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Histomorphometric analysis of minimodeling in the vertebrae in postmenopausal patients treated with anti-osteoporotic agents

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ABSTRACT

Minimodeling is a type of focal bone formation that is characterized by the lack of precedent bone erosion by osteoclasts. Although this form of bone formation has been described for more than a decade, how anti-osteoporotic agents that are currently used in clinical practice affect the kinetics of minimodeling is not fully understood. We performed a bone morphometric analysis using human vertebral specimens collected from postmenopausal patients who underwent spinal surgery. Patients were divided into three groups according to osteoporosis medication; non-treated, Eldecalcitol (ELD, a vitamin D derivative that has recently been approved to treat patients with osteoporosis in Japan)-treated, and bisphosphonate-treated groups. Five to six patients were enrolled in each group. There was a trend toward enhanced minimodeling in ELD-treated patients and suppressed of it in bisphosphonate-treated patients compared with untreated patients. The differences of minimodeling activity between ELD-treated and bisphosphonate-treated patients were statistically significant. The present study suggests that ELD and bisphosphonates have opposite effects on minimodeling from one another, and show that minimodeling also takes place in vertebrae as has been described for the ilium and femoral head in humans.

1. Introduction

Osteoporosis is characterized by reduced bone mass and the loss of microarchitectural integrity in bone tissue, ultimately leading to bone fragility and increased susceptibility to fracture (Kanis, 1994). Osteoporosis-related fractures in elderly patients severely compromise their quality of life and activities of daily living (ADL) and impose a major burden on society and the medical economy, especially in developed countries (Egermann et al., 2005). Therefore, it is imperative to learn more about the pathology of and prophylaxis for osteoporosis and osteoporosis-related fractures.

Minimodeling is a form of trabeculae modeling and is so termed based on the miniature nature of this process in vivo (Frost, 1990). In conventional remodeling, bone formation is preceded by bone resorption, and, therefore, the cement lines are usually irregularly shaped. In contrast, in minimodeling, bone formation occurs on quiescent bone surfaces and thus creates smooth cement lines (Frost, 1990; Jee et al., 2007; Kobayashi et al., 2003). The nature and function of minimodeling are not fully understood; however, it is likely to be an adaptive mechanism to strengthen the skeletal microstructure in response to mechanical stress (Frost, 1990). Past studies have shown that minimodeling can be enhanced in patients and animals who are treated with bone anabolic agents, such as PTH (teriparatide) (Lindsay et al., 2006; Ma et al., 2006) and prostaglandin E2 (Zhou et al., 2001; Yao et al., 1999). On the other hand, the potential effects of more common anti-osteoporotic agents, such as vitamin D3 and bisphosphonates (BPs) on minimodeling in humans have remained unaddressed.

In the present study, we aimed to evaluate the potential effects of a new vitamin D3 analog, Eldecalcitol (2β-(3-hydroxypropyloxy)-1,25-dihydroxyvitamin D3, henceforth referred to as ELD), and BPs on minimodeling in humans using surgical specimens that were collected from postmenopausal patients who underwent spinal surgery. In accordance with past reports (Jee et al., 2007; Kobayashi et al., 2003), minimodeling was readily observed also in the human vertebral specimens that were examined in the present study. Most importantly, we found that patients who had been treated with ELD prior to surgery tend to have increased minimodeling activity compared with the control patients and those treated with BPs. Our data suggest that ELD potentially activates minimodeling in postmenopausal patients while BPs have negative or little impact on this form of bone formation, and that each anti-osteoporotic agents have distinct effects on minimodeling in vivo.

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2. Materials and methods

2.1. Study design, subjects, and ethics statement

Of the female patients with lumbar degenerative disorder who underwent lumbar spinal surgery at our institution from October 2012 to July 2014, we enrolled those who confirmed by interview that they had reached menopause >3 years prior. Patients were excluded if they had primary hyperparathyroidism; Cushing's syndrome; premature menopause due to hypothalamic, pituitary or gonadal insufficiency, poorly controlled diabetes mellitus (HbA1c over 8.0%); or other causes of secondary osteoporosis. Patients were also excluded if they had taken glucocorticoids or hormone replacement therapy in the past 3 months or had clinically significant hepatic, cardiac, or malignant disorders. Sixteen patients were eligible for this study. Ten of these patients were taking osteoporosis medications. Five of these ten patients had taken BPs (BP group), while the other five had solely taken ELD (ELD group), for >6 months. Six patients had no history of osteoporosis medication (Ctrl group). Bone specimens were collected from the lamina of the lumbar vertebra that was removed during surgery. The present study was approved by the Institutional Review Board of Keio University School of Medicine (approval number, 20,130,109) and informed consent was obtained from each patient.

