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The human microbiota key role in the bone metabolism activity

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Abstract. **Data collection has suggested a complex correlation between the gut microbiota (GM) and bone homeostasis involving host-microbiota crosstalk. Although the GM is known to affect bone metabolism, the mechanisms linked with these effects remain unclear. The aim of this review is to current insight advances regarding how gut-derived hormones regulate bone homeostasis in humans, emphasizing gut-bone axis and bone regeneration. The GM may be engaged in bone metabolism and fracture risk. Additional investigations of the fundamental microbiota-related pathways in bone metabolism may uncover treatment strategies and enable the prevention of osteoporosis. A better knowledge of gut hormones' action on bone homeostasis may lead to new strategies for preventing and treating skeletal frailty related to age.**

Key Words:
Gut microbiota, Gut-bone axis, Bone metabolism, Metabolic disease.

Introduction

The key importance of the gut microbiota (GM) in the regenerative process of the body has been outlined by several authors. It is the place where everything commences before any symptom or pathology event is detected or evolves. The balance/unbalance between the gut constituent parts is known as symbiosis/dysbiosis, which accurately reflects a systemic health state[1-9]. The healthy human gut is dominated by six bacterial phyla: *Bacteroidetes*, *Firmicutes*, *Actinobacteria*, *Proteobacteria*, *Fusobacteria,* and *Verrucomicrobia*. *Bacteroidetes* and *Firmicutes* account for a large majority of the microbiota[10-16].

The regenerative mode and the equilibrium of the various components of the gut microenvironment play a key role in highlighting the anti-process and the core of Regenerative Medicine. Therefore, any therapeutic approach, including stem cells (SC) and immune therapy, must be conducted considering this sheer dynamism[13-19].

During the past two decades, the attention on the gut has revealed a few important features. The most critical designates the gut as a branch of the central nervous system (CNS) sharing many common physiologic and biochemical/neurochemistry traits; this is the reason why it was named the enteric nervous system (ENS), which is in charge of the entire gastrointestinal activities independently of the CNS.A second aspect discovered is the intimate interconnection between the two systems through the complex nerve-net pathways, so a disturbed ENS is often linked not only to different types of digestive disorders but could be affected by the pathogenicity occurring in the CNS and *vice versa*[20-28].

The gut's unique biological environment makes it comparable to superefficient structures in charge of absorbing, releasing, and producing many vital elements for life[29-36]. Microbes are differently distributed along the gastro-intestinal (GI) tract concerning their functions and activities, with a different presence from the stomach to the colon. A huge number of bacterial species exist from the mouth cavity through the GI tract, where the initial digestive reaction step occurs[37-45]. There are relatively stable microbial populations in the proximal part of the esophagus, while in the distal part, a unique microbial diversity dominates, constituted mainly by *Streptococcus* species together

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with minor amounts of different genera such as *Prevotella*, *Actinomyces*, *Lactobacillus*, and *Staphylococcus*[37,46-52]. The local genera tend to be stable in number and diversity and any increased level of microbial variety is linked to the insurgence of chronic inflammation responses and different types of dysplasia (Figure 1)[5,53-59].

Gut Microbiota and Bone Diseases: A Growing Partnership

Any clinical approach to regenerate damaged tissues should consider the patient's general metabolic condition. In fact, many of the systemic degenerative diseases that exist in organs and systems reflect a unique metabolic dysfunction[60-66].

These clinical disorders may include various conditions involving degeneration and loss of bone mass, skin, and epithelial destruction. Bone decay, for instance, is contradistinguished by a steady progressive decay linked to lower production of osteoid matrix, elastin, and collagens accompanied by a lower mineralization process in both cancellous and cortical bone substrates with an accelerated trend towards the remodeling mechanism due to an abnormal higher osteoclastic activity[67-72].

