•ACCELERATED FRACTURE HEALING BY TRANSDERMAL LOVASTATIN
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INTRODUCTION
Normal fracture healing is a complex, multi-step process involving cellular events influenced and regulated by local and systemic factors. The most common biological failure in fracture healing involves an improperly formed callus during the first weeks following fracture. Recent advances in understanding the regulatory factors controlling fracture healing have suggested that a number of compounds may be used to stimulate bone growth and initiate and enhance the cascade of events involved in callus formation and maturation.

BMPs, particularly BMP2 which is well known for its osteogenic activity, is highly expressed in the healing callus during fracture repair [1] which suggests an important role of these proteins in fracture healing.

Statins, a group of natural products widely prescribed for their capacity to inhibit the enzyme HMG Co-A reductase, and therefore decrease cholesterol biosynthesis, have been shown to increase transcription of the BMP-2 gene, and stimulate bone formation [2]. It has been recently demonstrated that statin treated fractures in mice show accelerated healing either when the statins are administered systemically or directly to the fracture area [3-4].

Observational studies in patients given statins for lipid-lowering oral doses have been difficult to evaluate, since some have shown a positive effect on fracture prevention, and some have shown no effect. Since the likely reason for the lack of a convincing effect in all of these retrospective human studies is that the statin concentration reaching the periphery has been too low in the doses used to produce a reproducible biologic effect, we examined the effects ofLovastatin (LV) given transdermally (TD) in a well-described preclinical rat model of fracture repair. Given the unique potency of statins to stimulate bone formation, the goal of this study was to determine the efficacy of transdermally delivered LV to enhance callus formation and fracture healing in this model.

METHODS
2-month old Sprague-Dawley female rats were weight-matched and divided into treatment groups. The study protocol was approved by the Institution’s Animal Care and Use Committee.

A uniform and reproducible unilateral fracture defect was created using a well-defined, pinned rat femoral model [5]. LV was administered transdermally (TD) at 0.1, 1, 2.5 and 5mg/kg/day, and compared with vehicle-treated control rats and rats treated with LV by oral gavage (PO). Healing was evaluated by several methods:
1) Radiological analysis (assessed blindly) using a grading scale based on rebridgement of the cortices.
2) Bone mineral density was assessed at the fracture callus using Piximus.
3) Biomechanical strength using 3-point bending.
4) Cell growth activity in the developing callus utilizing monoclonal antibodies against proliferating cell nuclear antigen and quantifying osteoclast number after the first week of fracture.

RESULTS
Radiological evaluation of bones treated with TD LV showed enhanced fracture repair at two weeks (Fig 1).

Bone mineral density (BMD) at the fracture callus at 6 weeks was also increased in the TD group compared to vehicle-treated controls (p<0.05). The force required to break TD-treated bones was 42% (Fig 2) greater than vehicle-treated controls (p=0.02) along with 90% increase in stiffness. PO LV at 5mg/kg/day had no effect. TD LV showed significant increase in stiffness even at 0.1mg/kg/day. A significant increase was also observed in the size of the callus, surrounding proliferating cell nuclear antigen (PCNA)-positive cells and osteoclast number in TD-treated rats compared to PO treatment and controls at day 8.

Fig 1. Radiographic score at 2 weeks. Results are expressed as percentage change from vehicle-treated groups (vehicle-treated=100%)

Fig 2. Three-Point Bending. Maximum force was significantly increased with TD LV at 0.1 and 1mg/kg/day

In summary, we have found that TD LV enhances callus formation and mechanical strength, and accelerates fracture healing in a manner similar to the effect reported with BMP-2 treatment. These studies emphasize the potential of transdermal delivery of statins as a new and effective therapeutic modality in fracture repair.


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