Bisphosphonates (BPs) are pharmacological agents widely used in clinical practice for the treatment of diseases characterized by increased bone remodeling, such as osteoporosis. Their main biological effect is the inhibition of osteoclast formation, maturation and activity, resulting in a strong inhibition of bone reabsorption processes. Nevertheless, there is increasing evidence that BPs can act not only through a direct action on osteoclasts, but also by an indirect effect mediated by osteoblasts, which may represent an alternative target and could be required for the complete anti-absorptive effects of these drugs.

The capacity of BPs to modify the osteoblast metabolism is only partially known; moreover, they often exert a contradictory effect on these cells depending on the dosage and the compound types studied. BPs may play a role in osteoblastogenesis, and many studies report that various BPs may modify proliferation, viability and several aspects of osteoblast metabolic activity in normal and pathological conditions, supporting the hypothesis that the overall positive effect of this class of compounds on bone mass and strength is due not only to their influence on osteoclast, but also on bone forming cells.

Recently, advances in understanding the physiopathology of bone metabolism have underlined the significant role of adipose tissue as independent endocrine and paracrine factor associated with the production of bioactive molecules, called adipokines, which are able to act as modulators of bone remodeling and have a significant effect on bone structure, presenting both stimulatory or inhibitory effects on osteoblast differentiation, growth, and mineralization. Particularly, experimental data have shown a relationship between plasma levels of adiponectin and body fat, bone mineral density, sex hormones, peri- and postmenopausal changes, suggesting that this adipokine may modulate bone metabolism. Adiponectin has been observed as a potential factor that may increase osteoblasts proliferation, differentiation and activity. It has previously been shown that adiponectin stimulates bone formation and inhibits bone resorption, advocating a possible positive role as regulator of bone mass. Several in vitro studies demonstrate that adiponectin stimulates the differentiation and mineralization of osteoblasts as well as the expression of osteocalcin. Recently, it has been reported that adipokines can be produced by other tissues other than adipose tissue; particularly, human osteoblasts have also been demonstrated to express various adipokines, previously considered adipocyte specific gene products, which can act through an autocrine/paracrine mechanism.

Here, we report the preliminary data concerning the effect of the BP alendronate on the production of adiponectin by human osteoblastic cells. Normal human osteoblasts were obtained from fresh bone fragments deriving from 10 adult healthy subjects undergoing surgery for traumatic fractures of limbs. None of the donors had been taking drugs which could interfere with bone metabolism and none was affected by metabolic bone disease. Osteoblast cell culture were obtained as previously described; osteocalcin production and phosphatase alkaline activity were evaluated to confirm the osteoblast lineage of cultured cells. Cell cultures were treated with alendronate at different concentrations (ranging from $10^{-6}$ M to $10^{-4}$ M) for 48 hours, before the evaluation of the adiponectin. We found that lower alendronate concentrations significantly increased the adiponectin production compared to untreated cells in a dose-dependent manner, but higher alendronate concentration significantly suppressed adiponectin production (Fig. 1). Also, osteocalcin production and alkaline
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Phosphatase activity were increased in alendronate-treated cells, but only with lower drug concentrations, whereas they were markedly suppressed by the higher concentration, probably due to a cytotoxic effect. Our results, although preliminary, further confirm the previously published data showing a direct effect of BPs on the metabolic activity of human osteoblasts and support the hypothesis that these drugs can modify the expression of substances, such as adipokines, that play an essential physiological role in bone metabolism. Additional studies would be useful to establish the effect of various BPs at several concentrations on the production of different adipokines also in pathological cells, particularly in osteoblasts deriving from osteoporotic subjects.

References