Overweight, obesity and associated metabolic complications, such as type 2 diabetes mellitus (DM-2), cardiovascular disease (CVD) and kidney disease, are not just a pandemic health issue but, as some studies[73-76] have confirmed, they are multifactorial complications mainly related to chronic disturbances of the GM and GI tract and possibly enhanced by specific genetic predisposition. An uncontrolled fat accumulation due to a hyperaccumulation of adipocytes tends to disrupt GM composition. Clinical studies performed on obese/overweight patients revealed a reduction in Bacteroidetes phylum, *Bifidobacterium* and *Bacteroides* with a proliferation of Firmicutes, *Staphylococcus*, *Enterobacteriaceae* and *Escherichia coli*. This dysbiosis eventually leads to a state of alteration of local immune mediators that in turn encourages the progression of chronic inflammation and metabolic dysfunction[77-79]. The first breakdown is the gradual destruction of the gut system's protective shield, known as the "mucosal firewall", adopted to keep stable gut internal homeostatic relationships within the microbiota by reducing, as much as possible, the direct interaction between microorganisms and the epithelial cell surface[29,80,81].

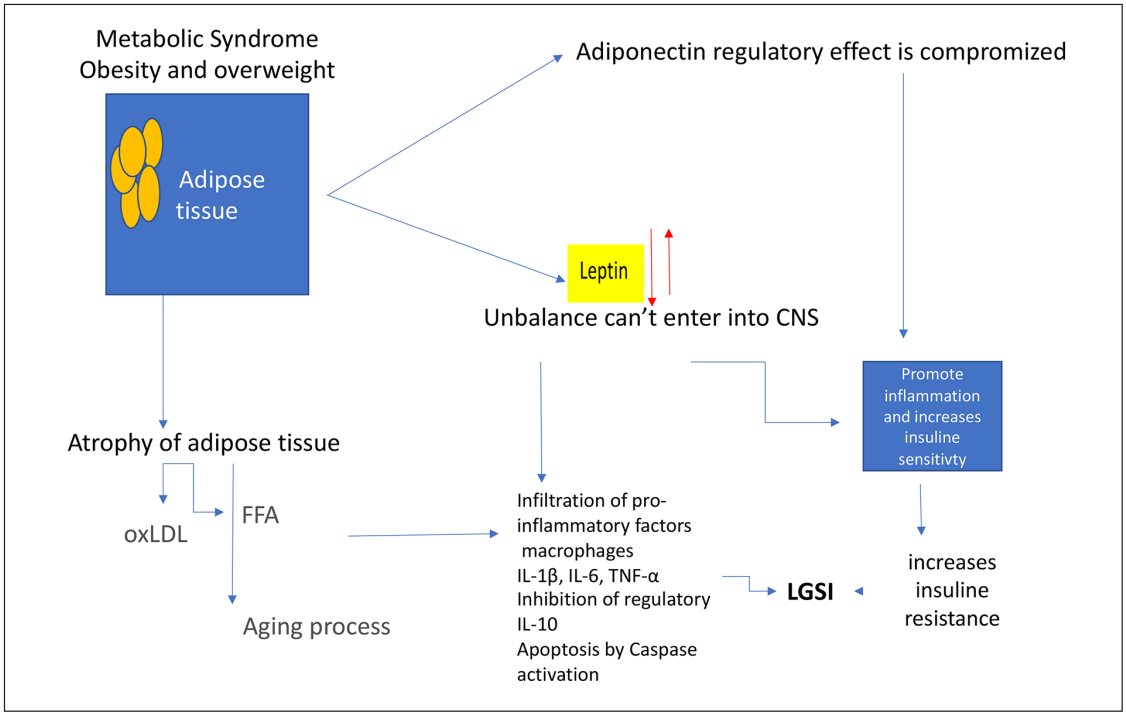

Figure 1. Structurally, the complexity of biochemical, immune, and regulatory functions of microbiota in metabolism involves the complete participation of different systems: Central Nervous (CNS), Gastro-Enteric, Cardio-Vascular, Immune and Adipose systems. Predisposing conditions that escalate in prevalence during aging, such as obesity, insulin resistance, inflammation, altered hypothalamus- hypophysis suprarenal axis, stress and hypertension are all directly and indirectly involved in the insurgence of metabolic syndrome (MS)[40].

However, what is the relationship between this issue and the bone system? Results from Wang et al[66], confirmed through the outcomes obtained from the RNA sequencing of 16S ribosomal of the intestinal microbial diversity in patients affected by primary osteoporosis, osteopenia, and a group control, that the mechanism by which bone strength and shape are determined might be the result of GM. Their conclusions revealed 3 different numbers and different typologies of bacteria evidenced in the 3 different groups of patients affected by osteopenia, osteoporosis, and normal controls. The osteopenia patients revealed an increased number of *Firmicutes* phyla with fewer *Bacteroidetes* compared to normal control patients. In addition, *Synergistetes* were detected in both osteoporosis and osteopenia patients but they were absent in the normal control group. Bacteroides, *Faecal* bacterium and *Prevotella* were the 3 main agents in the normal control group, *Prevotella* was consistently present in the osteoporosis group and low in the osteopenia group. The *Lachnoclostridium* and *Klebsiella* genera were highly present in osteoporosis and osteopenia compared to the normal control group[66].

The mechanism by which GM eventually interferes in bone metabolism inducing osteoporosis and osteopenia still remains to be fully elucidated. An initial assumption could be the disturbance of the immune-endocrine inflammatory axis that links the GM to bone metabolism. Much evidence has been collected from patients affected by the inflammatory process of Crohn's disease and ulcerative colitis, which eventually contributes to the insurgence and the development of osteoporosis. One of the mechanisms involved could be related to the immune-mediated bone metabolism that includes the receptor activator NF kappa B ligand NF-κB-RANK (RANKL) and osteoprotegerin (OPG) axis together with the immunoreceptor tyrosine-based activation motif (ITAM), all members of the TNF super-family that share the same signaling pathway of androgen hormones (Figure 2)[82].

More explicitly, the activation in mononuclear cells of NF-κB coordinates the transcription of IL-1, IL-6, IL-8 and other peptides important to the inflammatory response and up-regulates the expression of pro-inflammatory genes such as TNF-α, adhesion molecules, and different chemokines[83,84]. In addition, any disturbances in this axis contribute to a decreased presence of hormones estrogen/progesterone with a progressive augmentation of pro-inflammatory factors such as TNF that interfere in the physiological bone turnover and bone diseases, as well as in immune- tolerance and cancer[85,86].

Intriguingly, OPG, which has been shown to inhibit osteoclast genesis *via* RANK, is expressed primarily by bone marrow stromal mesenchymal stem cells. These cells can be activated in B lymphocytes, follicular dendritic cells, and can be up-regulated by TGF-β, IL-1, TNF, estrogen,

