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# Have we Reached a Time that Therapeutic Application of Gut Microbiota & Metabolites is Feasible for Avoidance & Therapy of Osteoarthritis & Bone Correlated Diseases: A Narrative Review

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**Abstract**

Osteoarthritis(OA) represents a frequent chronic degenerative disease where bone articular cartilage is implicated in case of middle aged in addition to older subjects that might lead to joint pain as well as impairment which further might end causing joint deformity. OA, over time with escalated event of ageing worldwide OA has assumed considerable importance in view of public health problem all over world. Getting insight regarding its etiopathogenesis is key in the generation of newer beliefs for better treatment options to be planned . Earlier we had reviewed the part of gut microbiota (GM)as etiological factors in obesity , type2 Diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD), GM, bone health and vascular calcification in Chronic Kidney Disease (CKD), role of probiotics and prebiotics in their treatment .In the last decade GM has been considered to be an organ possessing multiple functions, that is intricately correlated with numerous immune, metabolic along with inflammatory functions. Here we conducted a narrative review utilizing search engine pubmed, google scholar; web of science; embase; Cochrane review library utilizing the MeSH terms like; GM: Osteoarthritis; extraintestinal manifestations of OA;IBD;SLE;RA; mineral along with bone disorders (MBD); immune modulation; TMAO; beneficial bacteria; short chain fatty acids(SCFAs); vitamin generation; role of estrogen on bone metabolism; Parathyroid hormone; microbial - associated molecular patterns (MAMP); damage - associated molecular patterns(DAMP); Probiotics; Prebiotics; from 2000 till 2022 till date. We found a total of 400 articles out of which we selected 124 articles for this review. No meta-analysis was done. Greater human along with animal information has been updated that has pointed to the presence of gut- bone axis in addition to pointed that GM along with its metabolites are intricately correlated with the pathogenesis of generation of OA that might assume the probability of becoming a therapeutic target. Here we outline the modes implicated in GM along with its metabolites impacting OA regarding intestinal mucosal barrier manipulation, intestinal metabolites manipulation, immune modulation along with approaches for avoidance or therapy of OA with this acceptance of pathogenesis of GM along with its metabolites in OA, opening newer avenues for treatment of OA.

## Introduction

Osteoarthritis(OA) represents a frequent chronic degenerative disease where bone articular cartilage is implicated in case of middle aged in addition to older subjects that presents in the form of propagating breakdown of articular cartilage, subchondral sclerosis along with hyperplasia, periosteophyte generation besides synovial injuries which can cause joint pain along with impairment or result in joint defiguration or instability [1]. With the escalated event of global aging, OA has assumed a status of considerable public health problem all over world with enhancing social medical expenditure for basically middle aged in addition to older subjects [2]. As per a study by 2020 OA has assumed the 4$^{th}$ maximum prevalent disease throughout the world [3]. In the meantime in view of high prevalence as well as robust ensuing sequelae for patients of OA has become an issue of considerable importance regarding further research [4]. in the form of a complicated chronic degenerative disease there is no clarification regarding its etiopathogenesis with restricted treatment options. Currently approaches regarding treatment are inclusive of drug therapies ,physical strategies along with surgical options. Thus a

greater insight regarding the mode of generation of OA is key for the avoidance in addition to production of OA. Moreover greater corroboration has pointed that Gut Microbiota (GM) along with its metabolites possess a crucial part in the generation along with propagation of OA [5]. in view of the human intestine possesses large quantities of microorganisms, the gut works in the form of a huge storage house for large genome, which is 150 fold greater in contrast to the quantity of human genes. Hence GM is believed to be the second gene bank for humans thus it can't be separated from the human body [6]. Furthermore, GM possesses a key part regarding host health right from birth along with crosstalk amongst intestinal epithelial cells, microorganisms as well as their metabolites being the crucial modulators amongst intestinal epithelium along with other cell kinds [7]. This crosstalk further aids in intestinal epithelium maturation, intestinal nervous system, intestinal vascular system, as well as innate immune system [8]. Additionally, GM impacts the physiological function of the host (like digestion, absorption, energy metabolism, immune defense) via neuromodulation, immunomodulation as well as endocrine modulation regarding sustenance of homeostasis of the internal milieu [9].

Recently numerous investigators besides pointing regarding decontrolling of GM as well as its metabolites is implicated in the etiopathogenic events of intestinal diseases(like inflammatory bowel disease (IBD), Crohn's disease (CD) as well as colonic cancer) in addition to that further the imbalance regarding intestinal homeostasis might stimulate different osteoporosis extraintestinal immune along with metabolic diseases(like osteoporosis, psoriasis, systemic lupus erythematosus(SLE), as well as Osteoarthritis [10]. In this context, Sheth et al. [11], illustrated that about 10-40% patients with IBD might be afflicted by a minimum of an extraintestinal involved with maximum common being musculoskeletal injuries (like OA as well as osteoporosis).In a cohort study of patients with IBD in Switzerland, Schule et al. [12], found that 57% of them had correlated osteopenia, while 20% with osteoporosis, whereas rest were associated with OA .Therefore, the intricate association amongst GM in addition to taking place along with propagation is getting recognition of therapeutic implications. Regarding intricate association of gut-bone axis [13], the objective of this review is to detail the modes of GM along with its metabolites impacting OA from the point of view of intestinal mucosal barrier manipulation, as well as approaches for avoidance or treatment of OA dependent on the idea of GM in addition to its metabolites thus acknowledgement of its recognition. Having reviewed earlier the), role of gut microbiota (GM )in obesity, Type2 Diabetes mellitus (T2DM), non alcoholic fatty liver disease (NAFLD) regarding correlation of GM in CKD besides the association with bone health and utilization of probiotics for their treatmentof CKD with its association with bone mass complications, normal physiology of bone [14-25] we decided to conduct a narrative review regarding correlation of GM in CKD besides the association with bone health and mineral metabolism (Figure 1 & 2) [26].

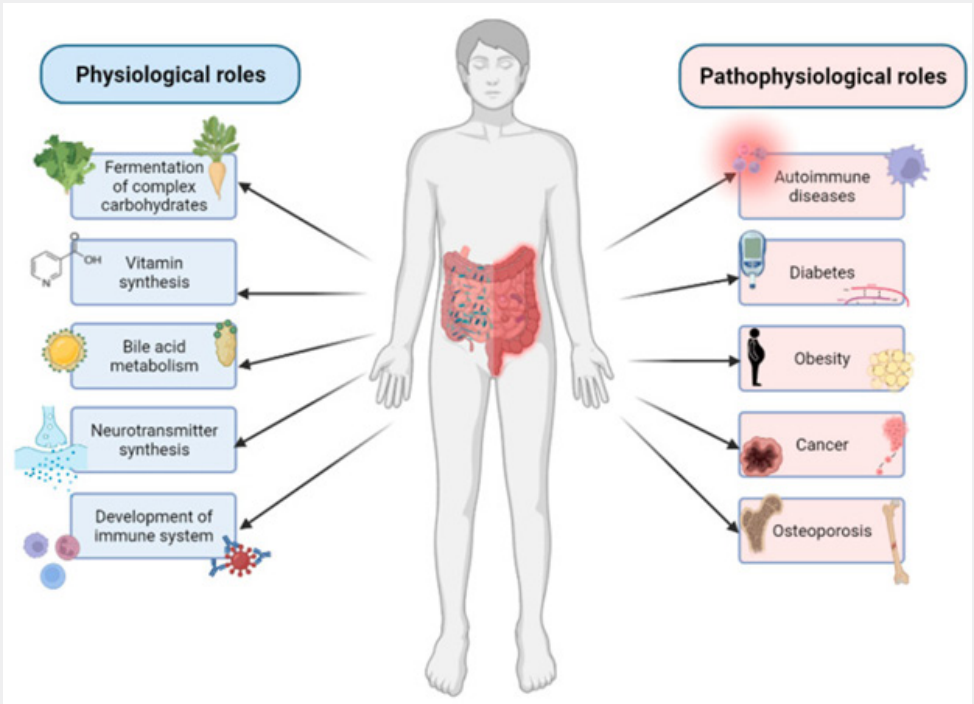


**Figure 1:** Courtesy ref no -26-The GM has various roles in the host organism. It can affect various physiological roles, such as fermentation of complex carbohydrates [25], immune system [25], synthesis of neuroactive compounds [16], vitamin synthesis [25] and bile acid metabolism [17]. It can also affect many pathophysiological (during dysbiosis) roles [21]. (Created with BioRender.com).


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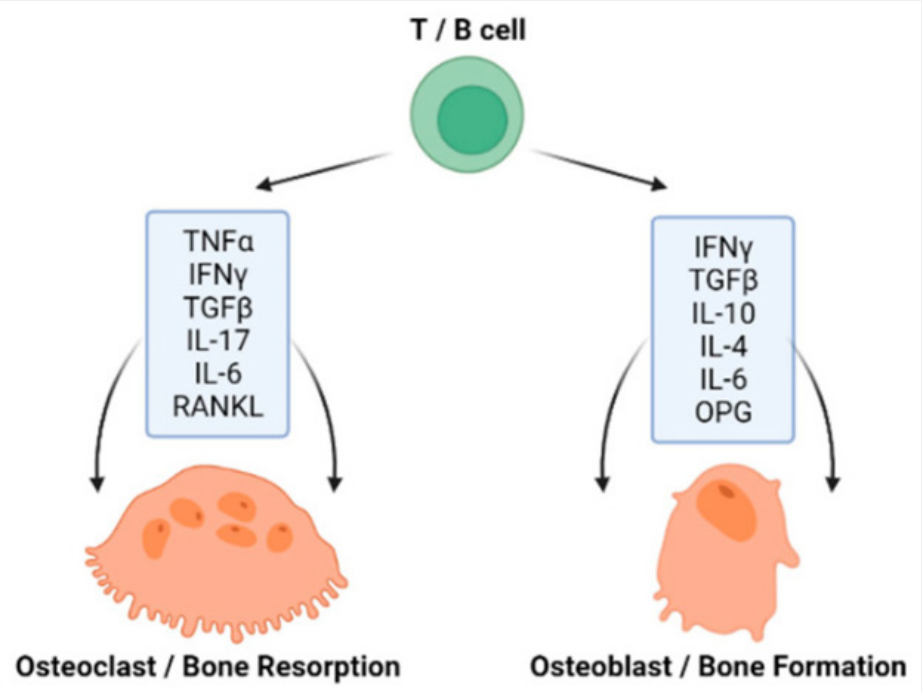


**Figure 2:** Courtesy ref no -26-Lymphocytes can regulate bone remodeling through the expression of cytokines, as well as RANKL and OPG[rev in 19].

