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SHORT COMMUNICATION

Bisphosphonates in Children with Osteogenesis Imperfecta may Improve Bone Mineralization but not Bone Strength. Report of Two Patients

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INTRODUCTION

Osteogenesis imperfecta (brittle bone disease) is a genetic disorder which affects fewer than 2,000 children in Argentina and about 20,000 in the USA. Its low incidence qualifies the disease as 'orphan', thus only limited pharmacological data have been obtained. Its main clinical expression is the fragility of bones which easily deform and break. Most forms of the disease are due to the poor quality of type I collagen, caused by mutations in the genes that encode the two protein components (pro-α1 and pro-α2 chains). At present there is no effective medical therapy. The pharmacological benefits of bisphosphonates in osteogenesis imperfecta have not been established.

We herewith report two patients studied by bone dual energy X-ray absorptiometry (DEXA), and recently by peripheral quantitative computerized tomography (pQCT). The latter includes quantitative assessments of volumetric bone density and of architectural variables such as bone diaphyseal area or cross-sectional moments of inertia. The system provides a bone stability index, also called the strain-stress index (SSI), which is a function of both density and architectural variables[1-3] and has been proved to be an indicator of bone strength (resistance to torque, SSIp, or bending, SSIx and SSIy, forces applied on the measured bone section).

These two patients are part of a phase I/II trial, aimed to obtain dynamic data of bone metabolism from a small sample of affected children treated with disodium pamidronate (APD)[4], and they have now been analyzed by pQCT.

KEY WORDS

bone mass, quantitative computerized tomography, bisphosphonate, osteogenesis imperfecta

PATIENT REPORTS

The first patient has osteogenesis imperfecta type III. He is currently 8 years old, weighs 22.0 kg, and is 112 cm tall. He had four fractures at birth (February, 1989), sat at the age of 15 months and now stands with supports. He has blue sclerae, hyperlaxity of joints, limb bowing, kyphosis, scoliosis, hip luxation and no dentinogenesis imperfecta. Oral APD treatment was started at 2.5 years (June, 1991) with his parents' consent, at the dose of 100 mg (1 enteric coated soft capsule; IG-7913, Gador SA, Buenos Aires) once every four days, in fasting conditions, plus 0.5 g of elemental calcium/day. Bone biochemical markers remained within the normal range during the period of treatment with APD (data not shown). Lumbar bone mineral density (BMD), performed with a DEXA Hologic QDR 1000 X-ray absorptiometer, was 0.377 g/cm^2 (z-score -2.0; 79% of normal value for age) at the beginning of therapy. It increased to 0.454 g/cm^2 after 2 years (+20.4% from basal). The BMD gain in the third year was smaller: 0.548 g/cm^2 (z-score -0.15; 98% of normal value for age), and in the fourth year even less, 0.550 g/cm^2 (z-score -0.64; 93% of normal value for age). Therefore lumbar

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BMD reached almost normal values but remained steady during the last months. APD was stopped (September, 1995) after 4 years of uninterrupted administration, continuing only with calcium and vitamin D supplementation. The first post-APD lumbar BMD was 0.607 g/cm^2 (z-score -0.09; 99% of normal value for age). During APD treatment no further fracture occurred. Nevertheless, due to severe progression of scoliosis, T3, T4 and L5 vertebrae were surgically fixated. In June 1997, he was studied by pQCT (XCT 3000, Norland-Stratec, Pforzheim). Cortical volumetric BMD (vBMD), cortical + subcortical, trabecular and total mineral densities were assessed at radial and tibial shafts (33% length from distal and proximal joints, respectively). Section areas and stability indexes, the strain-stress index (SSI) including both polar (SSIp) and sectional (SSIx) bone axes were estimated with the same equipment. Table 1 shows the main data obtained. It can be clearly seen that bone mineralization is normal in the long bones, similar to the previous assessment by DEXA of the spine. However, pQCT showed that the stability indexes are very low, meaning that the bones are still fragile, having poor resistance to torque or bending forces.