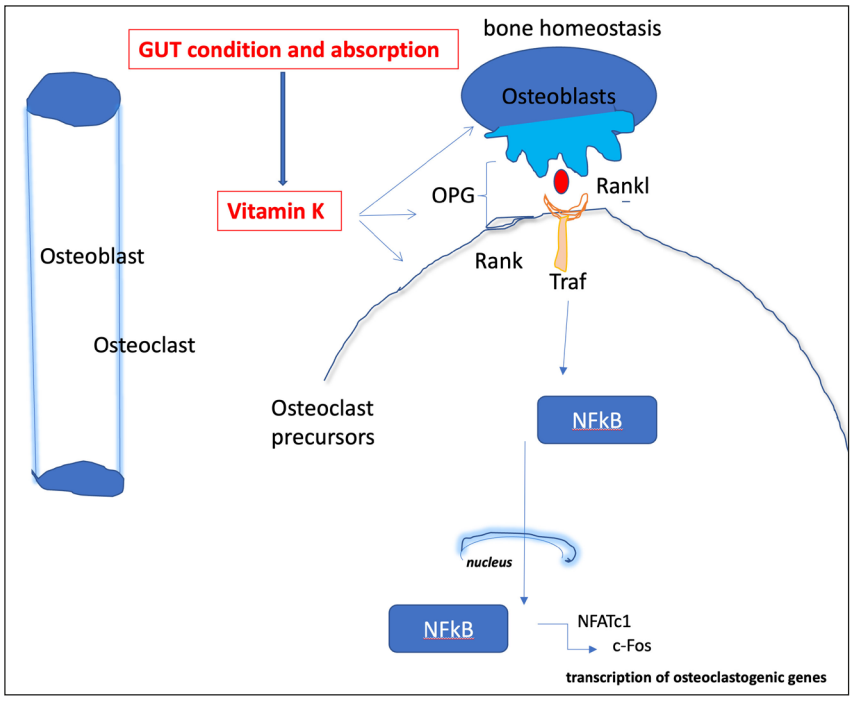

Figure 2. Normal osteoclastogenesis signaling intracellular pathway takes place with the initial presence of RANKL (ligand) which is a byproduct of osteoblasts activity under physiological conditions. Osteoblasts bind to RANK located on osteoclast precursors, once the bound is achieved, the adaptor protein TRAF6 bind on RANK and activate the NF-κB initiating the translocation into the nucleus. Within the nucleus, c-Fos is expressed acting with NFATc1 to switch on the transcription of osteoclastogenic genes. OPG, expressed by BM stromal stem cells, inhibits the initiation of the osteoclast activation by blocking the RANKL initiation phase[83].

Wnt ligands and down-regulated by prostaglandin E2 (PGE2) and glucocorticoids. Of note, in the situation of estrogen deficiency, the RANKL is over-expressed, and OPG is downregulated, promoting osteoclast hyperactivity, a condition that explains the bone loss in both males and females after a certain age[87-89]. Another important phenomenon that alters gut functions is the super-presence of osteoclast remodeling activity that is always connected to the equivalent over-expression of TNF-α, interleukins 1α and 1β, IL-6, IL-11, IL-17, TGF-α, epidermal growth factor (EGF), and prostaglandin E2[90,91].

The role of IL-6 has been investigated, and the results confirmed its involvement as a central actor in osteoporosis which also relates to a concomitant decrease of both male and female sex steroids. Interestingly there have been implied genetic variations in the IL-6 and IL-1 receptor antagonist genes that were strictly related to the inflammatory mechanism typical of bowel disease and correlated bone damage[92,93]. The possibility of changing the bone decay metabolism and increasing density and mass by reversing the inflammatory process passing through the treatment of GM, was achieved using specific probiotics that revealed an important immune-modulation activity on IGF-1, TNF-α and IL-1β and stimulated the presence of IL-7 and IFN-γ (Figure 3)[94-97].

The Dual Role of Vitamin K and D in "Bone-Gut Crosstalk": Effects on Bone Metabolism

The GM functions as a multitasking system and, more precisely, as a metabolic-nervous-immune-endocrine complex structure. The GM involvement in bone formation, density and homeostasis is extremely important. Both vascular calcification and osteoporosis share a similar etiopathogenetic mechanism that is mainly related to the deficiency of gut bacteria responsible for the synthesis of vitamin K2, causing the so-called "calcium paradox", that is contradistinguished by the lack of calcium in the bone and its ectopic deposit in the vessel walls, outside bone and joints[98-101]. Notably, the vitamin K correlated enzymes, epoxide reductase (VKOR) subunit 1(VKORC1) could also be used as-104 a marker for degenerative bone conditions[102-105]. The strategic function of VKORC1 as a main oxidoreductase enzyme is to permit the absorption of vitamin K quinone by dietary uptake, reducing it into the hydroquinone (KH2) form, allowing the entry of vitamin K into the whole vitamin K cycle[106-108]. The entire following cascade leads to the oxidation of vitamin K hydroquinone to vitamin K 2,3-epoxide (mechanism that takes place in the post-translational activation of vitamin K-dependent (VKD) phase), which involves pro-

