Age-related skeletal dynamics and decrease in bone strength in DNA repair deficient male trichothiodystrophy mice.

Abstract: Accumulation of DNA damage caused by oxidative stress is thought to be one of the main contributors of human tissue aging. Trichothiodystrophy (TTD) mice have a mutation in the Ercc2 DNA repair gene, resulting in accumulation of DNA damage and several features of segmental accelerated aging. We used male TTD mice to study the impact of DNA repair on bone metabolism with age. Analysis of bone parameters, measured by micro-computed tomography, displayed an earlier decrease in trabecular and cortical bone as well as a loss of periosteal apposition and a reduction in bone strength in TTD mice with age compared to wild type mice. Ex vivo analysis of bone marrow differentiation potential showed an accelerated reduction in the number of osteogenic and osteoprogenitor cells with unaltered differentiation capacity. Adipocyte differentiation was normal. Early in life, osteoclast number tended to be increased while at 78 weeks it was significantly lower in TTD mice. Our findings reveal the importance of genome stability and proper DNA repair for skeletal homeostasis with age and support the idea that accumulation of damage interferes with normal skeletal maintenance, causing reduction in the number of osteoblast precursors that are
required for normal bone remodeling leading to a loss of bone structure and strength.