TABLE 1

Mean variables assessed by pQCT in two children with osteogenesis imperfecta treated long term with disodium

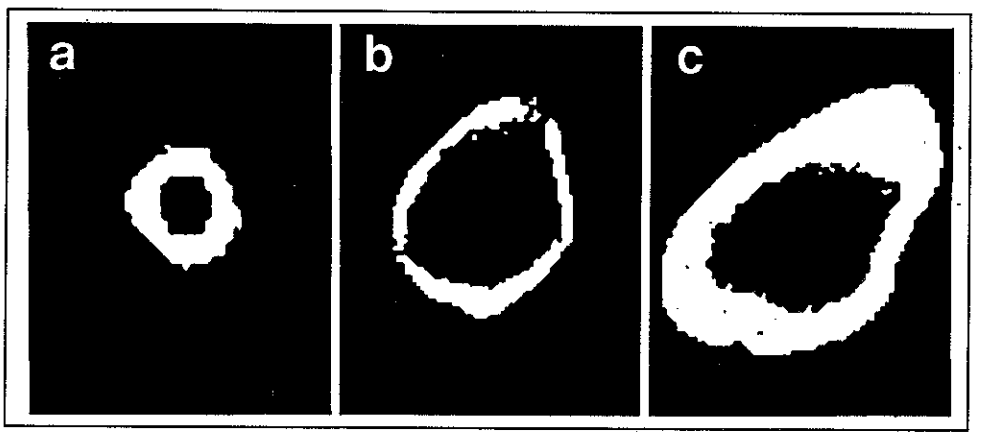
VARIABLE	UNIT	PATIENT 1	PATIENT 2
Age	years	10	8
Radial shaft			
Cortical vBMD [1,2]	mg/cm^3	1102.9 (-0.3%)	998.9 (-9.8%)
Cortical + subcortical vBMD	mg/cm^3	943.5	730.4
Trabecular vBMD	mg/cm^3	701.3	621.1
Total vBMD	mg/cm^3	809.6	681.4
SSIp [2]	mm^3	43.0 (-74.7%)	40.2 (-74.9%)
SSIx	mm^3	23.8	28.9
SSIy	mm^3	25.7	19.8
Cortical area [1]	mm^2	21.0	20.5
Tibial shaft			
Cortical vBMD [1,2]	mg/cm^3	1078.4 (+ 4.5%)	1001.1 (-1.9%)
Cortical + subcortical vBMD	mg/cm^3	922.0	714.7
Trabecular VBMD	mg/cm^3	611.3	520.6
Total vBMD	mg/cm^3	783.5	627.4
SSIp [2]	mm^3	65.3(-93.4%)	87.6 (-88.9%)
SSIx	mm^3	33.7	60.7
SSIy	mm^3	35.3	34.5
Cortical Area [1]	mm^2	28.4	10.0

[1] Data integrated with a density threshold of 900 mg/cm^3.
[2] Percentage of age-adjusted mean values for a healthy population (preliminary data).

The second patient also has osteogenesis imperfecta type III. He is now 10 years old, weighs 14.6 kg, and is 91.2 cm tall. He was born in September, 1986 with two fractures. He sat at the age of 12 months and now stands with supports. He has blue sclerae, hyperlaxity of joints, limb bowing, kyphosis, scoliosis, suffered 13 fractures before he was 7.5 years old and has dentinogenesis imperfecta. Biochemical tests showed hypercalciuria with normal values of PTH. In April, 1994 he started receiving APD infusions, 5 mg/day, during 4 consecutive days, after obtaining his parents' consent. Five cycles were repeated during the first year and in November, 1995 he started on oral APD, 300-400 mg per week, being currently under treatment (3.3 years of uninterrupted administration). During APD administration he suffered four new fractures. His scoliosis has progressed and surgical fixation is programmed. Lumbar BMD showed severe osteopenia, 0.214 g/cm^2 (z-score -5.6; 35% of normal value for age) at the beginning of APD therapy. It increased to 0.264 g/cm^2 after the first year (+23.4% from basal, during the intravenous treatment). The BMD in the second year was of 0.262 g/cm^2 (z-score -6.9; 45% of normal value for age), and femoral neck BMD was also very low, 0.141 g/cm^2. During his third year of therapy, pQCT data (Table 1) showed good cortical mineralization of the radial and tibial shafts, but low SSI. Figure 1 shows the sectional area, cortical vBMD and SSIp at the tibial shaft compared with the images of two normal children (from Roldán *et al.*, pQCT preliminary normal curve of values in Argentine population, unpublished).

