Effects of D-003 (10 mg/day) on Bone Mineral Density of the Lumbar Spine and Femoral Neck in Postmenopausal Women: A Randomized, Double-Blinded Study

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Background/Aims: Increased osteoclast activity is a pivotal finding in osteoporosis. This increase is mediated via the mevalonate-to-cholesterol pathway, which is involved in producing the intermediates required for osteoclast activity. D-003, a mixture of high molecular weight sugarcane wax acids, has been shown to inhibit cholesterol synthesis prior to mevalonate production, resulting in a reduction of bone loss and resorption in ovariectomized rats. Moreover, previous studies have demonstrated that short-term D-003 treatment reduces urinary excretion of deoxypyridinoline/creatinine in postmenopausal women.

Methods: We performed a double-blinded, placebo-controlled study to investigate the effects of D-003 (10 mg/day) treatment for 3 years on bone mineral density (BMD) in 83 postmenopausal women with low BMD.

Results: Over 3 years, D-003 treatment increased lumbar spine BMD (5.1%, \(p<0.01\)) and improved osteoporosis-related quality of life scores as compared with placebo-treated controls. D-003 was also well tolerated; the frequency of adverse events in the bone, joints, or muscle with D-003 treatment \((p<0.05)\) was lower than in the placebo group.

Conclusions: D-003 treatment (10 mg/day) for 3 years increased lumbar spine BMD and produced clinical improvements in postmenopausal women with low BMD. Further studies, however, will be required to confirm these results. (Korean J Intern Med 2011;26:168-178)

Keywords: Bone density conservation agents; Bone density; Bone remodeling; Osteoporosis, postmenopausal; Saccharum wax acids

INTRODUCTION

Osteoporosis is a chronic degenerative systemic disease characterized by low bone mineral density (BMD) and microarchitectural deterioration of bone tissue, which leads to increased bone fragility and fracture risk [1,2]. The incidence of osteoporosis increases with age and disproportionately affects older women and men, with postmenopausal osteoporosis being the most frequent type of primary osteoporosis [1,2].

A continuous bone remodeling process that involves the balance between bone resorption and bone formation maintains the integrity of the mature adult skeleton. This remodeling process is regulated by osteoclasts and osteoblasts, respectively. The imbalance of these processes in favor of the former leads to osteoporosis [3].

N-bisphosphonates, which are first-line antosteoporotic drugs, exhibit their antiresorptive effects through the
aliphatic acids purified from sugar cane wax, wherein octacosanoic \((C_{28})\) acid is the most abundant, and \(C_{24}, C_{26}, C_{28}, C_{30}, C_{32}, C_{33}, C_{35}\), and \(C_{36}\) acids are at lower concentrations [19].

D-003 has been shown to inhibit mevalonate formation by regulating the activity of HMG CoA reductase [20], leading to the production of cholesterol-lowering effects [21-23] and the inhibition of lipid peroxidation [22,24].

Based on these observations, the effects of D-003 on experimentally induced osteoporosis were investigated. D-003 treatment has been shown to increase osteoclast apoptosis, thus preventing bone loss and bone resorption in rats with ovariectomy- [25-27] or prednisolone-induced [28] osteoporosis. In addition, D-003 treatment (10 mg/day) for 6 months reduced urinary excretion of deoxypyridinoline/creatinine (DPD/Cr), a bone resorption marker, in postmenopausal women [29].

The current study investigated the effects of D-003 treatment (10 mg/day) administered for 3 years on the BMD of the lumbar spine and femoral neck in postmenopausal women with low BMD.

**METHODS**

**Study design**

This study was conducted in the Orthopedic Unit of the Surgical Medical Research Centre (Havana, Cuba) in accordance with the principles of the Helsinki Declaration and the Cuban Guidelines of Good Clinical Practices. The study protocol was approved by the institutional ethics and scientific board.

Postmenopausal women were enrolled after obtaining their informed written consent (Visit 1). A medical history, physical examination, and interview regarding osteoporotic risk factors were performed. All enrolled women underwent a placebo-baseline period for 2 weeks, in which blood samples for laboratory determinations were taken, and lumbar spine (L1-L4) and femoral BMD were measured. Hypercholesterolemic women were encouraged to continue or start a low-fat, low-cholesterol diet during the study. Eligible women were randomized (Visit 2), under double-blind conditions, to the placebo or D-003 (10 mg/day) groups for 3 years and attended visits after 1.5, 3, 6, and 12 months of treatment during the first year, and every 6 months thereafter (Visits 3-10). Physical examination, drug compliance, and adverse experience (AE) controls were also performed during the trial. Laboratory tests and quality of life interviews were performed at baseline and after 3, 6, and 12 months of treatment, and annually thereafter. BMD measurements were recorded at baseline and at yearly intervals.

**Patients**

We enrolled women (40 to 70 years) with amenorrhea of at least 12 months and ≥ 2 risk osteoporosis factors (personal or family history of fractures, low dietary calcium intake, physical inactivity, cigarette smoking, small, and thin frame; Caucasian or Asian race, excess of alcohol drinking, consumption of corticoids, and/or thyroid medications). Participants were eligible for randomization if they had a lumbar spine BMD value of at least 1 SD below mean normal peak levels provided by the densitometer manufacturer. This study, therefore, included both osteopenic and osteoporotic women.