## Methods

Here we conducted a narrative review utilizing search engine pubmed, google scholar; web of science; embase; Cochrane review library utilizing the MeSH terms like; GM: Osteoarthritis; Extraintestinal manifestations of OA;IBD;SLE;RA; mineral along with bone disorders (MBD); immune modulation; TMAO; beneficial bacteria; short chain fatty acids(SCFAs); vitamin generation; role of estrogen on bone metabolism; Parathyroid hormone; microbial –associated molecular patterns(MAMP); damage-associated molecular patterns (DAMP); Probiotics; Prebiotics; from 2000 till 2022 till date.

## Results

We found a total of 400 articles out of which we selected 124 articles for this review. No meta-analysis was done.

### The intricate association amongst osteoarthritis, gut microbiota along with obesity

Gut Microbiota (GM)is key factor regarding activation along with sustenance of intestinal physiological function , as well as possesses an inerasable part regarding sustenance of host's health in addition to its homeostasis. Under natural situations GM is implicated in sustenance of dynamic balance with the host as well as external milieu [27]. Furthermore, it is in general appreciated that the first colonizers are the microorganisms present in the vaginal canal or the milieu which babies come in relation with at the time of birth. At the initiation of babies birth its intestine possesses plenty of oxygen**,** basically in view of colonization of partial bacteria with greater requirement of oxygen like *Escherichia Coli* (E.Coli), as well as *Staphylococcus* [28]. Once there is reduction of oxygen with time, as well as reduction of pH takes place, certain anaerobic bacteria like *Bifidobacterium* as well as *Bacteroides* start colonizing**.** With the escalation of babies age , different bacteria are in the event of correlative impact. Not prior to 2 years of age an adult kind GM structure with stability is achieved [29]. Once old age approaches reduction of GM variations might be correlated with lifestyle alterations .Reduction in advantageous bacteria like *Lactobacillus***,** as well as *Bifidobacterium* decreased in numbers losing their dominance [30]. These factors further aid in the imbalance of as well as intestinal microecology, as well as the link amongst escalated age associated chronic diseases like heart disease, Alzheimer's as well as Parkinson's diseases [31].

GM are in a symbiotic association with the host impacting key associations like nutritional ingestion, food digestion, systemic metabolism, immune system generation , sustenance of physiological functions as well as building of disease defense for the human bodies [32]. In the meantime in particular in the recent past greater human as well as animal studies have pointed to the presence of gut-bone axis apart from intricate association of pathogenic event of OA, that time might assume a probable target of considerable significance for therapeutic interference [33]. Dependent on this Gleason et al. [34] highlighted the part of gut-joint axis regarding the pathogenic event of OA,


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besides acknowledging regarding correlation, implicating GIT microbiome, immune along with inflammatory reaction whose induction takes place by them as well as total joint health. In the meantime gut is believed to be an interesting in addition to innovative target regarding the treatment of OA, besides dietary manipulation or supplementation of fibers, Probiotics as well as Prebiotics might yield a positive impact on the gut- joint axis [35].

Obesity is of considerable importance regarding OA induction. Canonically the escalated joint wear secondary to enhanced stress locally in the obese joints is the basic etiology of OA. Nevertheless, greater investigators have pointed that escalated joint does not possess the capacity of offering reasons, regarding association amongst obesity along with OA [36]. Moreover, obesity possesses the capacity of escalating the prevalence of OA in joints which are not body weight bearing like hand joints [37]. It is the observation that non mechanical factors are implicated in the pathological event of obese OA [38]. In this event the loss of balance of GM along with its metabolites is key factor regarding triggering of escalated inflammation quantities as well as takes part in the generation of OA in obese people. Collins et al. [39], illustrated that the quantities of intestinal *Lactobacillus* reduced in obese rats along with enrichment of this particular bacteria possessed a negative association amongst the quantities of inflammatory factors in the blood, synovial fluid in addition to Mankins score of joints. This study further pointed that this loss of balance of GM as well as escalated intestinal permeability led to the escalated quantities of lipopolysaccharides (LPS) in the blood along with the inflammatory reaction stimulated by LPS might be implicated in the pathogenesis of OA. Li et al. [40], further highlighted the crucial importance of evaluation of part of nutrients- GM-bacterial metabolites axis in the pathogenesis of OA from various angles like obesity, aging as well as sex. From the point of view of obesity, the metabolic inflammation, insulin resistance (IR), along with other associated diseases secondary to the conditions whose etiology is GM along with its metabolites, which might aggravate the pathological event of OA.

Regarding human work it is well acknowledged that both prevalence as well as robustness of OA is considerably greater in case of women in contrast to men besides the incidence along with robustness of OA in women subsequent to menopause is greater significantly in contrast to prior to menopause [41]. In this event GM might manipulate the immune reaction by impacting the sex hormones. Like *Clostridium* possesses the capacity of transforming glucocorticoids into androgens along with the variation in addition to abundance of bacteria species(spp)are positively associated with the quantities of serum androgens [42]. In view of GM being implicated in the excretion along with circulation events of sex hormones, the belief of ''microgenderome'' pointed to the part of sex hormone on the GM has been posited over time [43] see figure 3for role of estrogen on bone loss [44].

In the mean time GM further undergoes a dynamic alterations in the body along with kinds of GM apart from advantageous bacteria escalate in infants. On bodies undergoing regression with age, both GM enrichment along with variation reduce as well as inimical bacteria escalate [45]. Xiangya OA group [46] conducted a population dependent study inclusive of1388 middle aged men as well as older subjects, which illustrated that the changes in the GM arrangement were found amongst those who took part in the study possessed the symptomatic hand OA with lesser comparative enrichment *of Roseburia*, however greater comparative enrichment of *Bilophila* as well as *Desulfovibrio* at genus level was commonly seen in case of symptomatic hand OA. In another population dependent study, Rushing, et al. [47], illustrated that in cases of patients with knee along with hand OA, unique faecal microbiome possessing the properties **o**f escalated products of proteolysis, disturbance in leukotriene metabolism along with alterations in the microbial metabolites in contrast to healthy controls occurred. Chen et al. [48], conducted assessment of GM in 57 patients with OA with equivalent healthy controls documented that the enrichment along with variations of GM inpatients with OA were correlated with significantly decreasing quantities of *Bifidobacterium longum* along with *Faecalibacterium* whereas there was escalated quantities of *Clostridium.* Wang et al. [49], conducted a prospective study that was inclusive of 182 stool samples from overweight OA (n=86 )besides overweight normal individual (n=96) along with observed reduction of variations of GM along with enrichment in overweight OA patients. As per the observations 9 branches in addition to 87 genera varied significantly amongst overweight OA patients along with overweight normal individuals. Lee, et al. [50], documented that the *Firmicutes: Bacteroides ratio* can be believed to be the probable pointer for the anticipation of generation of Rheumatoid Arthritis (RA) however, if other genera or particular spp could further possess an anticipator part needs future examination. With all the publications regarding GM along with OA agreed to the accumulating proof is there for GM taking part regarding pathological manipulation of OA [51] along with illustrated variations in makeup, enrichment as well as arrangement in variable quantities. Apart from sex, age, dietary consumption, lifestyle factors might have considerable association amongst GM along with OA.

Additionally, investigations conducted in **a**nimals by Guan et al. [52], illustrated that in mice with damage stimulated OA, the loss of balance of GM stimulated by antibiotics possessed the capacity of decreasing quantities of LPS along with inflammatory reaction ,thus escalated improvement of OA subsequent to joint damage [52]. Collins et al. [39], examined the association amongst GM, systemic LPS quantities along with local inflammatory status as well as OA in a fat rich sucrose rich diet stimulated obese rat model along with invented an intricate crosstalk association amongst GM in addition to adiposity obtained inflammation along with metabolic OA. Ulici et al. [53], saw that in contrast to particular pathogen free (PPF) mice with damage stimulated OA,


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the Germ Free (GF) mice possessed greater advantageous synovial scores besides articular cartilage structure pointing to factors associated with GM facilitated the generation of OA subsequent to joint damage. Furthermore, Hahn et al. [54], contrasted the early reaction to damage stimulated OA in the canonical in addition to GF mice along with documented that the variations in GF mice in contrast to canonical mice had an association with metabolic pathways which manipulated the inflammation correlated with the innate immune system (Figure3) With the animal studies that Liu et al. [55] had summarized slowly a direct gut-bone connection gets proven over time thus chance of generating innovative evaluation of pathogenesis of OA with subsequent probable new therapeutic strategies for OA.

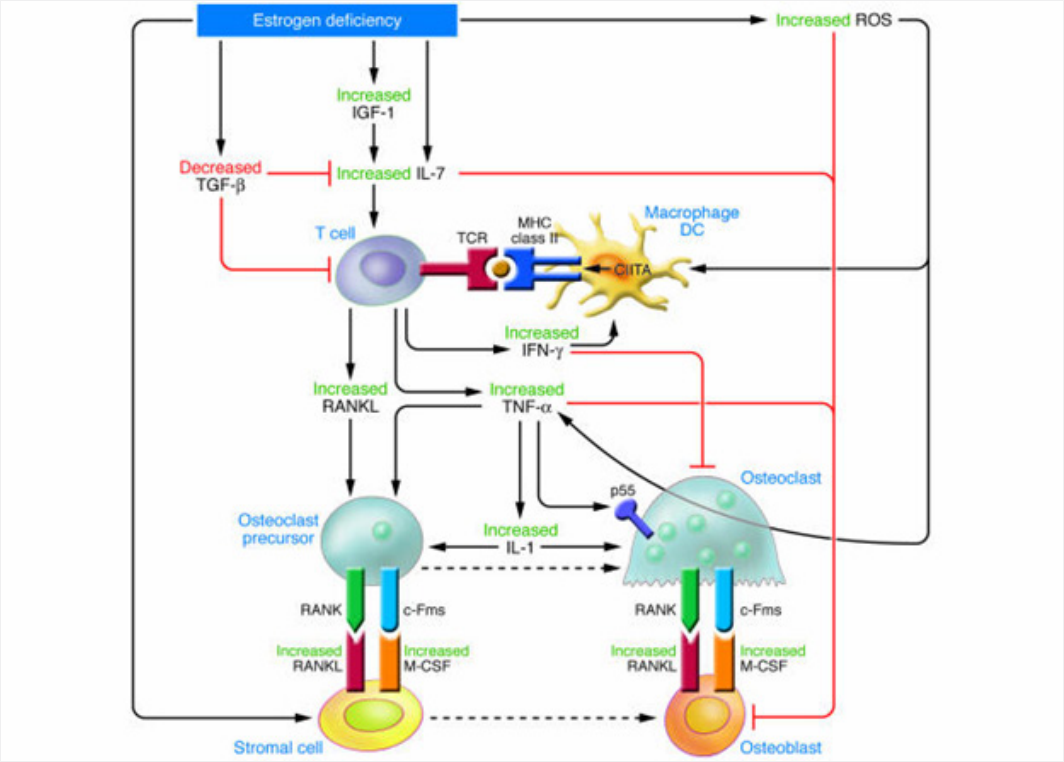


**Figure 1:** : Courtesy ref no-44Schematic representation of the main mechanisms and feedback interactions by which estrogen deficiency leads to bone loss. The bone loss induced by estrogen deficiency is due to a complex interplay of hormones and cytokines that converge to disrupt the process of bone remodeling. Estrogen deficiency leads to a global increase in IL-7 production in target organs such as bone, thymus, and spleen, in part through decreases in TGF-β and increased IGF-1 production. This leads to an initial wave of T cell activation. Activated T cells release IFN-γ, which increases antigen presentation by DCs and macrophages (Mϕ) by upregulating MHC class II expression through the transcription factor CIITA. Estrogen deficiency also amplifies T cell activation and osteoclastogenesis by downregulating antioxidant pathways, leading to an upswing in ROS. The resulting increase in ROS stimulates antigen presentation and the production of TNF by mature OCs. The combined effect of IFN-γ and ROS markedly enhances antigen presentation, amplifying T cell activation and promoting release of the osteoclastogenic factors RANKL and TNF. TNF further stimulates SC and OB RANKL and M-CSF production, in part via IL-1 upregulation, driving OC formation. TNF and IL-7 further exacerbate bone loss by blunting bone formation through direct repressive effects on OBs.