DISCUSSION

While bone metabolism seems to be normalized with APD treatment, in the long term apparent lumbar BMDs tended to increase toward normal in one patient and showed little improvement in the second. The different performance can be attributed to individual skeletal usage, the former child having better mobility. Cortical volumetric BMDs at the



Density (mg/cm^3)	1027.5	950.3	1050.1
Area (mm^2)	35.2	145.2	325.1
SSIp (mm^3)	65.3	868.9	2176.3

Fig. 1: pQCT partial analysis of the tibial shaft from (**a**) a 10 year-old child with osteogenesis imperfecta, treated during 3.3 years with pamidronate, compared to (**b**) a healthy untreated child of the same age, and (**c**) a healthy boy 16 years old. Notice that while cortical volumetric bone mineral densities (vBMD) are almost similar, the resistance to torque (SSIp) indexes, and sectional areas, are several times diminished in the affected child. Cortical areas have been integrated with a density threshold of 710 mg/cm^3.

tibial midshaft were found within the normal range, but bone resistance to torque and bending were highly depressed in both patients. Consequently, fracture risk persists. These data suggest that while the mineral properties of a bone can be improved by bisphosphonate administration, the adaptive architectonic changes of growing bones do not progress efficiently in these patients.

In children with osteogenesis imperfecta, the quality of bone tissue, and therefore their biomechanical competence, is affected by both the abnormal synthesis of collagen fibers and the concomitant high bone turnover, as shown by *in vivo* tetracycline labeling. Although bone mineral density is much lower than in normal children, high values of bone formation assessed by biochemical markers are frequently reported. The high bone turnover is interpreted as a defective repair mechanism, triggered to replace the incompetent tissue. This is by itself a cause of rapid accumulation of tissular errors and loss of critical bone architecture. APD is an agent that acts selectively on sites of increased bone destruction, partially inhibiting the resorption process. As bone resorption and formation are coupled processes, the latter is also lowered. It is speculated that under low bone turnover conditions, the reparative process may proceed with fewer matrix errors, and thus preserve bone structure. This may also reduce bone fragility (fractures and deformations), allowing a less severe evolution of the disease.

Apart from the above-mentioned argument, APD was chosen due to previously published patient reports on osteogenesis imperfecta[4-6], its known positive effects on bone mineral density in adults[7] and experimental biomechanical properties, i.e. improved load resistance and material properties of bone[8]. Moreover, it has been recently proved that natural mechanically induced bone formation is not hindered by APD[9] and that the compound does not adversely interfere with cartilage growth and calcium homeostasis, even when given for protracted periods[5]. The particular formulation used avoids drug exposure to the sensitive mucosae of the esophagus and stomach[10]. The above are all significant conditions to guarantee a positive benefit/risk ratio in these children.

APD has shown its ability to improve lumbar apparent BMDs in children with osteogenesis imperfecta during long term treatment[11]. Moreover, in these two children cortical vBMD was found within normal values after treatment. However, the impact on fracture rates and/or the prognosis of the disease cannot yet be determined. The SSIp and SSIx indexes were very low, strongly suggesting that the bones of these two children continue to be fragile, apparently due to their low sectional area development (Fig. 1), an effect that can be attributed to inhibition of the diaphyseal internal remodeling. It can be suggested that even if bone section geometry does not improve, according to the adaptative requirements of growth, single bone mass gain is of relative value in these patients.