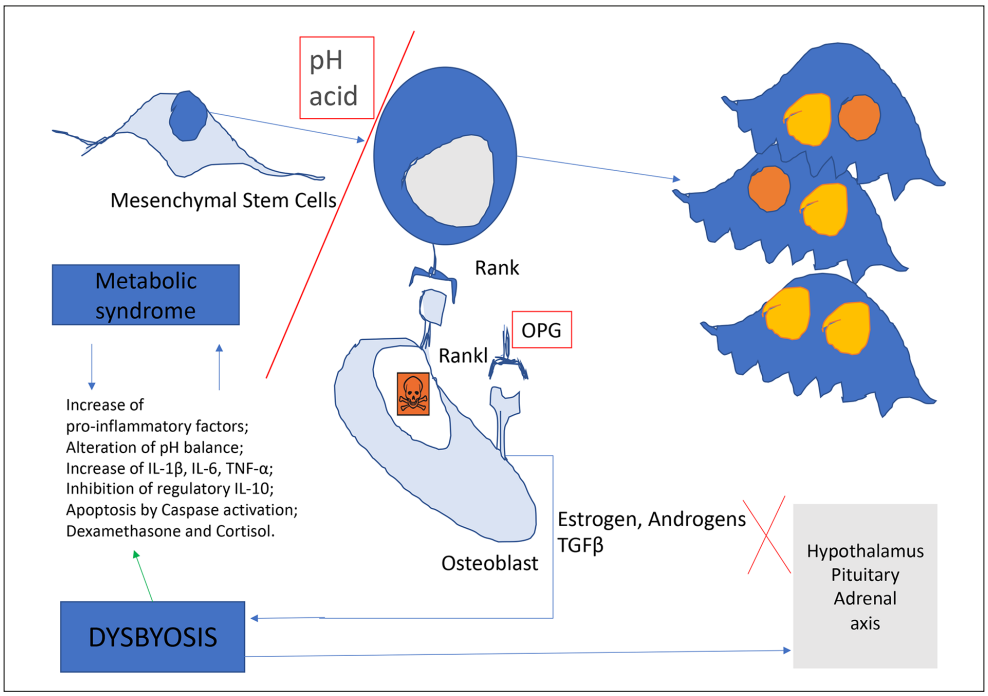

Figure 3. The possibility of changing the bone decay metabolism[97].

teins in charge of the enzymatic conversion of Glu residues into γ-carboxyglutamate (Gla) residues. The VKORC1 is in charge of completing the cycle by reducing the K>O to K and KH2, ensuring the efficient reuptake of vitamin K and proceeding to the necessary following sequences of γ-carboxyglutamate[107,109-113]. On the other hand, the Tsk gene was shown to be important in the collagen-accumulating mechanism, the Matn2 is involved in the formation of extracellular matrix like collagen, whereas CD14 controls both osteoblast and osteoclast producing modes through the B lymphocyte differentiation mechanism, indicating the SXR/PXR-vitamin K mechanism as a key regulator of bone homeostasis[19,114-119]. Bone cell's microenvironment is a 3-dimension structure composed through a cooperation of different proteins such as proteoglycans and glycosaminoglycans (GAGs) that compose the extracellular matrix (ECM). Bone tissue has a unique composition morphologically modulated through dynamic biomechanical and biophysical forces within the cellular microenvironment and is composed by the activity of multiple and different cell lineages[120,121]. Bone, as a system and structural support, tends to decay with age. The osteoclastic activity, with time and under the influences of endogenous metabolic adversities and hormonal deficiency, tends to increase. In contrast, the osteoblast activity tends to slow down and eventually stop completely[121]. Through an inevitable process, aging accelerates because of intrinsic and extrinsic factors leading to degenerative processes and diseases. Intrinsic influences may include a genetic predisposition and several micro-molecular and cellular environment abnormalities, hormonal and biochemical and metabolic diseases. External factors include lifestyle, nutrition, and comorbid medical conditions and drugs.

