THE COMBINATION OF OVARIECTOMY AND GLUCOCORTICOID TREATMENT EFFECTS DENSITY, STRUCTURE, AND MECHANICAL PROPERTIES OF TRABECULAR BONE IN SHEEP

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Introduction: Osteoporotic fractures remain a therapeutic challenge as they are often associated with complications in fracture fixation. In order to improve orthopedic procedures and to develop new implants and fixation strategies adequate animal models of osteopenic bone are required. A large animal model that has been frequently used is the sheep, because of having a bone size and bone remodeling which is similar to humans (1). So far osteopenia has been induced by ovariectomy, which has shown to reduce BMD (2), and to decrease mechanical properties (3). However, the effects on bone were minimal compared to sham operated control animals. An alternative protocol to induce osteopenia in sheep is a corticosteroid treatment, which resulted in a bone formation deficit (4). The objective of this study was to validate an animal model of osteopenic bone by a combination of ovariectomy and glucocorticoid treatment in sheep. We hypothesized that the combination of ovariectomy and glucocorticoid treatment results in a significant reduction of bone density, bone quality, and mechanical properties.

Methods: Fifteen ovariectomized merino sheep (4 yrs - 7yrs) either received a 6-month high dose glucocorticoid treatment (GLU; daily dose: 0.45 mg/kg Methylprednisolone) by subcutaneous injection or were left untreated (CONTROL). Trabecular bone biopsies (6mm diameter, 7-9mm height) from the tibia were harvested 6 months after ovariectomy. By that time the dosage of glucocorticoids was stepwise reduced to zero. To detect any signs of bone recovery after the cessation of glucocorticoid treatment the animals remained untreated for another 6 months. 12 months after the beginning of the study the animals were sacrificed and again bone biopsies were taken from the contralateral tibia and the lumbar spine. All biopsies were scanned for apparent BMD specimens. At the tibia the elastic modulus of GLU-biopsies was almost 50% lower (6 months: p=0.07; 12 months: p=0.02). By that time the dosage of glucocorticoids was stepwise

Results: Corticoid treatment resulted in a substantial reduction in bone density, bone quality, and mechanical properties. Differences were generally more pronounced at the tibia than at the spine. Compared to CONTROL (6 months: BMD = 410.5 mg/ccm; 12 months: BMD = 491.1 mg/ccm) bone mineral density of GLU-biopsies from the tibia was reduced by 19% after 6 months (BMD = 333.9 mg/ccm) and by 33% after 12 months (BMD = 328.0 mg/ccm; p<0.05). At the spine density decreased by 11% after 12 months. Parameters of bone morphology markedly changed after glucocorticoid treatment. At 6 months bone volume (BV/TV: -15%), bone surface (BS/BV: +14%) and trabecular thickness (Tb.Th.: -10%) of the tibia biopsies differed from CONTROL. At 12 months the differences were even more pronounced (BV/TV: -20%; BS/BV: +20%; Tb.Th.: -17%). The differences in bone surface and trabecular thickness were significant after 12 months (p<0.05). At the spine the structural parameters differed from CONTROL by at least 11% (BV/TV: -14%; BS/BV: +14%; Tb.Th.: -11%). Trabecular number was not affected by glucocorticoid treatment. The greatest impact of glucocorticoid treatment was found for the mechanical properties of the bone specimens. At the tibia the elastic modulus of GLU-biopsies was markedly reduced after 6 months by 45% and after 12 months by 55% (p<0.02). At the spine the elastic modulus decreased by 14% compared to CONTROL.

Discussion: In this study a 6-month glucocorticoid treatment of ovariectomized sheep resulted in significant changes of trabecular bone. These changes were induced within the first 6 months of glucocorticoid treatment and were maintained over another 6 months after the cessation of glucocorticoid administration. The successful induction of osteopenia was demonstrated by densitometric, morphometric, and biomechanical methods. The resultant deterioration of trabecular bone structure and of its mechanical competence was substantial. Bone loss was primarily induced at load bearing sites, which are potential target locations for the testing of orthopedic implants and fixation strategies developed for the treatment of osteoporotic fractures. Despite this successful induction of osteopenia, the animal model has several limitations. Bone loss in the presented sheep model was induced by the coaction of two different underlying mechanisms - estrogen deficit and administration of steroids. Both mechanisms have different effects on trabecular bone and it is possible that they were influenced by each other. Therefore, the model of glucocorticoid induced osteopenia in ovariectomized sheep does not mimic the situation of postmenopausal osteoporosis in humans. It has limited applicability to study pharmaceutical intervention for the treatment of postmenopausal osteoporosis. Furthermore, because sheep are ruminants they might differ from humans with respect to responsiveness to oral based osteoporotic therapies. In conclusion the ovarectomized and glucocorticoid treated sheep may serve as a large animal model of osteopenic trabecular bone and may be used for the development and testing of orthopedic procedures in osteoporosis research.

References: