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Invited Plenary Abstract
P25

Future of new Vitamin D analogs

Kyoji Ikeda
National Center for Geriatrics and Gerontology, Japan

The vitamin D hormone [1α,25$(OH)_2D_3$] exerts pleiotropic effects through the nuclear vitamin D receptor (VDR). The connection between vitamin D and bone resorption started in 1972, when it was reported that 1α,25$(OH)_2D_3$ stimulates bone resorption in fetal long bone cultures. In 1997-98, 2 important cytokines were discovered, osteoprotegerin (OPG), which protects bone by negatively regulating osteoclast formation, and OPGL or RANKL (receptor activator of nuclear factor-κB ligand) as an essential cytokine for osteoclast formation. The demonstration that 1α,25$(OH)_2D_3$ induces RANKL in ostoblastic/stromal cells provided the molecular proof that 1α,25$(OH)_2D_3$ is a bone-resorbing hormone that acts on osteoblasts to stimulate osteoclastogenesis indirectly.
Unexpectedly, through a series of experiments in osteoporosis models with accelerated bone resorption, we found that pharmacological doses of active vitamin D drugs inhibit bone resorption *in vivo*. I will summarize what has been learned from these pharmacology experiments, and present data on the anti-osteoclastogenic action of VDR, direct action of VDR on bone marrow macrophages, c-Fos protein as a target of VDR, and synthesis of mechanism-based, new vitamin D analogs.