior spine and total body minus the head are the most accurate and reproducible sites and should be used preferentially [14]. DXA results are expressed as z scores calculated from age, gender, and ethnicity-adjusted norms, and should be derived from normative databases specific to the brand of densitometer used [15].

Children with disabilities present unique challenges with regard to evaluation by DXA [16,17]. Contractures may prevent patients from lying in the proper fully supine position. Lumbar spine evaluation may be hindered by scoliosis and the placement of surgical hardware. Proximal femoral anatomy may likewise be disrupted as a result of hip dysplasia, subluxation, or dislocation, which may require placement of surgical hardware. The lateral distal femur is frequently used as an alternate imaging site in these patients, offering the advantages of easier positioning and rare interruption by surgical hardware. This area also offers the potential for subregional analysis, where bone may be separated into primarily cortical and trabecular compartments based on its location [16].

A number of limitations inherent in DXA technology complicate its application to children. Because BMD is greatly influenced by sex steroids, children with early or delayed puberty may be compared with children at a different pubertal stage. A primary limitation is the inability of DXA to account for bone depth. DXA approximates BMD by quantifying the bone mineral content of a 2-dimensional area of interest. Areal BMD is thus expressed in grams of mineral per centimeters squared, as opposed to true