The underlying mechanism of osteoporosis in older adults is strictly associated with hormonal deficiency linked with a gradual and progressive increase of bone resorption by osteoclasts and a significant osteoblast deficiency with a substantially reduced calcium matrix formation and loss of bone tissue.

The condition tends to worsen due to additional alterations of derived bone marrow stem cell differentiation predominantly towards an adipogenesis phenotype under the dominating effect of estrogen over testosterone and progesterone with a consequent lipotoxicity effect that inhibits matrix formation and mineralization.

The overall scenario is a faster decline in biochemical responses of bone remodeling with the predominance of bone resorption over bone formation[122,123]. The bone-forming matrix osteoblasts, the bone-resorbing osteoclasts, and mechanosensor/mediator osteocytes are all receptive to signaling sent through hormones, cytokines, minerals, and dietary molecules. The direct impact of sex hormones on bone health, matrix formation and density are performed through the bound of specific receptors (Androgen and Estrogen) and Mesenchymal Stem Cells (MSC).

One of the most important functions of testosterone and estrogen is their inhibitory activity on osteoblast and osteocytes premature death with a correspondent inhibition of osteoclastogenic cytokine production from immune cells such as IL-1, IL-6, IL-7, TNFα and M-CSF through the mediation effect of IgF-1[124-127].

An additional important factor in this cycle is the presence of osteocalcin (OCN), which is an osteoblast-specific non-collagenous protein. The relationship between OCN, osteoblasts and testosterone regards the way bones function as an endocrine system. The presence of OCN strictly depends on the qualitative level of osteoblasts and a deficient OCN level negatively affects the production of testosterone from Leidig cells [128-133]. Thus, Runx2 and Cyp11a1 play an important role in bone homeostasis and metabolism of non-osseous cell types like testis and breast cancer cells that confirm alternative biological participation of Runx2 in sterol/steroid metabolism pathway[126,134]. Additionally, hormones belonging to the Glp-1/leptin/insulin axis are also involved in this mechanism. The multi-task feature of GLP-1 sees this hormone involved in the expression of Runx-2 gene through the activation of osteoblast differentiation mechanism within bone marrow whilst increasing the mRNA of OCN and consequently the expression of AP and pro-peptide of type I procollagen (P1NP)[135-137].

However, to be active, OCN needs to be carboxylated at the level of three Gla residues with the presence of vitamin K, the carboxylation generates a high-affinity binding to hydroxyapatite (HAP) and allows the connection of carboxylated OCN to newly formed bone matrix[130,134,138-147].

Conversely, uncarboxylated OCN disrupts the OCN/hydroxyapatite bond supporting the OCN entrance into circulation. As previously mentioned, low levels of OCN negatively impact β cells, with greater accumulation of fat mass and decreased insulin sensitivity. This has been evidenced by the subcutaneous

infusion of recombinant OCN into mice that developed a better glucose tolerance and higher insulin sensitivity[130,147-156]. However, why and when will OCN not be able to attach to HAP? In clinical diagnostics, the circulating non-carboxylated OCN (ucOC) percentage would be used as a vitamin K biomarker. Thus, vitamin K important function reappears once again, as it affects the carboxylation process of OCN and is deeply involved in bone formation and homeostasis, as previously mentioned[157-168].

Conclusions

Mutually, this pattern of metabolic cofactors can switch gut barrier disruption and microbiota dysbiosis leading to the amelioration of bone loss progression by modulating major players of the gut-bone axis. While numerous studies report the therapeutic potential of probiotics and since the GM of certain pathological states has been relatively characterized, we speculate that the administration of certain bacterial species as probiotics could be reasonable as novel independent or adjunct therapies for several human pathologies.

Finally, these observations will lead to a better understanding of the relationship between bone homeostasis and the microbiota in aging.

Conflict of Interest
The Authors declare that they have no conflict of interests.

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Informed Consent
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Authors' Contribution
All the authors have made substantial contributions to the conception and design of the study, data acquisition, or data analysis and interpretation, drafting of the article or critically revising it for important intellectual content, final approval of the version to be submitted.

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