2.2. Measurement of BMD

The BMD of the L2-L4 vertebrae and bilateral femurs was measured prior to surgery by dual-energy X-ray absorptiometry (Prodigy; GE Healthcare, Tokyo, Japan). The mean value of the bilateral femoral neck BMD was used for statistical analysis.

2.3. Serum and urinary bone metabolic markers

The levels of serum PTH-intact and tartrate-resistant acid phosphatase-5b (TRACP-5b) were measured by enzyme immunoassay. Serum homocysteine and hydroxyproline were measured by high-performance liquid chromatography. Urinary type 1 collagen N-telopeptide (NTX) and deoxypyridinoline (DPD) were measured by an enzyme immunoassay. The intact amino-terminal pro-peptide of type 1 collagen (P1NP) was measured by a radioimmunoassay. Serum was collected and analyzed prior to surgery.

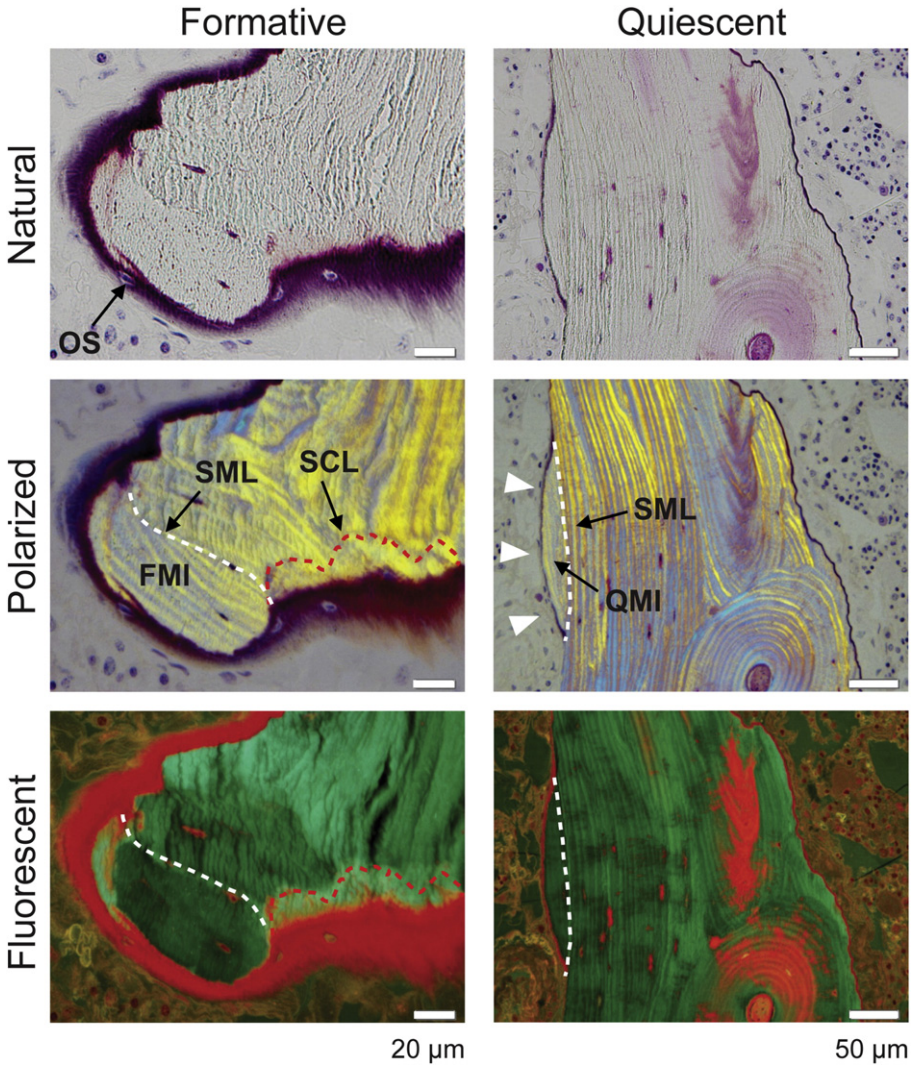

Fig. 1. Minimodeling sites on trabeculae. Conventional (a), polarized (b), and fluorescent (c) light micrographs of a trabecula with minimodeling in a lamina bone in a lumbar spine biopsy specimen from a 75-year-old woman who underwent lumbar decompression surgery for lumbar spinal canal stenosis. Note that bone surface is covered with osteoid in the formative minimodeling site (left panels); whereas, no apparent osteoid is found in the quiescent minimodeling site (right panels). OS, osteoid surface; QS quiescent surface; FMI, formative minimodeling; QMI, quiescent minimodeling; SCL, smooth cement line; SCL scalloped cement line.