I90. NOVEL THERAPEUTIC TARGETS WITH POTENTIAL TO INFLUENCE BONE/MUSCLE

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The prevention of fragility fracture relies on the triad of balanced nutrition, including calcium, protein and vitamin D; physical exercise; and pharmacological therapies. The goals of these measures are to modify the two main components of fracture risk, which are mechanical overload, i.e. falls, and mechanical incompetence, i.e. bone fragility. For the latter, new regimens are in development aimed at increasing bone mass and particularly bone strength, by influencing cellular and biochemical pathways not targeted by available anti-osteoporosis agents. For instance, to transmit to the osteoblast signals of mechanical loading or parathyroid hormone, osteocytes are using the WNT/beta-catenin pathway. This pathway is becoming the target of pharmacological intervention to decrease the expression of negative regulators of bone formation like sclerostin. Phase III trials, monoclonal antibodies against sclerostin, tested either against placebo, or alendronate, over 1 year, followed by denosumab, are ongoing. Odanacatib is a selective inhibitor of cathepsin K, which was tested in a 2-year phase IIb dose-ranging study given once weekly or placebo, and in extensions. Continuous treatment up to 8 years resulted in further gains in BMD. Bone-resorption markers remained reduced, while there was no significant change in bone-formation markers. The results from a phase III trials have demonstrated a consistent antifracture efficacy on vertebral and non-vertebral, including hip fractures. Other agents targeting these pathways are under development. Combined and/or sequential therapies with available agents are further considered. For the age-related reduction in muscle mass and performance, characterizing sarcopenia, various agents affecting the myostatin activin receptor system are under clinical development. In a phase II trial, monoclonal anti-myostatin antibodies were shown to increase appendicular lean mass and muscle power, as assessed by a stair climbing test. Interestingly, pathways such as muscle derived IGF-I during muscle contraction, or myostatin are capable of influencing bone turnover as well.

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