## The implications of intestinal mucosal barrier manipulation

The intestinal barrier comprises of mechanical barrier, chemical barrier in addition to biological barrier.

a. The mechanical barrier is made up of intestinal mucosal epithelial cells, intercellular tight junctions as well as bacterial studies have pointed to the presence of avoidance of inimical substances like bacteria along with endotoxins gaining entry from the intestinal mucosal [55].

b. The chemical barrier comprises of mucus liberated by epithelium, digestive juices, as well as anti- bacterial constituents generated by parasitic bacteria [56].

c. The immune barrier is constituted of intestinal mucosal lymphoid tissues(mesenteric lymph nodes as well as intraepithelial lymphocytes) could produce local mucosal immune reaction along with particular liberating secretory immunoglobulin (sIgA) In the context of avoidance of pathogenic antigens [57]. The biological barrier is constituted of the microspatial structure generated amongst the normal parasitic flora of intestinal tract besides that of host intestinal tissue [58]. Hernandez et al. [59], illustrated that the GM along with its metabolites possessed the capacity


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of resulting in aberrant intestinal mucosal barrier function by changing intestinal nutrients absorption, stimulating the alteration of intestinal immune function in addition to aberrant intestinal endothelial transport function, thus stimulating the formation along with propagation of disease like OA as well as osteoporosis .

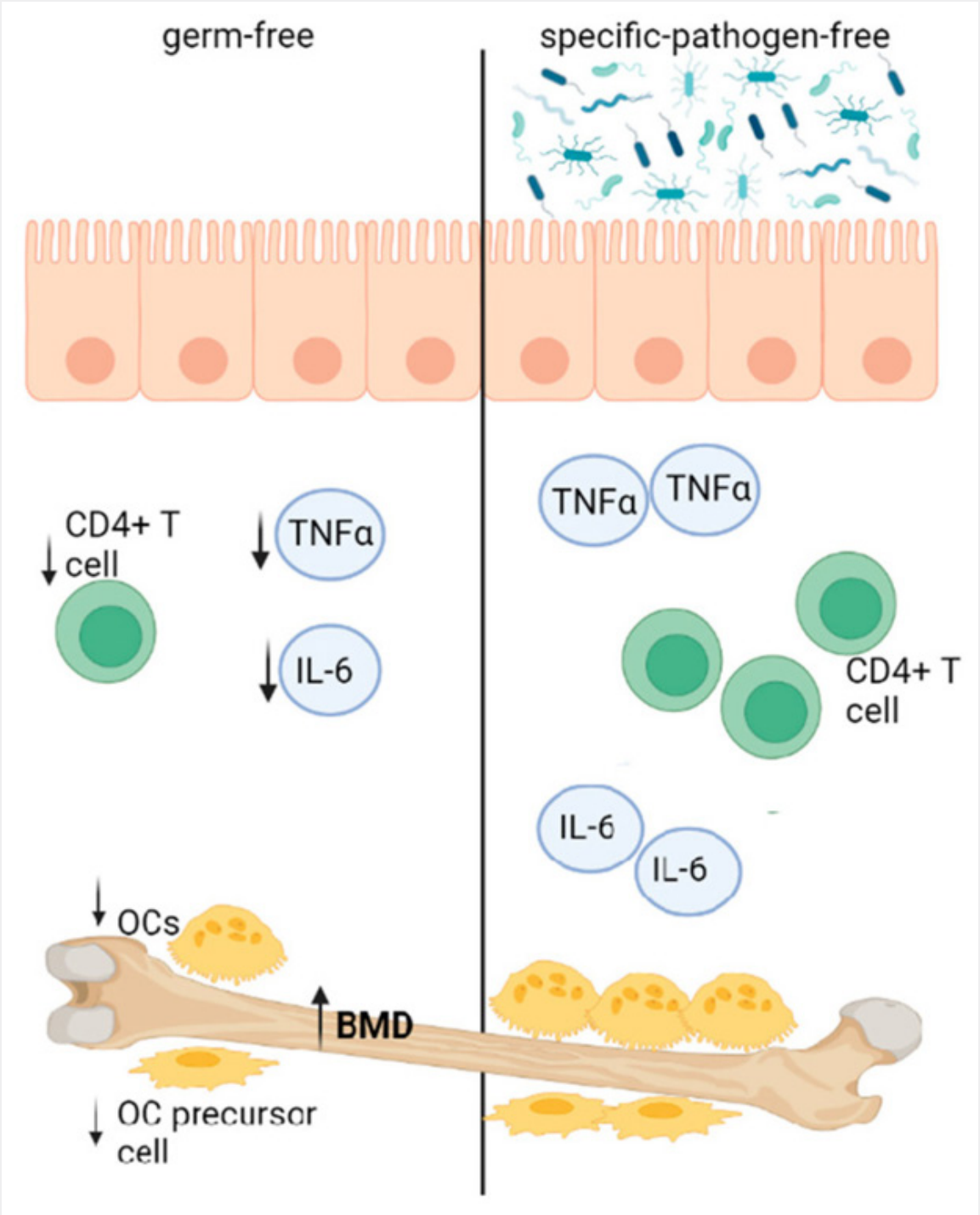


**Figure 4:** Courtesy ref no -26-Mice lacking GM exhibited increased trabecular BMD, which was associated with decreased OCs, CD4+ T cells and OC precursor cells and lowered TNFα and IL-6 expression . T cells are known to secrete osteoclastogenic cytokines such as TNF- α and IL-6 . Intestinal bacteria are needed to develop the immune system. In GF mice, the mucosal immune system is undeveloped, having reduced the lamina propria CD4+ T cells. Moreover, the spleen and lymph nodes are also affected, as they are relatively structureless with poorly formed B- and T-cell zones . (Created with BioRender.com).


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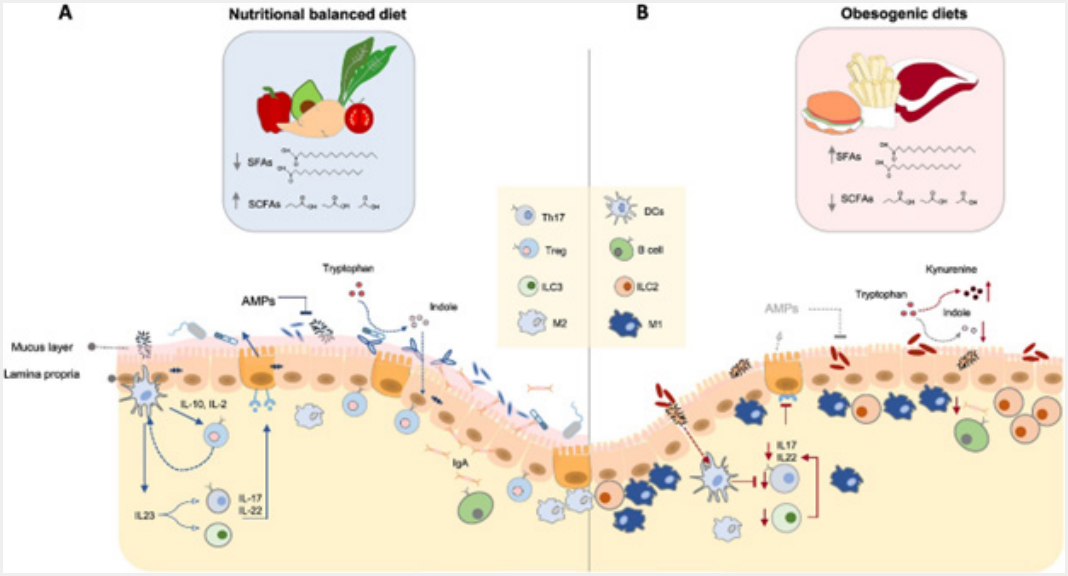


**Figure 5:** Courtesy ref no-71-(A) A well-balanced diet is rich in fruit and vegetables that prompt colonization by a highly diversified microbiota and provide fermentable substrates that the gut microbiota transforms into SCFAs. Epithelial cells control gut microbiota through the release of AMPs and secretory IgA by B cells. The immune system associated with the gut induces tolerogenic responses via DCs that induce Treg differentiation by releasing cytokines, such as IL-10 and IL-2, and stimulating ILC3s and Th17 responses by the release of IL-23. (B) In obesity, the gut microbiota is altered, and the species diversity reduced. A diet rich in saturated fat induces Pro-inflammatory responses directly by dietary components and mediated by a dysbiotic microbiota. There is also impaired production of AMPs and secretion of IgA. The gut microbiota sends signals that impair the functionality of DCs that hamper the Th17 response and Treg generation. Rupture of the intestinal homeostasis eases the recruitment of immune cells and interacts, aggravating the Pro-inflammatory milieu, which may precede systemic inflammation that worsens the metabolic disease. AMPs, antimicrobial peptides; DCs, dendritic cells; IgA, immunoglobulin A; ILCs, innate lymphoid cells; SCFAs, short-chain fatty acids; SFAs, saturated fatty acids; Tregs, T regulatory cells.

The intestinal permeability in general aids the substances possessing a molecular weight> 150KD regarding easy passage via the intestinal epithelium to gain entry into the circulation [60]. Herein the permeation mechanisms of intestinal epithelial permeability inclusive of transepithelial pathway along with the paracellular pathway.

i) The transepithelial pathway is made up of nutrients absorption occurring from the intestinal cavity via the intestinal epithelium gaining entry into the circulation , whereas selective limitation of inimical substances passage like endotoxin as well as inflammatory factors [61].

ii) The paracellular pathway is composed of the passive diffusion that takes place at the time of intestinal molecules passage via the epithelial space which is regulated by tight junctions amongst the epithelial cells that modulates the passing of intestinal products of microflora besides other macromolecules [62]. The alterations of intestinal mucosal permeability are correlated with different factors inclusive of exogenous factors like nutritional, variable types of cytokines along with actions of immune cells. These changes of GM possess the capacity of impacting the absorption of Vitamin B, VitaminC, VitaminD, VitaminK, tetrahydrofolate, carbohydrate as well as fats, the formation of Short Chain Fatty Acids (SCFA),hence impacting the growth along with propagation of intestinal mucosal cells. At the time of this event the primary concentration of metabolites basically inclusive of SCFA,5-hydroxytryptamine (5HT), tryptophan associated metabolites etc.

Significantly SCFA are the basic constituents obtained subsequent to resistant starch fermentation besides that of polysaccharides(the basic constituents of dietary fiber [63]. Once there is interference with this GM, their might be considerable alterations in the quantities of SCFA in the intestine].

Various investigators have corroborated the implications of altered acetate ,propionate as well as butyrate in bone metabolism [64]. Collins et al. [39], documented that High Fat Diet (HFD), possessed the capacity of significantly decreasing the quantities of *Lactobacillus* besides the generation of SCFA in the intestine, thus resulting in reduction of energy supply for the intestinal cells, along with bacterial enrichment was intricately correlated with the quantities of inflammatory factors in the blood besides the synovial fluid of the rat models with OA. In view of considerable importance of the constituents of the intestinal mucosal barrier ,there exists a susceptibility for decreasing of tight junctions protein zonula occludens 1(ZO1) by HFD along with changes in the intestinal permeability might change as well lead to large quantities of LPS gaining entry into the systemic circulation


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[65]. Furthermore, HFD further stimulates large quantities of saturated fat gaining access to the intestines, escalated the quantities of activated macrophages, hence liberating extra proinflammatory modulators along with adipokines that directly causes augmentation of inflammatory reaction as well as exacerbates clinical results of OA [66]. Dependent on this LPS is broadly present in the outer membrane of the intestinal gram negative bacteria that possess the capacity of stimulating inflammatory reaction as well as its escalated translocation into the circulation may work in the form of a factor which makes one prone to formation of OA. Moreover, LPS can result in activation of innate immune system, like macrophages along with neutrophils, besides form proinflammatory cytokines (like Tumor necrosis factor alpha[TNFα] as well as interleukin-1β[IL-1β]etc) leading to secondary inflammation in different joints right through body [51].

Additionally, 5 HT might interfere with the dynamic balance amongst bone generation as well as bone resorption thus impacting the sustenance of bone mass. GM possesses the capacity of generation of 5 HT along with prior studies have further pointed that GM might stimulate the chromaffin cells for generation of 5 HT with GM possessing the capacity of controlling gastrointestinal motility through the neural mode which gets activated by toll like receptors ( TLRs) [67]. Furthermore, 5 HT possesses double actions on bone metabolism . In the form of a hormone, intestinal obtained 5 HT can hamper bone generation, along with as a neurotransmitter, it can facilitate the brain obtained 5 HT, can facilitate bone generation via a cascade of pathways [68]. Tryptophan represents an aromatic amino acids that might work in the form of a biogenerational precursor for some microorganisms along with host metabolites ,hence manipulating bodily functions [69]. Tryptophan metabolism takes place in the intestine with the utilization of these pathways i)enterochromaffincells generate maximum of the 5 HT in circulation through tryptophan hydroxylase 1(TPH1)ii)partial metabolites can facilitate indoleamine 2,3 dioxygenase (IDO1) can facilitate metabolism of tryptophan to kynurenine iii)via GM actions tryptophan might be directly transformed to indole along with work as aromatic hydrocarbon receptor ligand [70,71] **(**Figure 5).

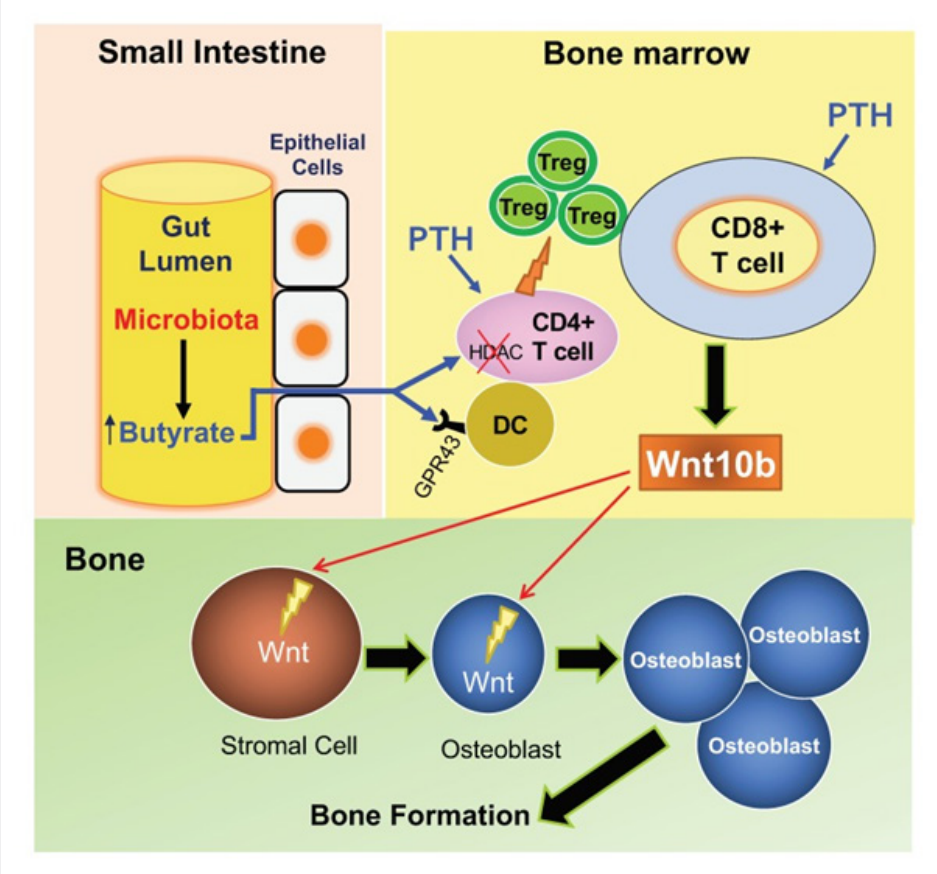


**Figure 6:** Courtesy ref no-84-Illustrating how bone formation based on Parathyroid hormone needs butyrate production via intestinal microbiota.


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Additionally, GM might modulate as well as hamper dietary inflammatory reaction generated in the food ingestion every day that possess a key part in the immune system [72]. In the form of a transmembrane transporter, the microbial-associated molecular patterns(MAMP)might impact physiological functions of far off organs along with tissues subsequent to access into the systemic circulation. As per Kim et al. [73], the MAMPs had the capacity of directly impacting the bone remodelling by stimulation of innate immune receptors present on osteocytes inclusive of manipulation of balance amongst osteoblasts along with osteoclasts .On MAMPs translocation ,the alive bacteria might cross the intestinal mucosal barrier ,with immediate clearance by the immune cells along with those bacteria not getting clearance gain access with MAMPs into the systemic circulation. Subsequent to induction of demise by immune cells within the limit of the barrier**.** Moreover, once MAMPs in circulation arrive at far off organs along with tissue**s** like various joints of limbs. MAMPs possess the capacity of activation of immune reaction as well as generate local inflammation [74]. Partial bacteria that gain access via the intestinal mucosal barrier possess the capacity of invasion of natural cells along with survival ,hence learn to avoid the effect of inflammatory reaction [75] .In general it has been acknowledged regarding the alterations in intestinal mucosal permeability as well as the of GM associated metabolites across the intestinal mucosal barrier might **i**mpact the generation as well as the propagation of OA to some degree.

## The role of immune modulation

An intricate association amongst GM along with intestinal mucosal immune system as well as the extent of alterations in intestinal microecology ascertains the stability regarding intestinal mucosal immune system in addition to systemic immune system **.**The direct touching amongst GM, its metabolites along with immune cells stimulate the immune reaction of intestinal mucosal barrier [76]. The immune cells (like T cells along with dendritic cells[DCs]) possess the capacity of crosstalk amongst GM along with migration to lymph node for activation of proinflammatory or anti-inflammatory reactions.In the meantime these cells can further liberate soluble proinflammatory or anti-inflammatory mediators/ cytokines into the systemic circulation along with **t**ake part systemic bone remodelling [77]. Besides this TLRs further work in the form of a bridge amongst intestinal mucosal barrier, GM along with the innate immune system, possessing a key part in the generation of GM. There is enrichment of dietary along with microbial antigens with the human immune system possessing the requirement of tolerating these antigens for formation of situations regarding survival of GM. TLRs is part of a significant immunosensors meant for sustenance of balanced of GM right through body [78]. TLRs is present in various innate immune cells like macrophages ,DCs along with intestinal epithelial cells that could recall the microorganisms, thus affecting the generation of anti- bacterial substances for modulating immune reactions [79]. A key association further exists amongst the innate immune reaction along with cartilage injury, that impacts the formation of OA. Articular cartilage with basic etiology comprising of numerous factors like ageing along with obesity, might stimulate the liberation of autoantigens along with damage-associated molecular patterns(DAMP),hence activation of innate immune reaction(i.e. activation of immune cells,(like immune cells , activation of complement cascade, along with liberation of anti cartilage constituents of the immune complexes) leading to formation of sterile inflammation along with further injury to the cartilage with generation of a vicious cycle [80] in the form of a broadly documented immunomodulator GM basically stimulate the host intestinal wall for collecting lymph nodes via the bacteria itself or cell wall constituents along with produce immune reactions to bacteria [71,81]. At the time of this event, the lymphocytes activation transfers the immune reactions to the full intestinal mucosal along with then generates secretory immunoglobulin(sIgA) for layering the full mucosal surface. IgA represents the maximum quantities of immunoglobulin liberated by body that might lead to avoidance of adhesion of pathological microorganisms in the intestine from gaining attachment to mucosal surface, neutralization of bacterial toxins along with possess a synergistic bactericidal part with complement along with isozyme [82]. Furthermore, GM might directly modulate immune cells, like *Prevotella capri* might result in facilitating the generation of Foxp3 + regulatory T(Treg)cells as well as $CD4^+$T cells (Th17cells) in the intestine, besides Tregs might facilitate the generation of retinoic acid -related orphan receptor γ(RORγt$^+$)-for further facilitating the differentiation of $CD4^+ROR\gamma t^+Foxp3^-$ (Th17 cells) [72,83, 84] (Figure 6).

Dependent on this GM possesses the capacity of manipulating type II hypersensitivity via Th17cells along with Tregs, for balancing immune reaction on the intestinal mucosal surface [85]. Furthermore, Ivanov et al. [86], pointed that the segmented filamentous bacteria(SFB) possessed the capacity of inducing differentiation of intestinal Th17 cells as *Bacteroides fragilis* as well could facilitate the differentiation of Th1 cells as well as Tregs. Atarashi et al. [87],posited that once the GM subsets(like SFB, Citrobacter, *Escherichia Coli 0157* along with some extracellular pathogens colonized along with become adherent with the intestinal epithelial cells, hence intestinal Th17 cells gets induced in addition to accrued together. More recently, DuTeil Espina et al. [88], observation in the study conducted by them was that of the etiologies of RA, the changes of oral bacteria besides oral diseases (like periodontitis) might lead to aberrant GM conditions, with its variations as well as enrichment might be decreased , whereas the generation of neutrophils along with biofilm possesses the inerasable part in this event.Apart from that intestinal citrullinated proteins oral modulation by oral pathogens (Porphyromonas gingivalis as well as *Actinobacillus*) can facilitate


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the generation of anticitrullinated protein antibodies. [89, 10rev by us in ref 26]. At the time of this event, the GM overgrowth might power theTh1cells reaction besides further hamper the Tregs activation by hampering the growth of *B.fragilis* resulting in immune balance loss in addition to RA formation, besides its propagation [90]. Thus it gets acknowledged that deep evaluation regarding immune modulation secondary to changed along with dyscontrolled GM offers an attractive target regarding intervening as well as avoidance besides treatment of OA.

## The approaches regarding avoidance/ treatment of osteoarthritis dependent on knowledge acquired from gm along with its metabolites

At the time of the event of continued investigations the researchers, inadvertently noticed that while attempting treatment of intestinal or extraintestinal diseases secondary to microecological conditions, partial patients of OA illustrated that they had got relieved of joint pains along with enhancement of capacity of exercise with further advances regarding treatment [91], that yielded an innovative knowledge besides greater issue regarding basic research in addition to utility in clinical therapy of OA. regarding this, the intestine represents the basic are of absorption of nutrientsin case of humans, as well as the dietary ingestion along with supplementation of miscellaneous substance /day exerts a considerable along with dynamic influence on the constitution as well as function of GM [92]. Diets possess a considerable impact on the shaping of the structure along with functional ability of GM, besides GM initiates various signal molecules via host receptors by carrying out metabolism of food obtained SCFAs along with signaling molecules like trimethylamine-N-oxide(TMAO)in a direct or indirect fashion impacting the organs at a distance(like bone, Kidney, skin, brain etc.) [93,rev by us in ref 25].The advantageous metabolites of particular foods aid in enrichment of advantageous bacteria to have a positive part regarding modulation of body homeostasis [94]. Thus this structure along with functional ability of GM can be manipulated with utilization of Probiotics as well as Prebiotics. Prebiotics, besides restoring bone depletion secondary to hypogonadism or ovariectomy,further act in enhancement of inflammatory bone correlated diseases [95].

Diet is intricately correlated with pathogenesis of OA along with magnesium, selenium as well as Vitamins [96]. Furthermore, Diets possessing escalated quantities of glucose along with HFD is directly correlated with OA. Glucose possesses a significant part in the growth along with generation of articular cartilage, besides any situation with involvement of glucose metabolism might exacerbate generation along with propagation of OA [97]. With escalat**ion** of studies illustrating that GM possess controlling action regarding glucose metabolism along with quantities of *Akkermansia muciniphilia* are significantly decreased in case of mice with type2 Diabetesmellitus (DM) or obesity . Nevertheless,on feeding these mice with polyphenol enriched canberry extract,a significant escalation of *A. muciniphilia* quantities took place that was correlated with enhancement of glucose tolerance along with insulin sensitivity based on quantities of escalated *A. muciniphilia* [98,99]. Akin to that ingestion of escalated quantities of HFD might lead to changes in the GM . Moreover, Nguyen et al. [100], documented *Lactobacillus plantarius PH04* supplementation had the capacity of efficaciously decreasing cholesterol along with triglycerides quantities of mice with hypercholesterolemia.In a pilot study Ramasamy et al. [101], pointed that *Parabacteroides, Butyricimonas, Pseudobutyrivibrio ,Odribacter, Gardinobacter* reflected the commonest bacteria in Vitamin D deficient patients with or without knee Osteoarthritis, along with these outcomes observed a non -minimal association amongst GM, Vitamin D, knee OA. Hence it is acknowledged that diet- GM axis is intricately correlated with the glucose along with lipid metabolism of body, as well as changing the dietary nutritional consumption might work out to be an efficacious strategy for ameliorating OA.

Regarding clinical scenario, the appropriate supplementation of microecological controllers is common tendency regarding rectification of microecological abnormalities as well as sustenance of homeostasis modulation. At present , the Probiotics and Prebiotics are in use broadly inclusive of in Clinical scenario along with day to day life [102]. The definition recognized by Food and Agricultural Organization of the United Nations (FAO) and world health organization (WHO) working group experts is that probiotics are live strains of strictly selected microorganisms, which once administered in adequate amounts, give a health benefit to the host . Probiotics supplementation in enough quantities aiding in the advantageous bacteria that might enhance the resistance of the host against pathogenic bacteria like *Escherichia Coli* (E.Coli) *Salmonella enteridis*, *Klebsiella pneumoniae* simultaneously, manipulate the working of intestinal mucosal barrier,make the intestinal milieu ideal along with sustenance of immune balance of body [103]. Tyagi et al. [104], found that supplementation of *Lactobacillus rhamnosus* GG possessed the capacity of escalating butyrate generating bacteria in the intestine, which facilitated formation of butyrate followed by escalating Wnt 10B along with enhance the bone mass via T regulatory cells(Tregs) expression to take part in manipulation of bone metabolism (Figure 3b). Pan et al. [105], documented that *Lactobacillus Casei* possessed the capacity of correcting GM disbalance along with restoration of enrichment of *Lactobacillus gasseri, Lactobacillusreuteri* along with *Lactobacillus vaginalis* to normal quantities besides escalated quantities of *Lactobacillus Acidophilus,*hence avoid of bone breakdown in adjuvant induced arthritis(AIA)rats. Henrotin et al. [106], carried out oral administration of freeze dried inactivated cultureof *Bifidobacterium longum* CBi0703 in a spontaneous model of OA in guinea pigs, of OA besides saw that structural cartilage damage along with breakdown of type II collagen that had occurred as a result of OA got significantly decreased observing that the probability of avoiding /treating . Sim et al. [107], further fed tyndalized *Clostridium butyricum*


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to rats for treatment or ameliorating OA, with experimental outcomes illustrating that quantities of inflammatory pointers along with markers of bone metabolism in serum got significantly decreased, whereas the quantities of interferony (IFN-γ) as well as glucosaminoglycans were significantly escalated**.** Thus this efficaciously conferred protection to cartilage along with synovium of knee joint along with decreased the generation of fibrosis. Additionally, contrasting actions of Probiotics possessing capsules inclusive of *Lactobacillus rhamnosus,Ssaccharomyces cerevisiae (boulardii)* in addition to *Bifidobacterium animalis ssp lactis* along with placebo capsules without Probiotics to those enrolled for OA. Taye et al. [108], observed that despite the reduction of pain scores associated with Probiotics treatment was **c**omparatively lesser, in clinical scenario its application might possess a considerable impact on the pain relief for patients with OA. Furthermore in the form of a newly discovered bacterium in human milk TC1633 (*Streptococcus. Thermophilus)* possesses the capacity of generating hyaluronanate in gastrointestinal tract(GIT). Lyu et al. [109], enrolled 80 patients with knee OA, conducted a randomized double blind, placebo controlled clinical study with TC1633 along with placebo, with outcomes illustrating that TC1633 might postpone propagation of kneeOA .

Conversely, Prebiotics represent a kind of indigestible food constituents which might possess an advantageous part in the host by changing the constitution of GM along with action of partial bacteria, or getting fermented by partial bacteria, along with possesses the capacity of stimulating along with activating intestinal Probiotics [110]. Prebiotics, are believed to be miscellaneous substances for bacterial growth facilitation that get protected from activity of hydrolytic enzymes along with variable kinds of proteases in addition to get transformed to SCFA subsequent to getting fermented by GM [111]. Schott et al. [112], found that *Bifidobacterium* in the intestine of obese rats got significantly decreased, besides changes of GM led to the accrual of systemic inflammatory downstream signals in addition to macrophages of synovium of joints, that exacerbated the propagation of OA. Nevertheless, by restoring GM by Fructoligosacchharides (FOS), supplementation resulted in reduction of systemic quantities of inflammation along with relieved the painful symptoms of OA. Hence the mode that might be applicable is that FOS supplementation possesses the capacity of escalating *Lactobacillus* hence sustenance of intestinal mucosal barrier along with avoidance of bacterial endotoxins or translocation of LPS as well as hampering the proliferation of *Enterobacteriaceae.* Tanabe et al.[113], on greater evaluation of the actions of Prebiotics on bone metabolism of ageing mice found that both FOS along with Glucomannans possessed the capacity of hampering bone resorption along with enhance bone metabolism of ageing mice awa further validate the objective of enhancing femoral calcium quantities basically in view of escalating quantities of Lactobacillus, Clostridium along with *Bacteroides.* Moreover absorption of FOS does not take place with ease in humans, with resistance to digestive juices of intestine thus reaching colon subsequent to consumption, act in the form of growth matrix for facilitation of ideal GM as well as indirectly possess parallel actions on human [114]. Wu et al. [115], further pointed that directly oral consumption of FOS possesses the capacity of relieving inflammatory reactions in mouse pups without changing kind ,levels along with enrichment of GM in mice. These outcomes pointed that Prebiotics might be possessing direct part regarding immunomodulation without participation of GM. Thus in particular for obesity correlated OA(basically in the form of an inflammatory response event) that is correlated with obesity associated dyscontrolling of GM might cause rectification of healthy microecological milieu by utilization of FOS fibers. FOS possesses the capacity of induction of changes of enrichment of crucial microorganisms in case of obese subjects, reduces the reaction properties of colonic macrophages, result in reduction of systemic along with local joint inflammation, confers protection to articular cartilage along with relieve OA propagation [116]. Hence accumulation of publications have corroborated that supplementation of Probiotics along with Prebiotics might decrease the expression of proinflammatory cytokines along with factors that **r**esult in cartilage in various joint tissues, escalate generation of anti-inflammatory factors as well as production of cartilage matrix cytokines for hampering both inflammation along with cartilage breakdown along with relieve the generational event of OA.

