Journal of Clinical Densitometry: Assessment of Skeletal Health, vol. 13, no. 2, 190–196, 2010

1094-6950/10/13:190–196/$36.00
DOI: 10.1016/j.jocd.2010.01.006

Original Article

Dual-Energy X-Ray Absorptiometry and Quantitative Ultrasound in Patients With Paget's Disease of Bone Before and After Treatment With Zoledronic Acid: Association With Serum Bone Markers and Dickkopf-1

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Abstract

The main aim of this study was to determine the effect of zoledronic acid (ZOL) on parameters of dual-energy X-ray absorptiometry (DXA) and quantitative ultrasound (QUS) in unaffected bones of patients with Paget's disease of bone (PDB). The secondary aim was the association of bone markers and Dickkopf (DKK)-1 with parameters of DXA and QUS. Ten consecutive patients with polyostotic PDB (median age: 63 yr) received a single 5-mg ZOL infusion. The patients were subjected to calcaneal QUS and DXA of both lumbar spine (LS) and femoral neck (FN). Blood samples for serum bone markers and DKK-1 were serially obtained for 12 mo. There was a significant increase in LS ($p = 0.005$) and FN bone mineral density (BMD) ($p = 0.021$) 12 mo after ZOL infusion. QUS parameters remained unaffected throughout the study. A significant correlation between broadband ultrasound attenuation and DKK-1 ($p < 0.001$) and between speed of sound and DKK-1 ($p = 0.033$) at baseline was found, which remained significant after adjustment for gender, age, and body mass index. Our data suggest that a single ZOL infusion significantly increases nonpagetic BMD 12 mo after treatment but has no effect on QUS parameters or DKK-1. Significant correlations were observed between QUS parameters and DKK-1 at baseline.

Key Words: Dickkopf-1; dual-energy X-ray absorptiometry; Paget's disease of bone; quantitative ultrasound; zoledronic acid.

Introduction

Paget's disease of bone (PDB) is the second most common metabolic bone disease after osteoporosis and is characterized by focally increased bone remodeling *(1)*. The primary abnormality is believed to lie in the osteoclasts, which are increased in both number and size, resulting in rapid bone resorption. Bone formation is also accelerated in the affected sites because of the coupling effect, but the newly formed bone is chaotic, with loss of its normal lamellar pattern. As a consequence, normal bone architecture and structure are disrupted, and mechanical strength is decreased *(1)*, thereby causing affected bones become denser but more prone to fractures *(2)*.

Received 11/06/09; Revised 01/03/10; Accepted 01/10/10.
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Dual-energy X-ray absorptiometry (DXA) is the most widely used measurement for the assessment of bone mineral density (BMD) *(3)*. DXA measures the amount and distribution of bone mineral, but it does not assess the bone quality *(2)*. BMD is increased in bones affected by PDB, but the proportion of cortical and trabecular bone remains within the ratio expected for normal bones *(2,4,5)*. Despite the increased BMD, affected bones have a higher fracture risk that should not be underestimated *(6)*.

Quantitative ultrasound (QUS) has been proposed to assess the mechanical properties of both cortical and trabecular bone, which are important determinants of whole-bone stiffness, failure load, and fracture risk *(2,7)*. QUS has been proposed to be sensitive to poor structural quality in PDB, an aspect of skeletal fragility that cannot be measured by DXA *(2)*.

Various bone resorption markers, including serum C-terminal cross-linking telopeptide of type I collagen (CTX) and bone formation markers, such as total serum alkaline phosphatase (TSAP) and bone-specific serum alkaline phosphatase (BSAP), have been used to monitor PDB course and response to treatment *(1)*. More recently, Dickkopf (DKK)-1 has been implicated in the pathogenesis of various bone diseases *(8,9)*, including PDB. DKK-1 is a secreted inhibitor of wingless int (Wnt)/beta-catenin signaling pathway, thus, having the potential to favor osteoclastogenesis *(10)*. Overexpression of DKK-1 was found in pagetic osteoblast culture *(11)*, but data on serum DKK-1 levels in human studies are conflicting *(12,13)*.

The treatment of PDB aims at the suppression of abnormal bone turnover, and bisphosphonates are currently the drugs of choice *(14)*. The third-generation nitrogen-containing bisphosphonate zoledronic acid (ZOL) is currently considered to be the most effective treatment for PDB *(1,14,15)*. Both risedronate *(16)* and pamidronate *(17–20)* have a positive effect on BMD of patients with PDB. However, there are no data for the effect of any bisphosphonate on QUS or for the effect of ZOL on DXA in patients with PDB.

