A *bona fide* model for age-related osteoporosis in accelerated aging trichothyiodystrophy (TTD) mice

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**Aims**

Osteoporosis typically manifests itself at old age. One potential mechanism by which aging can occur is through the accumulation of DNA damage, and premature aging can occur when repair of these damages is distorted [1]. By using DNA repair deficient mouse models as a tool, research in our laboratory focuses on the mechanism of aging and the etiology of aging related pathology. In this study, we used a mouse model that closely mimics the human premature aging syndrome trichothyiodystrophy (TTD). Much like human TTD patients, these mice show accelerated onset and progression of age-related diseases [2]. The goal of this study was to assess if TTD mice can be used as a model for spontaneous, age-related osteoporosis that mimics the human situation more closely.

**Method**

From a cohort of 120 female wild type (WT) C57Bl/6 and 120 TTD animals groups of mice (n=10/group) were sacrificed at defined time points (13, 26, 39, 45, 52 and 65 weeks of age), followed by dissection of femur and tibia. Separate groups of TTD mice (aged 26-65 weeks) were injected with ALN and PTH, to investigate if these drugs would have the same bone preserving effect in TTD mice as in human osteoporosis patients. Of each mouse, the bone phenotype was determined using micro-CT analysis (right femur), using the Skyscan 1076 scanner at a voxelsize of 9 µm. Bone strength was assessed using break tests (left femur), and transcriptional profiling was performed using micro-arrays (of tibia’s, n=50). Serum and plasma was collected for future biomarker approaches.

**Results**

At 13 weeks of age, the bone phenotype of WT and TTD animals was not significantly different, but from 26 weeks onwards TTD animals had a faster age-related decline both in trabecular and cortical bone (BV/TV at 65 wks: WT: 12.5±0.5%; TTD: 9.1±0.6%, Ct.Th.: 218.3±3.9µm, TTD: 194,1±5.9µm). Bone strength was significantly lower at 65 weeks of age (WT: 97.1 ± 5.7 N/mm, TTD: 53.4 ± 3.6 N/mm). Both ALN and PTH were able to overcome the bone loss and maintain bone strength. Micro array analysis of bone tissue from untreated TTD animals showed that typical bone markers (SOST, Bglap, Coll-1, ALP, Periostin, Runx2 and TRAP) had a similar pattern of expressional change.
Conclusion
TTD mice showed accelerated bone loss during aging which could be reversed with drug treatment. At young age their bone phenotype did not differ from WT animals. This makes the TTD mouse model a suitable screening tool for determining bone-preserving qualities of both existing and novel treatments. In addition, its spontaneous development allows the discovery of biomarkers that may predict osteoporosis onset.

References: