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The Joint-Gut Axis:Systemic Translocation of Ingested Plastics to Joint Spaces

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ABSTRACT:
The spread occurrence of micro and nanoplastics in food and potable water raises serious concerns about their health effects. The growing evidence points to the gastrointestinal tract being the main entry point for these small particles that initiate a cascade of reactions that go far beyond mild gastrointestical discomfort and ingestion, microplastics trigger oxidative stress responses, disrupt epithelial integrity, impair barrier function, and dysregulate the gut microbiota host dialogue. The gut microbiota is followed by increased intestinal permeability and entry of plastic particles into systemic circulation, either through the hepatic portal vein or lymphatic system, and activation of gut-associated lymphoid tissue. The activation of the inflammasome and increases the quantity of pro-inflammatory cytokines in the inflamed intestine. Monocytes, macrophages, and dendritic cells enter the blood circulation and invade the inflamed, fibrotic, and eroded joints, then the synovial cells, macrophages, osteoblasts, and chondrocytes ingest plastic material. In the joint, the presence of foreign material causes oxidative stress, activation of the inflammasome, and activation of metalloproteinases that lead to the destruction of cartilage, dysfunction of chondrocytes, and pathological remodeling of bone. In microplastics appear to be involved in a process that starts in the gastrointestinal tract and contributes to persistent inflammation of the joints. The mechanisms by which diet-derived plastics influence the gut microbiota-host immune interactions is critical for furthering the understanding of how microplastics affect the etiology and pathogenesis of joint diseases.

KEYWORDS: Joint-Gut Axis, Microplastics Translocation, Barrier Compromise, Intestinal Dysbiosis, Lymphatic Bypass, Monocyte Priming

INTRODUCTION:

The Extensive production and usage of plastics have led to the extensive invasion of the natural environments with microplastics (MPs; <5 mm) and nanoplastics (NPs; <1 μm). There are growing recognition of these contaminants, and they have already been found in drinking water, fish, salt and processed food. The role of eating in the exposure of people to plastic contaminants as the methods of transmission has become significant.[1] The Joint-Gut Axis that there is a connection between exposure to microplastics through diet and disruption of the joints. The connection goes farther just stating that plastic particles can damage the integrity of the intestine, penetrated the barriers of the epithelium and the immune system as well as spreading in the body through the blood and the lymph. As microplastics move through the body, they can also interact with immune cells in the intestine and provoke inflammation in the entire body and changes to monocytes and macrophages's activity affecting the immune response.[2]

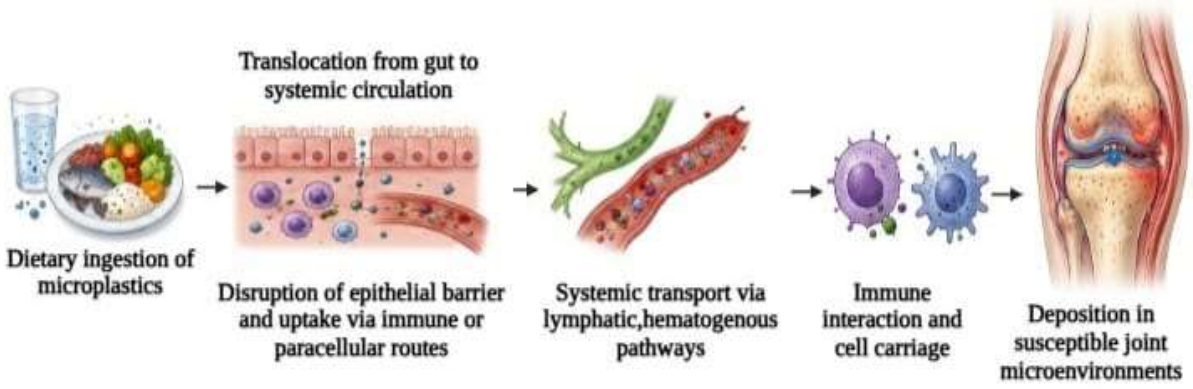

Figure 1: Pathophysiological Pathway of Microplastic Accumulation in Articular Joints.

1. DIETARY CONSUMPTION OF MICROPLASTICS AND EPITHELIAL BARRIER COMPROMISE IN THE GUT:

Mnps that are consumed affect the gastrointestinal tract structurally and chemically. Bigger microplastics work as physical irritants that scrape the protective mucin layer and cause microbial imbalances in the local area, while smaller nanoplastics take advantage of the breach to set off inflammatory responses such as nf-kappab and mapk.[3] the intestinal epithelium barrier consists of one layer of epithelial cells bound by tight junction proteins such as occludin, claudins, and zonula occludens-1 (zo-1), as well as a protective layer of mucus and immune cells. This complex barrier is important for controlling nutrient intake and preventing the entry of toxic substances or pathogens to the body.[4] the process by which microplastics bring on oxidative stress involves enhancing the intracellular levels of reactive oxygen species ,which ultimately leads to problems with the mitochondrial system and the activation of inflammatory pathways, notably nf-κb and mapk. In the inflammatory cytokines, which include tnf-α, il-1β, and il-6, are produced, resulting in impaired epithelial barrier function and delayed tissue regeneration. The development of a chronic inflammatory microenvironment in a "leaky gut" condition.[5] the smaller populations of beneficial bacteria and higher levels of opportunistic microorganisms lead to intestinal dysbiosis, which disturbs immune balance and heightens mucosal inflammation.[6]

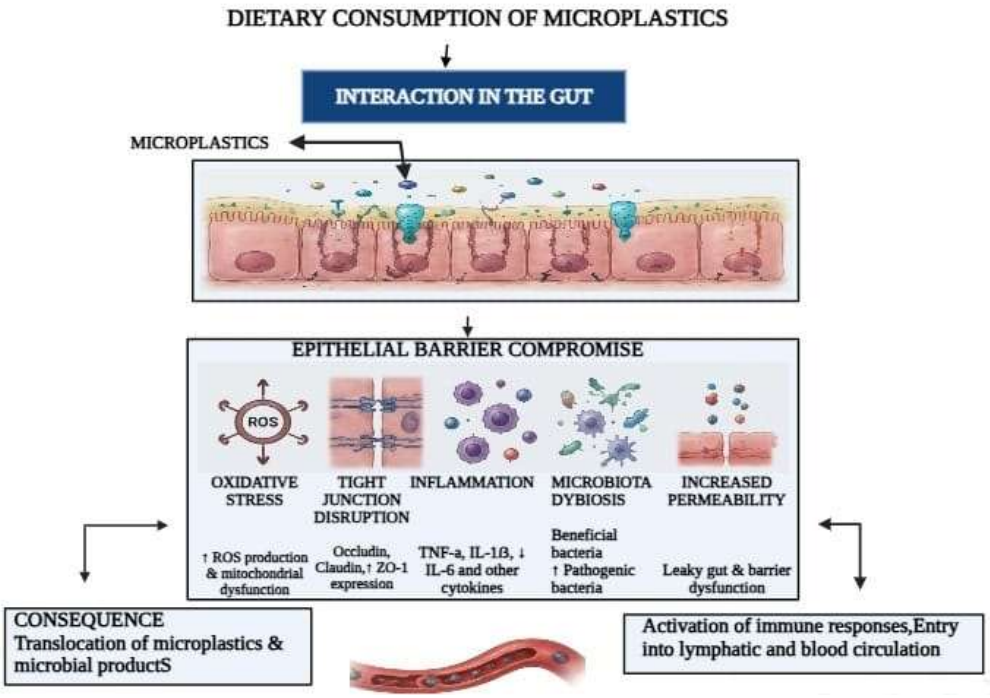

Figure 2: The cellular and systemic consequences of dietary microplastic consumption in the gastrointestinal tract. Ingested particles interact directly with the intestinal epithelium, leading to severe barrier compromise, localized cellular stress, and subsequent systemic translocation via the circulatory and lymphatic systems.

2. THE SYSTEMIC TRANSLOCATION PATHWAYS OF POLYMERIC PARTICLES:

Ingested microplastics and nanoplastics disrupt the gut epithelial barrier. They cross into the lamina propria, where properties of the materials—primarily size, charge, and type of protein coating. Whether they get into the bloodstream via the portal vein or lymphatic system.

