Osteoporosis is a major health problem, with approximately 100 million individuals at risk worldwide. As bone density decreases with age, usually beginning at menopause in women and at age 55 in men, fracture rates progressively increase, particularly in women. As life expectancy increases, the number of patients at risk for fractures is rising. Current therapies for the treatment of osteoporosis, including estrogen replacement therapy, selective estrogen receptor modulators, and bisphosphonates, are based primarily on blunting the resorption component of the bone homeostasis. Selective androgen receptor modulators, parathyroid hormone analogs, and oxytocin analogs, all with improved pharmacologic properties in bone, are among the potential approaches to eliciting anabolic effects in the skeleton.

However, despite recent successes with drugs that have positive effects on bone formation, there is a clear need for anabolic agents in individuals who have already suffered substantial bone loss. Mundy et al have shown statins, drugs widely used for lowering serum cholesterol, also enhance new bone formation in vitro in rodents. While many retrospective studies and animal models have suggested statins (3-hydroxy-3-methylglutaryl coenzyme A [HMG-CoA] reductase inhibitors) may increase bone mineral density, no exact in vivo, observational morphologic study has demonstrated their positive effect on bone formation.

This experimental in vivo animal model study examines the effect of statin on bone turnover.
Histologic Specimens

Specimens were fixed in formalin for 2 days. After separation of the soft tissues, specimens were treated in a decalcification solution of equal parts of 8% hydrochloric acid and 8% formic acid.\textsuperscript{5} Decalcification solution was replaced every other day, and tissue decalcification took place for 15 days.

Tissues were embedded in paraffin, and after conventional histologic processing, 6-µm slices were cut and stained with hematoxylin-eosin and Trichrome-Masson stains. Histopathologic examination was performed using a Zeiss Axioscope photomicroscope, and microphotographs were taken.

RESULTS

In contrast to the simvastatin-injected legs, no stimulated bone formation was seen in any of the control legs (Figure 1). In the 7-day group on the simvastatin side, osteoblasts were increased under the periosteum close to the bone and were arranged in a line for forming the appositional bone. On the other hand, membranous ossification regions also were present. In this region, osteoid tissue was present. Increased activation of new capillaries was directly proportional to the bone formation (Figure 2).

When the 14-day simvastatin group was compared with the 7-day simvastatin group, the new osteoid tissue was thicker, the osteoid tissue was well organized, and the formation of new capillaries had spread. The region between the periosteum and the bone was wide (Figure 3).

On examination of the 21-day simvastatin group, stimulated formation of new bone was seen (Figure 4). In the 21-day simvastatin group, new bone tissue and chondrocytes were present (Figure 5).
bone was increased. In contrast to the 14-day simvastatin group, although the formation of new capillaries was more prevalent, the tissue was stained insufficiently with blood and chondrocytes were arranged close to the bone (Figure 4). Because of the activation of cells and capillaries, the simvastatin side was enlarged. An enlarged chondral area also was observed close to the bone (Figure 5). The important difference in the 21-day simvastatin group was the beginning of calcification.

**DISCUSSION**

Osteoporosis is a major health problem worldwide, and the incidence and impact of osteoporosis have been studied in terms of cost, morbidity, and quality of life. Substantial bone loss continues throughout old age, with an accompanying exponential increase in fracture risk. Any reduction or arrest of bone loss will result in a concomitant reduction in the incidence of fractures.

The main efficacy criterion for drugs against osteoporosis is protection against fractures. Many resorption-inhibiting agents including estrogens, alendronate, risedronate, raloxifene, calcitonin, and calcium-vitamin D supplements meet this criterion, but anabolic agents still are urgently required.\(^3^,\(^6\,\)\(^7\) Therefore, this study investigated the benefit of simvastatin on bone formation in healthy animals.

HMG-CoA reductase inhibitors, or statins, interfere with the events involved in bone formation independent of their hypolipidemic properties.\(^8\) The issue of the efficacy of statins in bone formation continues to be debated, with a few in vivo observational studies yet to confirm the suggested benefit noted in epidemiologic studies. As observed by Mundy et al\(^1\) in their in vitro study, the results obtained in this study suggest the effect of statins include acceleration of the proliferation and differentiation of osteoprogenitor cells and advancement of blood supply.

Maritz et al\(^9\) investigated the effects of statins on femoral bone mineral density and quantitative bone histomorphometry and bone formation and increased bone resorption. The effects of simvastatin on quantitative bone histomorphometry also differed at different dosages. In the present study, the results indicated 5 mg/kg/day of simvastatin increased bone formation and resorption, while low doses (1, 5, and 10 mg/kg/day) decreased bone formation and increased bone resorption. The effects of simvastatin on quantitative bone histomorphometry also differed at different dosages. In the present study, the results indicated 5 mg/kg/day of simvastatin increased bone formation and resorption, while low doses (1, 5, and 10 mg/kg/day) decreased bone formation and increased bone resorption.

**What is already known on this topic**

- HMG-CoA reductase inhibitors are antilipidemic agents.
- HMG-CoA reductase inhibitors increase bone mineral density and enhance new bone formation in vitro cultures.

**What this article adds**

- This article shows the effects of statins on new bone formation and induction of osteogenesis in vivo.
- Use of statins is an alternative osteoporosis treatment with future medications, such as gene-altering therapy and recombinant human parathyroid hormone.

Any reduction or arrest of bone loss will result in a concomitant reduction in the incidence of fractures.

In one recent study, Rejmark et al\(^11\) reported an antiresorptive effect based on their data that showed plasma levels of bone turnover markers were lower in statin-treated subjects than in controls. In another study, Das\(^12\) reported estrogen, statins, and essential fatty acids, in addition to their other modes of action in the prevention of osteoporosis, have the ability to augment constitutional nitric oxide generation, which is known to be beneficial in osteoporosis.

Mundy et al\(^1\) suggested that in bone cells, statins increase the gene expression of bone morphogenetic protein-2 (BMP-2), which is an autocrine-paracrine factor for osteoblast differentiation. The development of knowledge about the cellular and molecular mechanisms by which BMPs elicit bone formation over time offer important insights into the mechanisms of response to the treatment. The osteoinductive capacity of BMPs has been demonstrated in preclinical models, and the efficacy of BMPs for the treatment of orthopedic patients is currently being evaluated in clinical trials.\(^13\)

**CONCLUSION**

In this in vivo observational study, simvastatin had a positive effect on bone formation, indicating the use of statins for bone formation might be targeted to the
BMP-2. Further clinical and experimental studies are needed to confirm these findings and to investigate their mechanism of action.

REFERENCES


