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PROTECTIVE ACTION OF CLODRONATE ON OSTEOARTHRITIC CARTILAGE

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Bisphosphonates enhance bone mass and prevent bone resorption in patients affected by chronic inflammatory and degenerative arthropaties. In details, in animal models, clodronate shows an anti-inflammatory effect and decreases cartilage damage. In patients with rheumatoid arthritis, clodronate decreases plasma levels of proinflammatory factors secreted by synovial macrophages.
Since a few informations about clodronate action on chondrocytes are available, we studied the effect of clodronate (1 μM - 1 mM) on human articular chondrocytes from cartilage of osteoarthritic patients. Biological and molecular effects of clodronate have been evaluated as follows: - Proliferation and viability by cell counting and Trypan Blue staining. - Apoptosis by chromosome ladder analysis and Hoechst 33342 nuclear staining. - Mucopolysaccarides production by PAS reaction. - Metalloproteinases 9 (MMP9) and TIMP-1 expression by quantitative Real Time-PCR. - Intracellular ATP evaluation by chemoluminescent luciferase assay. - Osteoprotegerin (OPG) and RANK-Ligand (RANK-L) release by ELISA test on culture media. - Collagen I and II expression by Reverse Trascriptase-PCR and Real Time-PCR. Higher doses of clodronate inhibit cellular proliferation and maintain >80% cell viability along 6 days of incubation. Cell number decrease was due to apoptotic events, as evidenced by chromosomic ladder and picnotic nuclear fragmentation (10% for 100 μM and 13% for 1 mM clodronate versus 5% of control). MMP9 expression is strongly reduced while OPG and RANK-L release is not altered. Clodronate doesn't affect mucopolysaccarides production. Intracellular ATP significantly increases in the presence of 10 μM of clodronate, when compared to control (26.92±0.23% of increase). Collagen I and mainly collagen II expression are significantly enhanced after incubation with clodronate. These results show that clodronate acts on chondrocytes promoting a protective and regenerative action on osteoarthrtitic cartilage.

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