Moreover, in the last decade investigators have concentrated on Faecal microbiota transplantation(FMT) that implies transplantation **of** bacteria from the faeces of a human donor to a recipient by intragastric /oral delivery ,thus changing the makeup, structure along with enrichment of GM in recipient [117]. At the time of this event FMT could realter the architecture of intestinal micromilieu, cause improvement of inflammation along with immunity, besides metabolism of recipient's gut , hence provision of innovative strategy for numerous intestinal along with systemic diseases [118]. Huang et al.[119], pointed that FMT from a human donor that was metabolically compromised to a recipient possessed the capacity of exacerbating the event of OA in mice along with the alterations of *Fusobacterium, Faecalibacterium,* along with *Ruminooccaceae* were illustrated to have a key part of these specific microbiota in accelerating OA. In addition to that Glucosamine, as well as chondroitin sulfate-proteoglycans dependent nutraceuticals. In theory their consumption has the capacity of stimulating chondrocytes for generating new collagen as well as proteoglycans, hence aiding body in cartilage healing injured by OA [120]. Nevertheless, partial studies illustrated that these substances could in general decrease pain taking place secondary to OA, along with heal articular cartilage in some wks to mths of initiation of therapy [121]. Hence despite greater patients at present are utilizing it globally ,even now larger randomized controlled Clinical trial are required regarding confirming safety besides efficaciousness of Glucosamine, as


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well as chondroitynsulfate in OA. Moreover, nonsteroidal anti-inflammatory drugs(NSAID)is used in general in the form of therapy for OA along with prior documented part of NSAID in the control of OA from the point of view **of** GM**.** Boer et al. [122], pointed that NSAID delivery can impact the composition of GM along with some association amongst enrichment of particular groups along with pain intensity of knee OA. Vitetta et al. [123], documented that Pharmacologic agents used for therapy for OA might interfere with intactness of intestinal mucosal barrier along with cause intestinal inflammation. Usually patients who require NSAID for relief of OA correlated pain, the GM abnormalities having the properties of aberrant proliferation of gram negative bacteria can stimulate aberrant intestinal mucosal immune reaction that can lead to intestinal inflammation along with intestinal damage whereas Probiotics along with rifaximin can significantly relieve damage caused by NSAIDs [124].

## Conclusion

Thus, to summarize greater insight regarding OA greater accumulation of proof pointed to that GM along with its metabolites are intricately correlated with OA pathogenesis in addition to presence of gut- bone axis. Despite, the precise mode of the association amongst are still ill understood besides under massive assessment one can forecast that this association of GM along with its metabolites might assume the probability of becoming a great diagnostic along with therapeutic target besides for avoidance of generation of OA or other bone associated diseases. Figure 7 summarizes the functional association amongst GM along with its metabolites with OA.

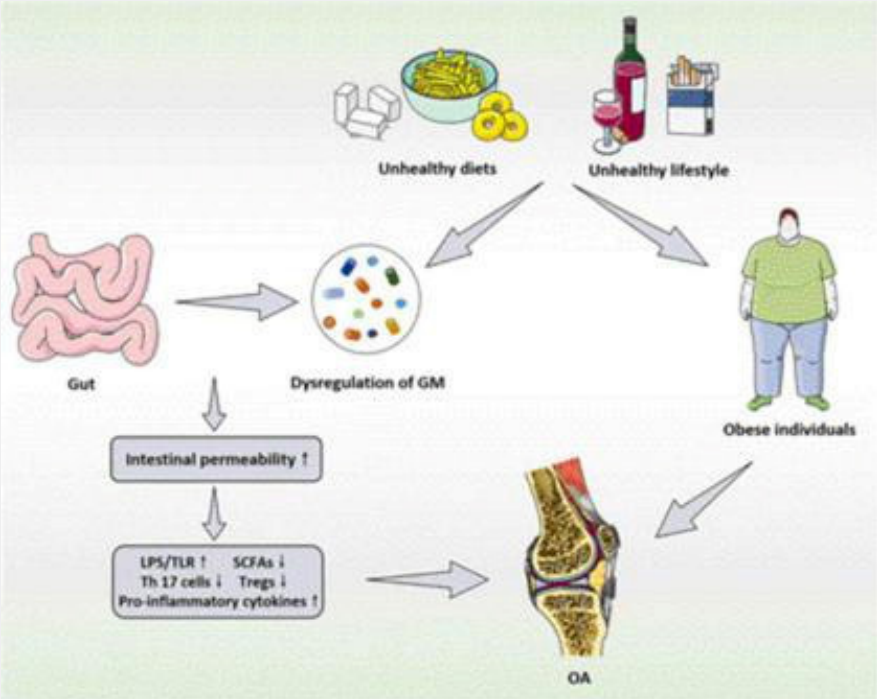


**Figure 7:** Courtesy ref no55-The functional relationship and mechanisms between GM and its metabolites and OA. GM, gut microbiota; OA, osteoarthritis; LPS, lipopolysaccharide; TLR, toll-like receptors; SCFAs, short chain fatty acids; Tregs, regulatory T.

## References


1. Bucci J, Chen X, La Valley M ,Nevitt M, Turner J, et al. (2022) Progression of knee Osteoarthritis with use of intraarticular glucocorticoidsversus hyaluronic acid. Arthritis Rheumatol 74(2): 223-226.
2. Prirto AD, Judge A, Javaid MK, Cooper C, Diez PA, et al. (2014) Incidence and risk factors for Clinically diagnosed knee hip and hand Osteoarthritis: influence of age, gender and Osteoarthritis affecting other joints. Ann Rheum Dis 73(9): 1659-1664.
3. Peterson KL, Himman RS, Metcalf BR, Campbell PK, Menz HB, et al. (2021) Podiary intervention versus usual general practitioner care for symptomatic radiographic Osteoarthritis of the first metatarsophalyngeal joint a randomized Clinical feasibility study. Arthritis Circ Res 73(2): 250-258.
4. Eriksen EF, Shabestari M, Ghouri A, Conaghan PG (2021) Bisphosphonates as a treatment modality in Osteoarthritis. Bone 143: 115352.
5. Yan Y, Yi X, Duan Y, Jiang B, Huang T. et al. (2021) Alterations of the gut microbiota in rhesus monkeys with spontaneous Osteoarthritis. BMC Microbiol 21: 328.
6. Yang G, Wei I, Liu P, Zhang Q, Tian Y, et al. (2021) Role of the gut microbiota in type2 Diabetes mellitus and related diseases. Metabolism 117: 154712.



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7. Gershon MD, Margolis KG (2021) The gut, its microbiome and the brain. J Clin Investig 131(18): 143768.

8. Jing Y, Yu Y, Bai F, Wang L, Yang D, et al. (2021)Effect of faecal microbiota transplantation on neurological restoration of spinal cord injury mouse model involvement of brain -gut axis. Microbiome 9: 59.

9. WuY, Wan J, Chou U, Pham O, Schoene NW, et al. (2019) Interaction between food and gut microbiota impact on human health. Annu Rev Food Sci Technol 10: 389-408.

10. Chen BD, Jia XM, Xu JY, Zhao LD, Jun Yi Ji, et al. (2021) An autoimmunogenic and proinflammatory profile defined by the gut microbiota in untreated patients with systemic lupus erythematosus. Arthritis Rheumatol 73(2): 232-243.

**11.** Sheth T, Pitchumani CS, Das KM (2014) Musculoskeletal manifestations in inflammatory bowel disease J Clin 48: 308-17.

12. Schule S, Russel JB, Frey D, Biedermann L, Schad M, et al. (2017) Widely differing screening and treatment practices for osteoporosis in patients with inflammatory bowel disease in the Swiss (IBD) cohort study. Medicine 96: 6788.

13. Hansen MS, Frost M (2022) Alliances of the gut and the bone axis. Semin Cell Dev Biol 123: 74-81.

14. Kulvinder Kochar Kaur, Allahbadia GN, Singh M (2020) Will Probiotics Provide the Answer for Therapy of Non-alcoholic Fatty Liver Disease (NAFLD)? - A Systematic Review. Biochem Physiol 9(1): 257.

15. Kulvinder KK, Allahbadia GN ,Singh M (2018) Weight Loss Associated with High Protein Diet Intake in Obesity: Interactions of Gut Microbiota in ProteinSources Influencing this Positive Effect. Acta Scientific Nutritional Health 2(7): 80-89.

16. Kulvinder Kochar Kaur (2021) Delivered a talk on 30th September on Advantages and Limitations of utilizing Clostridium species as Probiotics-A Sytematic Review'' in a webinar held by Gastroenterology conference on 30th September.

17. Kaur KK, Allahbadia GN, Singh M (2020) The association of dietary fatty acids and gut microbiota alterations in the development of neuropsychiatric diseases: A systematic review. Obes Res Open J 7(1): 19-45.

18. Kaur KK, Allahbadia GN, Singh M (2020) Advances in Probiotics use with the Utilization of Engineering for Diseases beyond Obesity, Non Alcoholic Fatty Liver Disease, to Treat Neurodegenerative Diseases, Metabolic Diseases like Type1 Diabetes, Infectious Diseases and Infections-A Systematic Review. J Endocrinol 4(1): 1-12.

19. Kochar KK, Allahbadia GN, Singh M (2020) Normal Anatomy of the Human Skeleton with Factors Modifying its Development as well as Regeneration. EC Clinical and Experimental Anatomy 3(11).

20. Kaur KK, Allahbadia GN, Singh M (2020) Intestinal Immune System in the Regulation of Obesity and Metabolic Syndrome-Therapeutic Implications-A Systematic Review. EC Clinical and Experimental Anatomy 3(7): 07-22.

21. Kaur KK, Allahbadia GN, Singh M (2022) An update on the Association of Gut-Liver Axis with Gut Microbiome Dysbiosis Correlated NAFLD along with NAFLD- HCC with Potential Therapeutic Approaches: a systematic review. Accepted for publication by J Hepatol Gatroenterol.

22. Kaur KK, Allahbadia GN, Singh M (2020) Normal Anatomy of the Human Skeleton with Factors Modifying its Development as Well as Regeneration. EC Clinical and Experimental Anatomy 3(11).

23. Kaur KK, Allahbadia GN, Singh M (2020) The association of dietary fatty acids and gut microbiota alterations in the development of neuropsychiatric diseases: A systematic review. Obes Res Open J 7(1): 19-45.

24. Kaur KK, Allahbadia GN, Singh M (2023) Therapeutic Clinical Implications of Crosstalk amongst Gut Microbiota, Bone Health and Vascular Calcification in Chronic Kidney Disease: A Narrative Review. J Endocrinol 7(1): 1-19.

25. Kaur KK, Allahbadia GN, Singh M (2023) The importance of Dysbiosis in Intestinal flora Subsequent to ischaemic Stroke: Implications in Therapeutic Management and Biomarkers for Prognosis-A Narrative Review under review.

