A prostaglandin EP4 agonist stimulates bone formation and arrests bone loss in ovariectomized adult rats.

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Disturbance of the equilibrium of bone resorption and formation will result in bone pathologies such as postmenopausal osteoporosis. The increase in bone resorption being greater than that in bone formation results in a net decrease in bone mineral density (BMD), leading to an increased susceptibility to bone fractures in this common disease. Prostaglandins (PGs), in particular those of the E subtype, play an important role in bone metabolism. Of the four cell surface receptor subtypes mediating the biological and pharmacological actions of PGE₂, EP2 and EP4 seem to have the most pronounced anabolic effects in bone biology. Literature data indicate an opportunity for the development of selective EP4 agonists in the treatment of metabolic bone diseases, including osteoporosis. The present study examined the effect of ONO-4819, a prostaglandin EP4 agonist, in a validated rat model for postmenopausal osteoporosis. A broad number of bone parameters was evaluated in an 8-week experiment. Immediately after ovariectomy (OVX) treatment was started using a subcutaneous osmotic mini pump. BMD measurements were performed using dual X-ray absorptiometry on several bone regions in the rat. Biomarkers for bone formation and resorption were measured in serum and urine. MicroCT (18 µm resolution, at 60 kV and 100 µA) was used to quantify ex vivo cortical and trabecular bone morphometry within the femoral mid shaft and the proximal femur, respectively. To determine bone formation rate and mineral apposition rate, rats were injected with tetracycline and with calcein, respectively 14 or 5 days before sacrifice. Specific histological staining then results in a blue-green staining of mineralised bone, and a red-orange staining of osteoid. Treatment with ONO-4819 induced a sustained increase in whole body BMD, and counterbalances OVX-induced decrease in BMD in whole femur. Increase in bone turnover after OVX was indicated by increased levels of osteocalcin and of collagen type I fragments. This increase in both markers was more pronounced during ONO-4819 treatment. OVX strongly affects trabecular bone, resulting in a reduced bone volume, trabecular number and increased trabecular separation. In ONO-4819 treated rats however, the percent bone volume normalizes towards control values.

The present study demonstrated that the treatment of ovariectomized rats with ONO-4819, an EP4 agonist, results in an increased BMD and ultimately in an increased bone strength.