Results Exposure to hypoxia induced a significant increase in cellular RANKL mRNA and protein expression, with minimal changes of the cellular OPG. In contrast soluble OPG levels significantly decreased following hypoxia exposure with no changes in the soluble levels of RANKL. Concomitant exposure to both hypoxia and TNFα had an additive effect resulting in a further increase of the RANKL/OPG ratio. Small interfering RNA against HIF 2α but not HIF 1α was able to abolish hypoxia effect on cellular RANKL expression. Hypoxia mimicking by prolyl hydroxylases inhibitors acted synergistically with TNF in inducing pit formation and resorption of synthetic osteologic bone discs.
Conclusions TNF and hypoxia act synergistically to promote bone destruction potentially through a HIF2α dependent mechanism. These findings add on the current understanding of bone destruction in the setting of chronic inflammation.

8. Bone and cartilage-regeneration—Imaging

1 HYPOXIA AND INFLAMMATION SYNERGISTICALLY PROMOTE BONE DESTRUCTION

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Objective Rheumatoid arthritis (RA) is a chronic inflammatory disease characterised by synovial inflammation and consecutive local hypoxia, leading to cartilage and bone destruction. Hypoxia promotes osteoclasts formation in vitro but its role in mediating bone destruction in the presence of chronic inflammation has not previously been investigated. The authors aimed to investigate the effect of hypoxia on the RANKL/OPG system and bone destruction in the presence of pro inflammatory stimuli.
Methods The authors investigated the in vitro effect of hypoxia on RANKL/OPG expression in osteoblast-like (Saos2) cells. Cells were cultured in normoxic (21% pO_2) or hypoxic (0.5% pO_2) conditions with or without tumour necrosis factor α (TNFα). Expression of RANKL and OPG mRNA was detected by rtPCR. Cellular and soluble forms of RANKL and OPG proteins were determined by western blot and ELISA respectively. Hypoxia effect on bone resorption was evaluated in a dentine pit formation assay using peripheral blood mononuclear cells from RA patients. Statistical analysis was performed using one-way analysis of variance.