26. Zemanova N, Omelka L, Mondockova V, Kovakova V, Martiniakova M (2022) Role of gut microbiome in bone and its relationship with bone related diseases. Biology 11(10): 1402.

27. Wang M, Zhao J, Fusheng H, Chunquan C , Wang H, et al. (2019) Alterations of the gut microbiota associated epitopes in children with Autism Spectrum Disorders. Brain Behav Immunol 75: 192-199.

28. FernandezI, Langa S, Martin V, Maldonado A, Jimenez E, et al. (2013) The human milk microbiota origin and potential roles inhealth and disease . Pharmacol Res 69(1): 1-10.

29. Ley D, Dessey JL, Mischke M, Knol J, Turk D, et al. (2017) Early life origin of intestinal inflammatory disorders. Nutr Rev 75(3): 175-187.

30. Comnar V, Vodnar DC (2020) Gut microbiota and old age: modulating factors and interventions for healthy longevity. Exp Gerontol 140(1): 111095.

31. Conway J, Niharika AD (2021) Ageing ADN of the gut microbiome: potential influence on immune Senescence and inflammaging. Ageing Res Rev 68: 101323**.**

32. Chang EB, Martinez GK (2019) Small intestinal microbiota : the neglected stepchild needed for fat digestion and absorption. Gut microbes 10: 235-240.

33. Zhang H, Q L , Qing s, Wang R (2021) Comparative analysis of the bioactive compounds in chicken cartilage: protective effects of chondroitin sulfate and type II collagen peptides against Osteoarthritis involve gut microbiota .Front Nutr 9: 843360.

34. Gleason B, Chisari E, Parvizi J (2022) Osteoarthritis can also start in the gut: the gut-joint axis. Indian J Orthop 56(7): 1150-1155.

35. Dunn CM, Jeffries MA (2022) The microbiome in Osteoarthritis: A Narrative Review of recent human and **a**nimal model literature**.** Curr Rheumatol Rep 24(5): 139-148.

36. Schroeder A, Nazet U, Mushter D, Grassel S, Proff P, et al. (2019) Impact of mechanical load on the expression profile of synovial fibroblasts from patients with and without Osteoarthritis. Int J Mol Sci 20: 585.

37. Kolasinski ST, Neoti T, Hochberg MC, Oatis C, Guyatt G, et al. (2020) American College of Rheumatoid Arthritis Guidelines for the management of Osteoarthritis of the hand, hip and knee. Arthritis Rheumatol 72(2): 149-162.

38. Qin J, Barbour KE, Murphy JB, Nelson AF, Schwartz TA, et al. (2017) Lifetime risk of symptomatic hand Osteoarthritis: the Johnston county Osteoarthritis project . Arthritis Rheumatol 69: 1204-1212.

39. Collins KH, Paul HA, Reimer RA, Seeratian RA, Hart DA, et al. (2015) Relationship between inflammation, the gut microbiota, and metabolic Osteoarthritis development: studiesin a rat model. Osteoarthritis Cartilage 23: 1989-98.

40. Li Y, Luo W, Deng Z, Lie G (2016) Diet, intestinal microbiota axis in Osteoarthritis: a possible role. Mediat Inflamm 2016: 3495173.

41. Avci D, Bachuman GA (2004) Osteoarthritis and osteoporosis in postmenopausal women: Clinical similarities and differences. Menopause 11(6Pt1): 615-21.




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42. Yuan X, Chen R, Zhang X, Lin X, Yang X (2020) Gut microbiota effects of pubertal status. BMC Microbiol 20(1): 334.

43. Yoon K, Kim N (2021) Role of sex hormones and gender in the gut microbiota. J Neurogastroenterol Motil 27: 314-325.

44. Weitzmann MN, Pacifici R (2006) Estrogen deficiency and bone loss an inflammatory tale. J Clin Investig 116(5): 1186-94.

45. Ji MW, Sheth RU, Dixit PD, Tchourine K, Vilkup D (2020)Macroecological dynamics of gut microbiota. Nat Microbiol 5: 768-775.

46. Wei J, Zhang C, ZhangY, Zhang W,Doherty M, et al. (2021)Association between gut microbiota and symptomatic hand Osteoarthritis: data from the Xiangya Osteoarthritis study. Arthritis Rheumatol 73: 1656-62.

47. Rushing BR, McRitchie S, Arbeva L, Nelson AE, Azcarate Peril MA et al. (2022)Faecal metabolimics reveals products of dysregulated proteolysis and altered microbial metabolism in obesity related Osteoarthritis **.** Osteoarthritis Cartilage 30: 81-91.

48. Chen I, Wang A, Wang Q (2021) Dysbiosis of the gut microbiome is a risk factor for Osteoarthritis in the older female adults: a case control study. BMC Bioinformatics 22: 299.

49. Wang Z, Zhu H, Jiang Q, Zhu YZ (2021) The gut microbiome as non invasive biomarkers for identifying overweight people at risk for Osteoarthritis. Microb Pathol 157: 104976.

50. LeeJY, Mannaaa M, Kim Y, Kim J, Kim GT et al.(2019) Comparative analysis of Faecal microbiota composition between Rheumatoid Arthritis and Osteoarthritis patients.Genes 10: 748.

51. Loesser RF, Arbeva L ,Kelley K, Podo AA, Sun S, et al. (2021) Association of increased serum lipopolysaccharides but not microbial dysbiosis with obesity related Osteoarthritis. Arthritis Rheumatol 74: 227-36.

52. Guan Z, Jia J, Zhang C, Sun T, Zhang W, et al. (2020) Gut microbiome dysbiosisalleviates the progression of Osteoarthritis in mice. Clin Sci 134(23): 3159-3174.

53. Ulici KK, Azcarate Peril MA, Cleveland RJ, Sartor RB, et al. (2018) Osteoarthritis induced by destabilization of medial malleolus is reduced by germ free(GF) mice . Osteoarthritis Cartilage 26: 10981-1109.

54. Hahn AK, Wallace GW, Weinasen HD, Brooks F, Sleniping M, et al. (2021) The microbiome mediates epiphyseal bone loss and metabolimic changes after joint trauma in mice. Osteoarthritis Cartilage 29: 882-93.

55. Liu L, Tian F, Li GW, Xu W, Xia R (2022) The effects and significance of gut microbiota and its metabolites on the regulation of Osteoarthritis:close coordination of gut-bone axis . Front Nutr 9: 1012087.

56. Celebi SZ, Cevhertas L, Nadeau K, Akeis M, Akdeis CA (2020) environmental factors in epithelial barrier dysfunction. J Allergy Clin Immunol 145: 1517-1528.

57. DoronJ, Mesko M, Li AV, Kusakabe T, leonardi L, et al. (2021) microbiota induced IgA antibodies regulate fungal commensalism in the gut and are dys regulated in Crohn's disease. Nat Microbiol 6: 1493-504.

58. Varela SAM, Matos M, Schlupp J (2018) The role of mate choice copying in speciation and hybridization. Biol Rev Camb Pilos Soc 93: 1304-1322.

59. Hernandez CJ, Guss JD, Luna M, Goldrings SR (2016) Links between the microbiome with bone. J Bone Mineral Res 31: 1638-46.

60. Fine RL, Manfreda VS, Gilmore MS, Kriegel MA (2020) Mechanisms and consequences of gut commensals translocation in chronic diseases. Gut Microbes 11: 217-30.

61. Brennan CA, Clay SL, Lavoie SL, Bai S, Lang JK, et al. (2021) Fusobacterium nucleatum drives a proinflammatory intestinal microenvironment through metabolite receptor dependent modulation of IL-12- expression. Gut Microbes 13: 1987-90.

62. Buckley A, Taylor JB (2018) Cell biology of tight junction barrier regulation and mucosal disease. Cold Spring Harb Perspect Biol 10: a029314.

63. Koh A, De Vadler E, Kovatcheva DB, Backhed F (2016) From dietary fibers to host physiology: short chain fatty acids as akey bacterial metabolite. Cell 165: 1332-1345.

64. Lucas S, Qinata Y, HoffmannJ, Bottchier M, Iljazovic A, et al. (2018) Short chain fatty acids regulate systemic bone mass protects from pathological bone loss. Nat Commun 9: 55.

65. Rohr MW, Natamsihulu CA, RudeskiRohr TA, Parthasarthy S (2020) Negative effects of a high fat diet on intestinal permeability. Adv Nutr 11: 77-91.

66. Griffin TM, Batushensky A, Hudson J, Lopes EBP (2020) Correlation network analysis shows divergent effects of long term high fat diet and exercise on early stage Osteoarthritis phenotypes in mice. Sport Health Sci 9(2): 119-131.

67. WangJ, X W, Wang R, Cheng R, Tang Z, et al. (2020) The outer membrane protein Amnic 1100 of *Akkermansia muciniphilia* promotes intestinal 5HT biosynthesis and extracellular availability through TLR signaling . Food Funct 12: 3597-610.

68. Lavone B, Lian D, Mawe GM (2017) Regulation of bone metabolism by serotonin. Adv Exp Med Biol 1033: 35-46.

69. Agus A, Planchais J, Sokol H (2018) Gut microbiota regulation of tryptophan metabolism in health and disease. Cell Host Microbe 23(6): 716-724.

70. Gao K, Mu CL, Farzi A, Zhu WY(2020) Tryptophan metabolism: link between the gut microbiota and brain. Adv Nutr 11: 709-23.

71. Licbana Garcia R, Olieviera M, Bullich VC, AlmelaI L, Romani PM, et al. (2021) The gut microbiome as a versatile immunomodulator in obesity and associated metabolic disorders. Best Pract Res Clin Endocrinol Metab 35: 101542.

72. Bolic LA, VichVila LA, ImhaanF, Collij V, Gaces R, et al. (2021) Long term dietary pattern are associated with proinflammatory and anti-inflammatory features of the gut microbiome. Gut 70: 1267-74.

73. Kim SI, Chen Z, Chamberlain ND, Esami AR, Vohra MV, et al. (2014) Ligation of TLR 5promotes myeloid cells infiltration and differentiation into mature osteoclasts **in** Rheumatoid Arthritis and experimental Arthritis. JImr 193: 3902-13.

74. Ma X, Claus LAN, Leshe MP, Tan K, Wu Z, et al. (2020) Ligand induced monoubiquitination of BIK1 regulates plant immunity. Nature 581: 199-203.

75. Kurashima Y, Guto Y ,Kiyono H (2013) Mucosal innate immune cells regulate gut homeostasis and inflammation . Eur J Immunol 43: 3108-3115**.**

76. RenZ, Pan LL, Huang Y, Chen H, Liu Y, et al. (2021) Gut microbiota-CRAMP axis shapes intestinal barrier factor function and immune in dietary gluten induced enteropathy. EMBO Mol Med 13: e14059.

