Effects of Cessation and treatment of risedronate on multiple skeletal implications of corticosteroid exposure

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Introduction

Treatment with supraphysiological levels of corticosteroids (CS) results in decreased bone formation and enhanced bone resorption, thus leading to accelerated osteopenia. We have previously described a longitudinal approach to evaluate the short-term implications of excess CS exposure by means of MR micro imaging (μ-MRI) in a rabbit model [1]. This prior study revealed that 2-week treatment with dexamethasone induced a significant reduction in trabecular bone volume fraction (BVF), a conversion of hematopoietic to yellow marrow in the metaphysis and atrophy of the femoral epiphyseal growth plate. In the present study, we investigated whether, or how soon after cessation of CS exposure, recovery of these adverse skeletal effects would occur. Further, we investigated whether antiresorptive treatment with bisphosphonates (BP), had protective and/or therapeutic effects when the BP treatment started synchronously with or delayed after CS exposure was started.

Materials and Methods

Sixteen New Zealand white male rabbits (6 month old) were either subcutaneously implanted with pellets for slow-release of dexamethasone (0.6 mg/kg/day) or sham operated, immediately after the first MRI/S sessions. Then, all animals were divided into four groups: the cessation (CE), early BP treatment (ET), late BP treatment (LT) and sham control groups. The implanted pellets were removed from the animals in the CE group 2 weeks after CS exposure. Treatment of risedronate (Procter & Gamble) was started immediately or 2 weeks after initiation in the ET- and LT-groups, respectively. Micro-MRI was repeated every 2 weeks for up to 8 or 10 weeks to monitor the skeletal alterations. In-vivo μ-MRI was performed on a 1.5T whole-body imager (GE Signa™) with a home-made Helmholtz coil. Trabecular morphology in the distal femoral epiphysis was quantified based on 3D FLASE [2] images of 97x97x300 μm^3 voxel size. Scan parameters were: TR/TE=80/11ms, 5cm FOV, 60 slices, 512x256 matrix size, scan time = 21 minutes. A 60-slice 3D data set from a 18mm-thick slab was processed from each animal using BVF mapping technique used previously [1]. Thickness of the growth plate was measured on the re-sliced longitudinal (sagittal) images. Bone marrow composition was measured spectroscopically in axial sections in the metaphysis using a multi-echo gradient-echo (IMGE) CSI pulse sequence, which allows measurement of fat fraction in the marrow quantitatively [3].

Results and Discussion

Two slices from different time points (2 weeks CS-exposure and subsequent repeat study after beginning of treatment of BP) show precise matching of the two 300 μm slices (as is evident from the identical architectural features visible), which is critical in longitudinal studies (**Fig.1**). In the control group, BVF remained unaltered throughout the duration of the protocol. Thinning of growth plate and conversion to fatty marrow occurred gradually though these changes were not significant. Only two weeks of dexamethasone exposure induced approximately 10% reduction in BVF (**Fig. 2**). In the CE-group, BVF recovered to normal levels within 2 weeks after cessation of CS, remaining unaltered through the remainder of the protocol. The reduction in BVF was completely inhibited and even increased when treatment with risedronate was started at the same time as CS-exposure (ET-group). Further, BVF was found to rise beyond the initial level within 2 weeks and subsequently increased with delayed start of risedronate treatment (LT-group). However, other skeletal complications such as thinning of the epiphyseal growth plate and bone marrow conversion (hematopoietic to fatty) could not be reversed even 10 weeks after the cessation (**Fig. 3).** In CS-induced osteoporosis (unlike postmenopausal OP), bone atrophy occurs without changes in the bone's topological make-up [4]. Finally, growth plate thinning and conversion to fatty marrow appear to be irreversible. The findings might have implications on high-dose steroid treatment of the pediatric population.

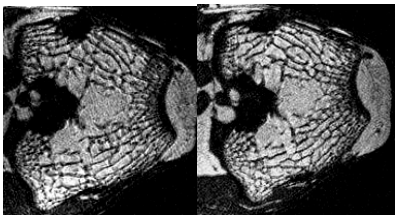

Fig.1. Typical micro-MR images of trabecular bone in the rabbit distal femoral epiphysis before and after 2 weeks of risedronate treatment under CS-exposure in the same animal, showing perfect matching of trabecular architecture.

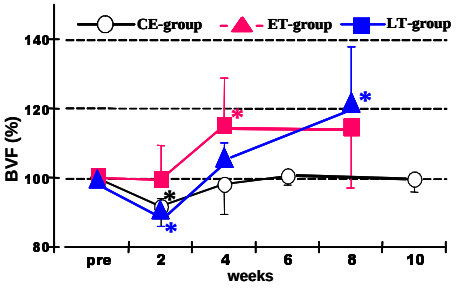

Fig. 2. Changes in trabecular bone volume fraction in the cessation (CE), early treatment (ET) and late treatment (LT) groups. Values are expressed means and standard deviation. * p<0.05 by Tukey-test vs. pre in each group.

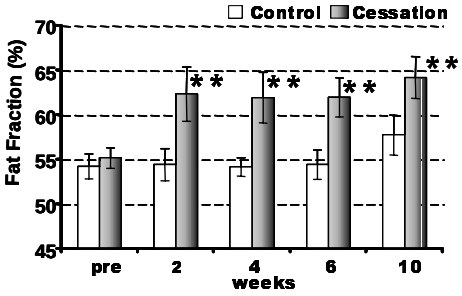

Fig. 3. Changes in bone marrow composition in the control and cessation groups (means and standard deviation. **p<0.01 by student's t-test vs. control group.

References: 1. M. Takahashi, *et al PNAS 99*, 4574 (2002). 2. J. Ma, *et al*. *MRM 35*, 903 (1996). 3. L. Hilaire, *et al*. *MRI* 18;777 (2000). 4. JE Aaron *et al*. *Clin Orthop* 243, 294 (1998).