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Background:
Industrialized countries face an amplified prevalence of metabolic disorders as a consequence of increased amount of fat in daily food intake. The main social and economic burdens of these pathologies lay in their complications including cardio-vascular diseases, cancers and osteoporosis. However, from a "bone" point of view, mechanisms linking fat intake to bone alteration remain quite controversial.

Objectives:
By demonstrating the expression of the free fatty acid receptor G-coupled Protein Receptor 40 (GPR40) in bone cells, we hypothesized that this receptor may play a role in mediating the effects of fatty acids on bone remodeling.

Methods and Results:
Using µCT analysis, we showed that GPR40-/- mice exhibit osteoporotic features suggesting a positive role of GPR40 on bone density. In primary cultures of bone marrow, we revealed that GW9508, a GRP40 agonist, abolished bone resorbing cell differentiation. This alteration of the Receptor Activator of NF-κB Ligand (RANKL)-induced osteoclast differentiation occurred via the inhibition of the Nuclear Factor κB (NF-κB) signalling pathway as demonstrated by decrease in gene reporter activity, inhibitor of κB kinase (IKKα/β) activation, inhibitor of κB (IkBα) phosphorylation and Nuclear Factor of Activated T cells 1 (NFATc1) expression. The GPR40-dependent effect of GW9508 was confirmed using shRNA interference in osteoclast precursors and GPR40-/- primary cell cultures. In addition, *in vivo* administration of GW9508 counteracted ovariectomy-induced bone loss in wild-type but not GPR40-/- mice enlightening the obligatory role of the GPR40 receptor.

Conclusions:
In a context of growing prevalence of metabolic and age-related bone disorders, our results demonstrate for the first time in translational approaches that GPR40 is a relevant target for the design of new nutritional and therapeutic strategies to counter bone complications.

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