77. Yin C, Zhao Q, Li W, Zhao Z, Wang J et al. (2020) Biomimetic anti-inflammatory nano-capsule serves as a cytokine blocker and M2 polarization for bone tissue repair. Acta Biomat 102: 416-426.

78. Perniss A, Schmidt P, Soultanova A, Papadakis T, Dahilke K, et al. (2021) Development of epithelial cholinergic chemosensory cells of the urethra and trachea of mice. Cell Tissue Res 385: 21-35.




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79. Pang XX, Ansari AR, YangWJ, Niu XY, Dong J, et al. (2021) visfatin regulates inflammatory in mouse intestinal mucosal through toll like receptors. Arch Immunol Ther Exp 69(1): 11.

80. Lambert C, Zappia I, Sanchez C, FlorinA, Dubuc JE, et al. (2020) The damage - associated molecular patterns(DAMP)-as potential targetsto treat Osteoarthritis: perspectives from a Review of the literature. FrontMed 7: 607186.

81. ChenY, Wang X, ZhangC, LiuZ, LiC, et al. (2022) Gut microbiota and bone diseases. Front Microbiol 13: 877776.

82. Huus KE, Petersen C, Finlay BB (2021) Diversity and dynamic of IgA microbiota interaction. Nat Rev Immunol 21: 514-25.

83. Jetten AM, Cook DN (2020) (Inverse )agonists of retinoic acid -related orphan receptor γ:regulation of immune responses, inflammation and auto immune disease. Annu Rev Pharmacol Toxicol 60: 371-90.

84. Li JY, Yu M, Pal AS, Tyagi AM, Dar H, et al. (2020) Parathyroid hormone dependent bone formation requires butyrate production by intestinal microbiota. J Clin Investig 130(4): 1767-81.

85. Ang QY, Alexander M, Newman R, Tian Y, CaiJ, et al. (2020) Ketogenic diets alter the gut microbiome resulting in decreased intestinal Th17 cells. Cell 181(6): 1263-1275.

86. Ivanov II, Atarashi K, Manel N, Brodie EL, Shima T, et al. (2009) Induction of intestinal Th17 cells by segmented filamentous bacteria Cell 139(3): 485-98.

87. Atarashi K, Tanoue T, Ando M, Kamada N, Nagano Y, et al. (2015) Th17 cell induction by adhesion of microbes to intestinal epithelial cells. Cell 163: 367-80.

88. Espina DTM, Gabarrini G, Harmsen HJM, Westra J, Van Winkelhoff AI, et al. (2019) Talk to your gut: the oral gut microbiome axis and its immunomodulatory role in the etiology **of** Rheumatoid Arthritis. FEMS Microbiol Rev 43: 1-18.

89. Hamamoto Y, Ouhara K, Munenaga S, Shoji M, Ozawa T, et al. (2020) Effect of Porphyromonas gingivalis on gut dysbiosis and resultant arthritis exacerbation in mouse model. Arthritis Res Ther 22: 249.

90. Stewart I, Edgar HDM, Blakely G, Patrick S (2018) Antigenic mimicry of ubiquitin by the gut bacterium Bacteroides fragilis:a potential link with autoimmune diseases. ClinExp Immunol 194(2): 153-165.

91. Rida MA, Chandran V (2020) Challenges in the clinical diagnosis of psoariatic arthritis. Clin Immunol 214: 108390.

92. Weingarden AE, Vaughn BP (2017) Intestinal microbiota, Faecal microbiota transplantation and inflammatory bowel disease. Gut Microbes 8(3): 238-252.

93. Yoo W, Zieba JR, Foegeding NT, Torres FP, Shelton CD, et al. (2021) High fat diet induced colonocyte dysunction escalates microbiota derived trimethylamine-N-oxide. Science 373(6556): 813-818.

94. Requena T, Martinez-Cuesla MC (2018) Diet and microbiota linked in health and disease. Food Funct 9(2): 688-704.

95. McCabe J, Brittany RA, Paratheswaran N (2015) Probiotics, and Prebiotics regulation of bone health: role of the intestine and its microbiota. Curr Osteoporosis Rep 13(6): 363-371.

96. Thomas S, Browne H, Mohasheri A, Raynean MP (2018) What is the evidence for the role of diet and nutrition in Osteoarthritis. Rheumatology 57(Suppl4): 461-474.

97. Chen L, Zheng JJY, Li G, Yuan J, Ebett JR, et al. (2020) pathogenesis and Clinical management of obesity relatedknee Osteoarthritis: impact of mechanical loading. J Orthop Transl 24: 66-75.

98. Hagi T, Belzer C (2021) The interaction of *Akkermansia muciniphilia* with host derived substances, bacteria and diet. Appl Microbiol Biotechnol 105(12): 4833-4841.

99. Remely M, Hippe B, Zanaer I, Auneuller E, Brath H, et al. (2016) Gut microbiota of obese type2 Diabetic individuals is enriched in Faecalibacterium prausnitzii, *Akkermansia muciniphilia* and *Peptostreptococcus anaerobius* after weight loss. Endocrin Metab Immune Disord Drug Targets 16(2): 99-106.

100. Nguyen TD, Kang JH, Lee MS (2007) Characteristization of *Lactobacillus plantarius PH04:a* potential Probiotic with cholesterol lowering effects Int J Food Microbiol 113: 358-361.

101. Ramasamy B, Magne E, Tripathy SK, Venugopal G, Mukherjee D (2021) Association of gut microbiome and Vitamin D deficiency in knee Osteoarthritis patients . Nutrients 13: 1772.

102. Li D, Liu Y, Yang X, Kong L (2021) The role of Probiotics , and Prebiotics in osteoclastogenesis and immune relevance. Curr Med Chem 28: 5228-47.

103. DaSilva TE, Casarotti SN, Da Oliviera GLV, Penna ALR (2021) The impact of Probiotics , Prebiotics and symbiotics on the chemical, biochemical, Clinical and immunological markers as well as on the gut microbiota of obese mice. Crit Rev Food Sci Nutr 51: 337-55.

104. Tyagi AM, Yu M, Darby TM, Vaccaro C, Li JY, et al. (2018) The microbial metabolites butyrate stimulates bone formation via T regulatory cells mediated WNT 10B expression . Immunity 49: 1116-31.

105. Pan H, Gao R, Ju Y, Wang Q, Zhu J, et al. (2019) A Single bacterium restores the microbiome dysbiosis to protect bones from destruction in a rat model of Rheumatoid Arthritis. Microbiome 7: 107.

106. Henrotin Y, Patrie S, Pralus A, Roche M, Nivoliez A (2021) Protective effects of oral administration of *Bifidobacterium longum* CB 0703 in spontaneous Osteoarthritis in dunkin Hartley guinea pig model. Cartilage 13: 1204s-13s.

107. Sim BY, Choi HJ, Kim MG, Jang DG, Lee DG, et al. (2018) Effects of ID-CBT5101 in preventing and alleviating Osteoarthritis symptoms in a monosodium iodoacetate induced rat model. J Microbiol Biotechnol 28: 1199-208.

108. Taye I, Bradbury J, Grace S, Avila C (2020) Probiotics for pain of Osteoarthritis, an N-of -1 trial. Complement Ther Med 54: 102548.

109. Lyu JL, Wang TM, Chen YH, Chang ST, Wu M, Ly H, et al. (2020) Oral intake of *Streptococcus. Thermophilus* improves knee Osteoarthritis degeneration :a randomized double blind, placebo controlled Clinical study. Helliyon 6: 03757.

110. Quigley EMM (2019) Probiotics and Prebiotics in digestive health. Clin Gastroenterol Hepatol 17: 333-344.

111. Wang H, Geier MS, Howarth GS (2016) Prebiotics: A potential treatment strategy for chemotherapy damaged gut? Crit Rev Food Sci Nutr 56: 946-56.

112. Schott EM, Farnsworth CW, Greier A, Lillis JA, Sonniwala S, et al. (2018) Targeting the gut microbiome to treat the Osteoarthritis of obesity. JCI Insight 3(8) : 95997.

113. Tanabe K, Nakamura S, Moriyama HM, Kitajima M, Ejima H, et al. (2019) dietary fructoligosacchharides and glucomannans alter gut microbiome and improve bone metabolism: in Senescence accelerated mouse. J Agric Food Chem 67: 867-74.

114. Wang Z, Tauzin AS, Laville R, Tedesco P, Letisse F et al. (2020) Harvesting of Prebiotic fructoligosacchharides by non beneficial human gut bacteria. mSphere 5: 00771.




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115. Wu RY, Mattanen P, Napper S, Seroten F, Li B, et al. (2017)Non digestible oligosaccharides directly regulate host kinome to modulate host inflammatory responses without alterations in the gut microbiota. Microbiome 5: 135.

116. Costa GT, Vasconcelos O, Aragiao GF (2022) Fructoligosacchharides on inflammation, immunomodulation, Oxidative stress and gut immune responses a systematic review. Nutr Rev 80: 709-722.

117. Wang N ,Ma S, Lingjie Fu (2022) Gut microbiota dysbiosis as one cause of osteoporosis by impacting intestinal barrier function. Calcif Tissue Int 110: 225-235.

118. Zhao Z, Ning J, Bao XO, Shang M, Ma J, et al. (2021) Faecal microbiota transplantation protects rotenome induced Parkinson's disease mice via suppressing inflammation mediated by the lipopolysaccharide-TLR-4 signaling pathway the microbiota - gut -brain axis. Microbiome 9: 26.

119. Huang Z, ChenJ, Li B, Zeng B, Chen CH, et al. (2020) Faecal microbiota transplantation from metabolically compromised human donors accelerates Osteoarthritis inmice. Ann Rheum Dis 79(5): 646-56.

120. Arden NK, Perry TA, Bannuru RR, Breyer O, Cooper C, et al. (2021) Nonsurgical management of knee Osteoarthritis: comparison of ESCEO and OARSI 2019 Guidelines. Nat Rev Rheumatol 17(1): 59-66.

121. Clegg DO, Reda DJ, Harris CI, Klein MA, O'Deal JR, et al. (2006) Glucosamine, chondroitynsulfate and the two combination for painful knee Osteoarthritis. N Engl J Med 354(8): 2795-808.

122. Boer CG, Radiabzadeh D, MedinaGomez C, Garn S, Schiphol D, et al. (2019) intestinal microbiome and its composition in joint pain and its inflammation. Nat Commun 10: 48881.

123. Vitetta L, Coutson S, Linnane AW, Butt H (2013) The gastrointestinal microbiome and musculoskeletal diseases:a beneficial role for Probiotics and Prebiotics. Pathogens 2(4): 606-626.

124. Mizokami Y, Oda T, Funao N, Nishimura A, Soen S, et al. (2018) Venoprazen prevents ulcer recurrence during long term NSAID therapy: randomized lansoprazole controlled non inferiority and Single blind extension study Gut 67(6): 1042-1051.


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