The main aim of this pilot study was to determine the effect of ZOL on parameters of DXA and QUS in unaffected bones of patients with PDB. The secondary aim was to investigate the association of bone markers and DKK-1 with BMD and parameters of QUS before and after the administration of ZOL.

Materials and Methods

This was a prospective open-label cohort study. The patients with PDB were recruited on an outpatient basis. The diagnosis of PDB was based on clinical features, imaging, and increased bone turnover markers (i.e., TSAP) *(21)*. The inclusion criteria in this study were as follows: (1) PDB documented by plain radiographs, bone scintigraphy, and increased TSAP on 2 consecutive measurements; (2) symptomatic PDB or bone lesions on the skull or cervical spine or close to joints *(14)*. The exclusion criteria were as follows: (1) recent fracture; (2) PDB that affected vertebrae L2–L4 or both femurs or both calcanei; (3) calcitonin or bisphosphonate therapy within 12 mo before baseline assessment; (4) hypocalcemia or hypercalcemia; (5) 25-hydroxyvitamin D (25-OH-D) lower than 20 ng/mL; (6) abnormal liver or kidney function tests; (7) medication that could affect bone metabolism. All participants provided informed consent before enrollment, and the study protocol was approved by the local ethics committee. ZOL (5 mg) was administered as a single 30-min intravenous infusion. Patients received calcium carbonate (1500 mg) and vitamin D (400 IU) daily, as it has previously been described *(15,22)*, for 10 d before and after ZOL infusion, until serum calcium was normalized *(23)*.

Baseline assessment included history, physical examination, and body mass index (BMI) calculation (body weight [kg]/height^2 [m]). Morning (8–9 AM) fasting blood samples were obtained from all PDB patients before ZOL infusion (baseline) and at 3, 6, and 12 mo after ZOL infusion. Serum total calcium, phosphate, TSAP, albumin, urea, and creatinine were measured within 1 h after blood drawing, using an automated analyzer (Olympus AU2700; Olympus, Hamburg, Germany). Serum was immediately centrifuged and stored at −30°C for the measurements of BSAP (Enzyme-linked immunosorbent assay [ELISA]; Quidel corporation, San Diego, CA—intra-assay coefficient of variation [CV]: 3.9–5.8%; interassay CV: 5.0–7.6%), CTX (ELISA; Nordic Bioscience Diagnostics, Boldon, UK—intra-assay CV: 1.7–3.0%; interassay CV: 2.5–10.9%), DKK-1 (ELISA; Biomedica, Vienna, Austria—intra-assay CV: 7–8%; interassay CV: 9–12%), and 25-OH-D (Radioimmunoassay [RIA]; Biosource, Nivelles, Belgium—intra-assay CV: 3.3–4.7%; interassay CV: 5.2–5.3%). Measurements of BSAP, CTX, DKK-1, and 25-OH-D were performed in 1 session at the end of the study. 25-OH-D was measured only at baseline.

The patients were subjected to bone scintigraphy at baseline. Spot images of the entire skeleton were acquired 3 h after intravenous injection of 740 MBq of technetium-99m-hydroxymethylene bisphosphonate, using a large-field-of-view, dual-headed gamma camera (AXIS; Philips, Cleveland, OH). Plain radiographs of all scintigraphically detected bone lesions were obtained before ZOL administration.

A QUS of the left calcaneous and DXA of lumbar spine (LS) (L2–L4) and left femoral neck (FN) were both performed by a single experienced operator. Right calcaneous and/or right FN were chosen if the left ones were affected by PDB. QUS and DXA were performed the same day at baseline and at 12 mo. QUS was also performed at 3 mo after ZOL infusion. Two parameters of QUS were measured by using the DTU-one ultrasound scanner (Osteometer MediTech, Rodovre, Denmark): the attenuation slope or broadband ultrasound attenuation (BUA) in decibels per megahertz (dB/MHz) and the ultrasound velocity or speed of sound (SOS) in meters per second (m/s). The short-term in vitro CV was 1.6% for BUA and 0.1% for SOS, and the long-term in vitro CVs were 3.8% and 0.2%, respectively, for BUA and SOS. The short-term in vivo CV was 2.9% for BUA and 0.1% for SOS, and the long-term in vivo CVs were 4.5% and 0.5%, respectively, for BUA and SOS. The areal BMD in grams per square centimeter (g/cm^2) of the anteroposterior