Nevertheless, it has been proved that the fracture rate can be reduced to a certain extent with APD treatment in children with osteogenesis imperfecta[11], who generally live under restricted conditions of mobility. In order to achieve a better quality of life (and supporting a greater mechanical challenge), a greater bone strength should be acquired by improving the architectural parameters as well as the bone density.

To our knowledge only continuous bone usage can reasonably improve skeletal modeling and remodeling[12,13]. Therefore, active or passive physical activities should be encouraged as much as possible in these patients. If regional exercises can be performed according to each individual SSI value, the mechanostatic regulation of bone structural configuration could be promoted, avoiding the potential risk of microcracks.

REFERENCES

1. Schiessl H, Ferretti JL, Tysarczyk-Niemeyer G, Willnecker J. Noninvasive bone strength index as analyzed by peripheral quantitative computed tomography (pQCT). In: Schonau E, ed. Pediatric Osteology: New Developments in Diagnostic and Therapy. Amsterdam: Elsevier Science B.V., 1996.
2. Ferretti JL. Noninvasive assessment of bone architecture and biomechanical properties in animals and humans employing pQCT technology. J Jpn Soc Bone Morphom 1997; 7: 115-125.
3. Jamsa T, Jalovaara P, Peng Z, Vaanamen HK, Tuukkanen J. Comparison of three-point bending test and peripheral quantitative computed tomography analysis in the evaluation of the strength of mouse femur and tibia. Bone 1998; 23: 155-161.

4. Pasqualini T, Plantalech L, Roldán E. A phase I/II study of pamidronate (APD) in children with osteogenesis imperfecta (OI). Acta Physiol Pharmacol et Therap Latino Am 1996; 46: 272 (abst).
5. Brumsen C, Hamdy NA, Papapoulos SE. Long-term effects of bisphosphonates on the growing skeleton. Studies of young patients with severe osteoporosis. Medicine 1997; 76: 266-283.
6. Devogelaer JP, Malghem J, Maldague B, Nagant de Deuxchaisnes C. Radiological manifestations of bisphosphonate treatment with APD in a child suffering from osteogenesis imperfecta. Skeletal Radiol 1987; 16: 360-363.
7. Zanchetta JR, Spivacow RF, Bogado C, Sarli M, Plotkin H, Roldan EJA. Uso prolongado, hasta 6 años, de un amino-bisfosfonato oral en pacientes con osteoporosis establecida. Medicina (Buenos Aires) 1997; 57 (Suppl 1): 37-44.
8. Ferretti JL, Cointry G, Capozza R, Montuori E, Roldán E, Pérez Lloret A. Biomechanical effects of the full range of useful doses of (3-amino-1-hydroxy-propylidene)-1,1-bisphosphonate (APD) on femur diaphysis and cortical bone tissue in rats. Bone Miner 1990; 11: 111-122.
9. Jagger CJ, Chambers TJ, Chow JWM. Stimulation of bone formation by dynamic mechanical loading of rat caudal vertebrae is not suppressed by 3-amino-1-hydroxypropylidene-1-bisphosphonate (AHPrBP). Bone 1995; 16: 309-313.
10. Spivacow FR, Zanchetta JR, Kerzberg EM, Frigeri A, Fiasché R, Roldán EJA. Tolerability of oral pamidronate in elderly patients with osteoporosis and other bone diseases. Curr Ther Res 1996; 57: 123-130.
11. Bembi B, Parma A, Bottega M, Ceschel S, Zanatta M, Martini C, Ciana G. Intravenous pamidronate treatment in osteogenesis imperfecta. J Pediatr 1997; 131: 622-625.
12. Frost HM. Perspectives: bone's mechanical usage windows. Bone Miner 1992; 19: 257-271.
13. Ferretti JL. Biomechanical properties of bone. In: Genant HK, Guglielmi G, Jergas M, eds. Osteoporosis and Bone Densitometry. Berlin: Springer Verlag, 1997; Chap. 8.