2.1 The Hematogenous Route: Direct Capillaries and First-Pass Hepatic Filtration:

-The smaller polymers, especially nanoplastics, can easily pass through the subepithelial basement membrane and reach the fenestrated capillary beds of intestinal villi.[7]

-Even if absorbed by paracellular diffusion or enterocyte transcytosis, they get transported to the mesenteric venous blood and join the hepatic portal vein. After entering hepatic sinusoids, microplastics come in contact with first-pass metabolism which involves clearing process done by resident liver macrophages . However, high amounts of microplastics inhibit this process.[8]

2.2 The Lymphatic Route: Persorption And Bypassing First-Pass Clearance:

-The presence of high molecular weight microplastics inside blood vessels is limited due to the dense basal membrane of mucosal capillaries. The larger types of polymers depend on the lymphatic system of the intestines since uptake of this class of macromolecules occurs through sampling by specialized cells called m-cells that are part of peyer's patches or through the process of persorption.

-Which refers to the movement of large solid particles through mechanical openings that are formed between morphological gaps created in the cells of intestines that die. After arriving in the interstitial fluid of the tissue, particles are either captured by lacteals which are a kind of lymph vessels or engulfed by dendritic cells.

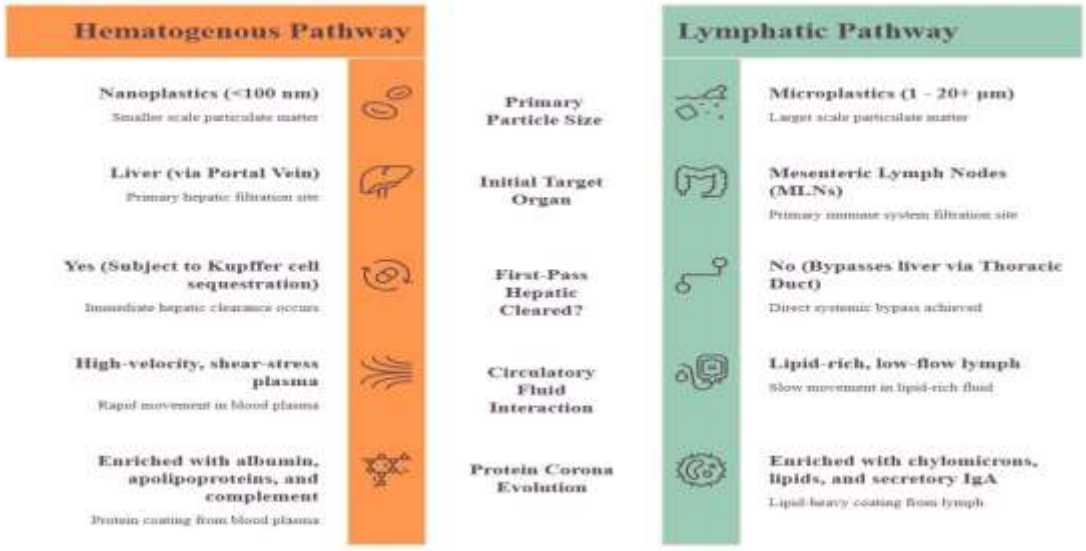

Figure 3: The contrasting biokinetic routes governing micro- and nanoplastic dissemination, juxtaposing the rapid, high-shear hematogenous clearance of sub-100 nm particles against the low-velocity lymphatic transport of larger particulates. The schematic highlights how nanoplastics encounter immediate first-pass hepatic sequestration upon portal clearance, whereas microplastics preferentially drain through mesenteric lymph nodes, bypassing hepatic filtration while acquiring a specialized lipid and immunoglobulin-rich biomolecular corona.

2.3 Bridges in the structural approaches to joint targetability:

The lymphatic system allows for a straight path for microplastics to find their way into the main bloodstream without coming in contact with any filters. The nanoparticles remain unchanged with respect to the environmental substances attached to their surfaces.once the nanoparticles are in the bloodstream, they can enter the blood vessels in the joints. The mechanical strains and inflammation lead to the opening of blood vessels and the release of the substances into the joint.[9]

3. PRIMING OF GUT-ASSOCIATED LYMPHOID TISSUE (GALT) AND SYSTEMIC CIRCULATING MONOCYTES:

The gut-associated lymphoid tissue (galt) is the main biological access point for ingested micro- and nanoplastics (mnps) to enter the host's immune system. The galt is found in the peyer's patches located in the distal ileum. The gut-associated lymphoid tissue (galt) is the main biological access point for ingested micro- and nanoplastics (mnps) to enter the host's immune system. Microfold (m) cells are specialized epithelial cells that have few microvilli and do not produce mucus.[10]

3.1 Intracellular Engagement and NLRP3 Inflammasome Activation:

After mnps enter the epithelial layer, antigen-presenting cells (apcs) acquire them via endocytosis and macropinocytosis. The uptake of plastic particles in the inert state or functionalized state also leads to lysosomal destabilization, damage to the mitochondrial membrane, and intracellular production of reactive oxygen species [11] activation of the nlrp3 cascade leads to the enzymatic cleaving of pro-caspase-1 into active caspase-1, driving the robust maturation and secretion of key pro-inflammatory cytokines, their specifically:

- Interleukin-1 beta {il-1}
- Interleukin-18 {il-18}

- Tumor necrosis factor-alpha {tnf-}
- Interleukin-6 {il-6}

3.2 Monocyte Priming and Phenotypic Reprogramming:

Flaming the current occurrences of mediators infusing GALT, this leads to the local change in chemotactic gradient leading to the portable arrival of classical monocytes through the bloodstream causing them to reach the lamina propria and the mesenteric lymph nodes. This discovery when the monocytes are subjected to the storm of cytokines and submicron particles is referred to as having utilized the process of converting their natural state into the stage of innate immunity or trained immunity.

3.2.1 Increase in the amount of Receptors Present:

The number of cells or receptors of types such as adhesion, or chemokine, heists, and M1 gets stimulated significantly and extensively.

3.2.2 Transformation into the state of inflammation:

Monocytes become engaged in cellular activities concerning the secretion scheme due to their activation with regard to emerging genes geared for stimulation of the inflammatory processes.

3.2.3 Prevention of Apoptosis:

Interaction of monocytes cells during the process of absorption with halting the cost relating to the polymeric filters enables their life processes to take place.[12]

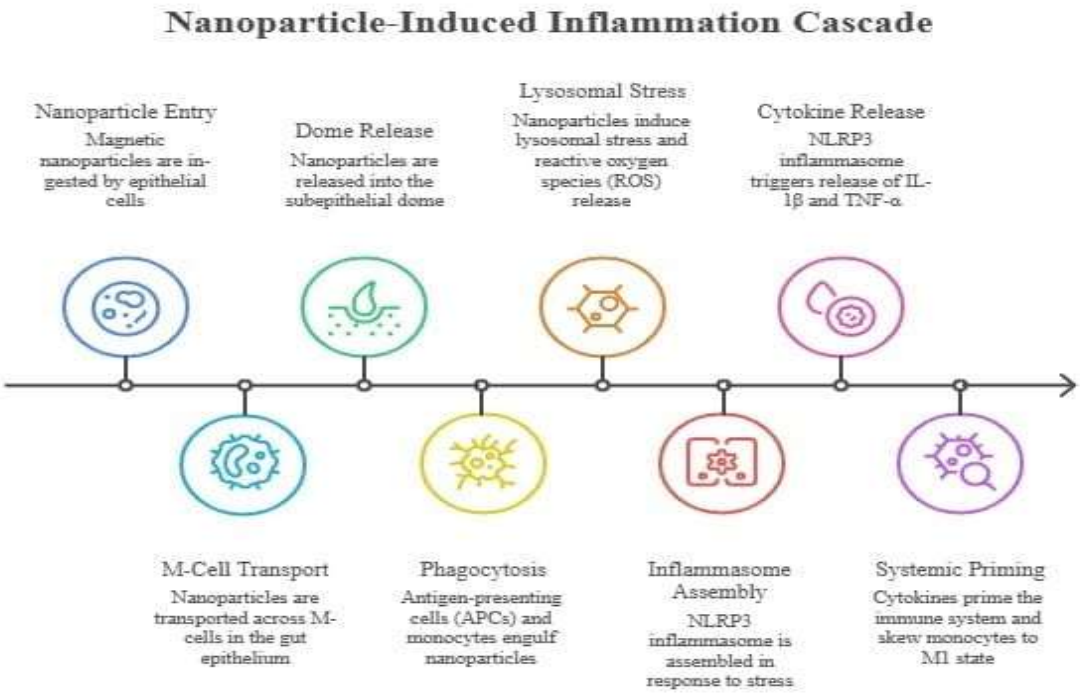

Figure 4: Nanoparticle-Induced Inflammation Cascade depicts the sequential pathway where ingested nanoparticles cross the gut epithelium, undergo phagocytosis by immune cells, trigger lysosomal stress and NLRP3 inflammasome assembly, and ultimately release pro-inflammatory cytokines (IL-1\beta and TNF-\alpha) that induce systemic immune priming.

4. ROLE OF THE GUT MICROBIOME IN MICROPLASTIC-INDUCED JOINT INFLAMMATION:

4.1 Gut Microbiome As A Regulator Of Immune Homeostasis:

The gut microbiome constitutes a mass of trillions of microorganisms responsible for the integrity of the intestinal barrier, regulation of the host's metabolism, as well as for the innate and adaptive immunity. Under normal circumstances, these organisms produce end products of metabolism such as short-chain fatty acids (scfas) contributing to the creation of tight junctions between epithelial cells, thus eliminating unwanted inflammatory signals and promoting the differentiation of t-cells.one of the environmental factors that can disturb the microbiome's balance is the dietary intake of microplastics.[13]

4.2 Microplastic-induced gut dysbiosis:

The prolonged consumption, microplastics interact directly with microorganisms in the intestine. As major changes take place in the structure of microbial flora of the intestines. drastic drops in the number of such beneficial microorganisms as Lactobacillus, Bifidobacterium, Akkermansia muciniphila, etc., with an increased number of potentially pathogenic ones represented by Escherichia-Shigella, Clostridium, and Desulfovibrio. Dysbiosis in decreased microbial diversity and loss of ecological balance in the intestine. If we keep in mind that beneficial microorganisms play an important role in nutrient processing, mucus protection, and immune regulation, their absence promotes a continuous pro-inflammatory process.[14]

4.3 Alteration of Microbial Metabolites and Barrier Integrity:

Dysbiosis caused by microplastics can be related to major transformations in the metabolism of bacteria. The mentioned SCFAs act as the basic source of energy for the epithelial cells of the intestines and favor the synthesis of the proteins, such as occludin, claudins, and zonula occludens-1, necessary to form the junctions between these cells.Decreased production of SCFAs leads to a decrease in the integrity of the epithelial barrier and a higher degree of permeability of intestines (so-called "leaky gut").

5. CELLULAR UPTAKE AND INTRACELLULAR FATE OF TRANSLOCATED MICROPLASTICS IN JOINT CELLS:

5.1 Size-dependant Mechanisms of Internalization in Synoviocytes and Chondrocytes:

The synovial membrane and avascular cartilage matrix are the major entrances to the joint microenvironment. Fibroblast-like synoviocytes, macrophages (type A synoviocytes), and chondrocytes use endocytic mechanisms to internalize microplastics based on their size and charge.

5.2 Clathrin and caveolae mediated endocytosis:

The small nanoplastics are rapidly captured by using its receptor as nanoparticles. In both the chondrocytes and fibroblast-like synoviocytes, the clathrin and caveolin-1 vesicles are created around the particles, allowing their location in early endosomes.

5.3 Macropinocytosis and phagocytosis:

The bigger micro-particles are ingested by means of macropinocytosis or phagocytosis. The latest techniques have shown that the presence of the particles can change the structure of actin filaments formed in the cytoplasm allowing the movement of polystyrene and polyethylene debris into the spaces around the nucleus.[15]

6. TARGET-SPECIFIC DEPOSITION: WHY CIRCULATING PLASTICS PREFERENTIALLY LOCALIZE IN WEIGHT-BEARING AND INFLAMED JOINTS:

There's a plastic micro-and nano-form particles are able to move freely in the organism after they left the

intestine, yet their distribution in various tissues is not the same. The available indicate that the arthritic joints under mechanical stress are more likely to accumulate these particles. Several factors apply here, including increased vascular permeability, influence of inflammatory mediators, and disorders of lymphatic circulation, which all together contribute to microplastic accumulation.[15] The chronic inflammation of joints leads, upon the actions of pro-inflammatory cytokines, to endothelial activation and an increase of the vascular permeability of the synovial membrane, causing dysfunction of the vascular barrier and allowing nanoscopic polymer particles to enter the joints. A similar mechanism has long been observed in inflammatory arthritis, with active infiltration of the inflammatory cells and circulating macromolecules.

After deposition, the internalization of plastic particles by synovial macrophages and fibroblast-like synoviocytes may enhance inflammation. Various show that intracellular microplastics can activate oxidative stress mechanisms, as well as the NF-κB and MAPK signaling pathways, which lead to the production of IL-6, IL-8, TNF-α, and matrix-degrading enzymes promoting cartilage damage. These responses imply that the retained particles become persistent mediators of inflammation rather than neutral agents[16]

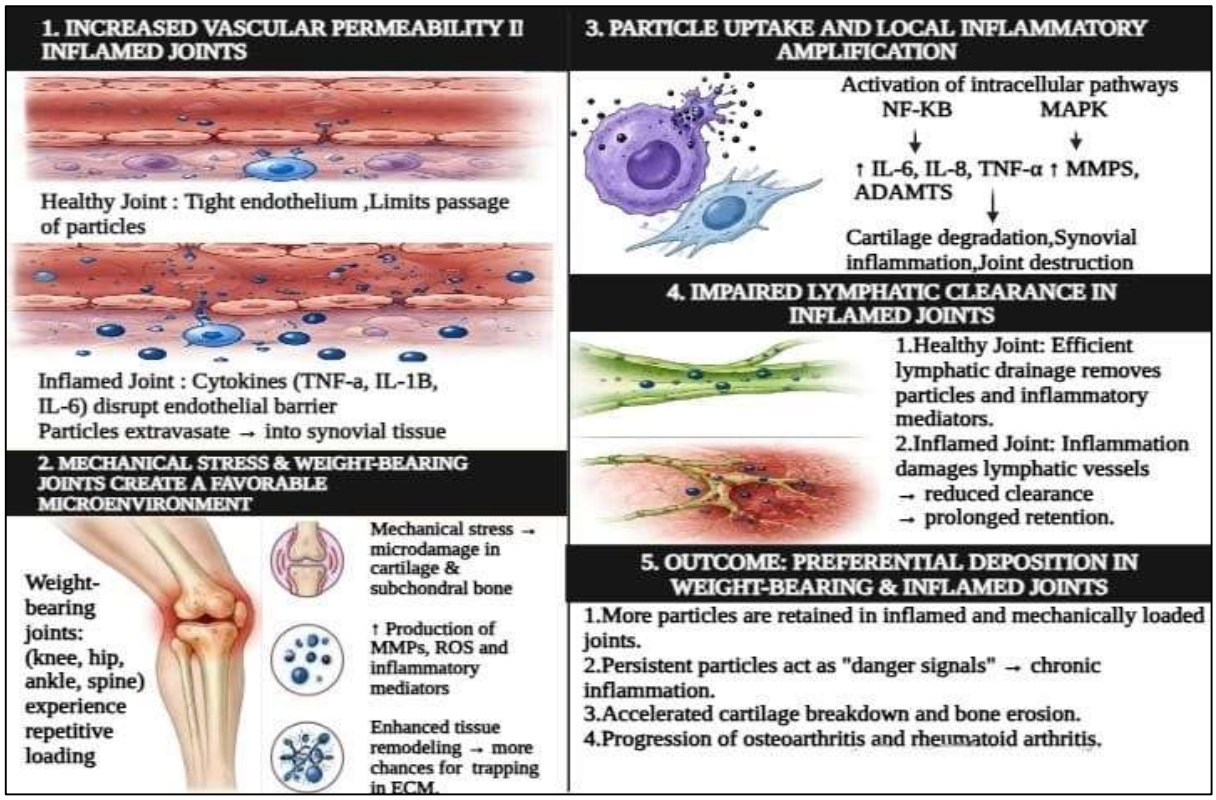

Figure 5: The Elevated endothelial permeability, mechanical joint stress, intracellular NF-kappaB and MAPK signaling, and compromised lymphatic drainage act together to trap particles in synovial tissue, triggering cytokine release and matrix degradation that worsen joint damage in arthritis.

7. BIOLOGICAL CONSEQUENCES OF PLASTIC RETENTION: CARTILAGE DEGENERATION AND BONE REMODELING:

The presence of microplastics within joint compartments leads to joints that have been damaged beyond repair, as this leads to the degradation of cartilage matrix, the death and aging of chondrocytes, and the alteration of subchondral bone remodeling. Microplastics that remain in the joint cause significant changes

to the way mitochondrial and genes function, leading to the chondrocytes being under significant oxidative stress.[17]

7.1 Chondrocyte Apoptosis, Senescence, And Extracellular Matrix (Ecm) Breakdown:

- Chondrocyte Death via Apoptosis and Programmed Cell Death: Microplastics interfere with the mitochondrial membrane potential, leading to an increase of intracellular ROS levels. These processes lead to activation of apoptosis through the ion channel cytochrome c release, Bax overexpression, and triggering of caspases-3 and -9. This decrease of viable chondrocytes which compromises maintaining the surrounding cartilage matrix integrity.
- Door Learning-Induced Premature Senescence (SIPS): Continuous exposure to plastic particles makes chondrocytes find themselves in a situation of premature aging represented by expression of p16INK4a and p21 and acquiring a Senescence-Associated Secretory Phenotype (SASP). Senescent chondrocytes secrete pro-inflammatory mediators like IL-6 that are responsible for spreading paracrine cellular senescence to neighboring healthy cells.
- Rapid Extracellular Matrix Destruction: Senescent and activated chondrocytes increase the level of catabolic enzymes such as metalloproteinase (MMP-1; MMP-3; MMP-13), and aggrecanases (ADAMTS-4 and ADAMTS-5), which actively decompose key structural components in the tissues—the network of type II collagen and aggrecan proteoglycans—and cause progressive cartilage degradation, sputtering at the surface, and significant decline of the cushioning properties of the joint.

7.2 Subchondral Bone Remodeling Uncoupling And Pathological Osteoclastogenesis:

- The inhibition of osteoblastic and bone formation:microplastics that are absorbed by the cells of the bone marrow could lead to the inhibition of osteogenic differentiation. This is possible due to the decrease in the activity of the main transcription factors runx2 and osterix (osx). The stress created in the endoplasmic reticulum of the organisms will inhibit the productiveness of type i collagen, osteocalcin, and alkaline phosphatase (alp) and thus hinder the development of the mineralized bone matrix.
- Increased rankl secretion and activation: some stress-stimulated chondrocytes, dying osteocytes, and activated macrophages release a lot of rankl, while lowering the quantity of osteoprotegerin (opg). The increased rankl/opg index in the hyperactivity of the precursor macrophages and their transformation into osteoclasts.
- The pathological resorption and erosion of subchondral bone: hyper-activated osteoclasts produce lacunae of resorption that leads to too much loss of subchondral bone and to the resorption of the trabecular bone with the corresponding appearance of the changes in the structure of the subchondral bone marrow.[18]

CONCLUSION:

The Joint-Gut Axis Hypothesis as role of Nanoplastics and the Development of Osteoarthritis Pathogenesis Mechanism Essay the Joint-Gut axis, a recently identified pathological loop wherein food-borne micro- and nano-plastics trigger an inflammatory cascade by disrupting the intestinal barrier through oxidative stress and mucosal stripping, leading to the downregulation of key tight junction proteins such as occludin and ZO-1 and promoting a leaky gut syndrome characterized by dysbiosis. Upon entry into the systemic circulation, smaller nanoplastics evade first-pass hepatic clearance through the hepatic portal vein while larger microplastics bypass this barrier via intestinal lacteals and mesenteric lymphatic vessels. The Gut-Associated Lymphoid Tissue (GALT) becomes a focal point for immunological activation,

wherein the plastic particles trigger lysosomal dysfunction and NLRP3 inflammasome activation, leading to the polarization of circulating monocytes to anti-apoptotic M1 macrophages. Recruitment to the joint is mediated by enhanced vascular permeability, mechanical loading-induced stress, and impaired lymphatic drainage, resulting in the enrichment of these pro-inflammatory cells in the synovial microenvironment together with free polymer chains. The persistence of polymeric debris in the joint cavity promotes chondrocyte apoptosis and premature senescence, enhances matrix-degrading enzyme production through the induction of MMP-13, ADAMTS-4/5, and RANKL, and accelerates subchondral bone remodeling.

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