Review Article

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Relationship between Digestive Micro Ecological Changes and Atherothrombosis

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Abstract

Atherosclerosis (AS) is a chronic inflammatory condition that affects large- and medium-sized arteries. It is the leading cause of Cardiovascular Disease (CVD), which includes ischemic heart disease, strokes, and peripheral vascular disease and has a high mortality rate. Plaque formation in AS is pathological due to lipid infiltration into the vessel wall, endothelial dysfunction, and persistent low-grade inflammation. As of late, an ever increasing number of researchers certainly stand out to the significance of digestive microecological messes in the event and improvement of AS. Digestive G-bacterial cell wall Lipopolysaccharide (LPS) and bacterial metabolites, for example, oxidized Trimethylamine (TMAO) and Short Chain Unsaturated Fats (SCFAs), are engaged with the improvement of AS by influencing the incendiary reaction, lipid digestion, and pulse guideline of the body. In addition, AS progresses more quickly when intestinal microecology interferes with the body's normal bile acid metabolism. This review provides a summary of the research on the connection between AS and the maintenance of a dynamic balance in intestinal microecology, which may be useful for AS treatment.

Keywords: Atherosclerosis • Chronic inflammatory • Cardiovascular disease • Lipopolysaccharide • Short chain unsaturated fats • Microecology

Introduction

The four components of intestinal microecology make up a dynamic and well-balanced system: the gastrointestinal life structures, mucosal discharges, food admission, and microorganisms colonizing the digestive system. The human digestive system, a piece of the intestinal system, is separated into the small digestive tract and internal organ as indicated by its morphology, capability, and construction. The mucosal epithelium is made up of absorptive cells, cup cells, and Paneth cells. These cells make the small intestine the main part of the human body that absorbs nutrients. The wall of the small intestine has a mucosal layer, sub-mucosal layer, muscular layer, and outer membrane. Although the epithelial lamina propria of the large intestine contains dense colonic glands, which are the primary locations for absorbing water from food residues and forming feces, the large intestine wall is similar to the small intestine wall. Over 100 trillion microorganisms make up the intestinal microbiota. Bacteria, primarily those belonging to the Bacteroides and Firmicutes phylas, make up 90% of the total intestinal microorganisms. Fusobacteria, Bacteroidetes, and Verrucomicrobiaphylum, among other intestinal microflora, are found in much smaller quantities [1].

Intestinal Micro Ecology associated Atherosclerosis

Bacterial cell wall lipopolysaccharide and atherosclerosis

Endotoxin, also known as LPS, is a lipid A, O antigen, and core polysaccharide found in the outer cell wall of Gram-negative bacteria. It is typically released when the bacterial cell wall is disrupted or when the bacteria divide, triggering a strong immune response in the host that causes acute infection symptoms like fever, sepsis, infectious shock, and respiratory

distress syndrome. Additionally, lipid-A plays a significant immunostimulatory role in the host's other chronic immune-mediated diseases, which are closely linked to LPS [2].

Toll-Like Receptor 4 (TLR4) activation is triggered by LPS, which is a component of the outer membrane of Gram-negative bacteria. This causes the body's inflammatory response to be triggered, which in turn encourages the development of AS. Lipopolysaccharide (LPS) can bind to Lipopolysaccharide Binding Protein (LBP), High Density Lipoprotein-2 (HDL2), or chylomicrons, allowing LPS to enter the liver through the portal vein or the lymphatic system into the body's circulation. Targeting oxidized phospholipids that are derived from the intestines may limit the inflammatory response that promotes AS by limiting LPS uptake in the intestine. LPS invigorates fiery reactions in a TLR4-subordinate way and assumes a significant part in supportive of leukocyte enactment and arrival of provocative go betweens, dendritic cell development and relocation, macrophage autophagy, expansion in Responsive Oxygen Species (ROS) and Receptive Nitrogen Species (RNS) development, and effort of a large number of consequences for vascular endothelial cells. By increasing the expression of Fc/R receptors on the surface of macrophages, LPS also encourages the binding of oxidized LDL/IgM complexes and the formation of foam cells. Subclinical doses of LPS can also reduce Interleukin-1 Receptor-Associated Kinase M (IRAK-M) in mice and increase miR-24 expression in monocytes. This disrupts monocytes' low grade inflammatory phenotype and encourages AS development. It has been exhibited that LPS speeds up atherosclerotic plaque development through TLR4 by advancing lipid aggregation and the creation of chemokines, for example, MCP-1 in human extravascular fibroblasts by means of the TLR4-subordinate pathway. By reducing IL-1, IL-6, NLRP3, SOD-1 antioxidant protein, and reactive oxygen species and suppressing the NF-B and MAPKs signaling pathways, inhibition of Sema3A, a specific membrane-associated secretory protein, weakens LPS-stimulated inflammatory factor release. This proposes that restraint of Sema3A could be a likely restorative methodology for treating AS [3].

Trimethylamine oxide (TMAO) associated with AS

Atherothrombosis and atherosclerotic lesions have both been linked to the metabolite produced by intestinal bacteria called Trimethylamine Oxide (TMAO). Trimethylamine (TMA), which is found in foods that contain choline, phosphatidylcholine, and L-carnitine like red meat, dairy products, eggs, and some fruits, vegetables, and cereals, is the source of TMAO. Through various microbial enzymes like Choline TMA lyase, Carnitine monooxygenase, TMAO reductase, and Betaine reductase, gut microorganisms facilitate the formation of TMA and promote the release of TMA precursors from these foods. Flavin containing Monooxygenase-3 (FMO3) then converts TMAO to TMA. Through renal filtration, TMA and TMAO are primarily excreted in the urine. Many kinds of microbes can deliver TMA, including normal human commensal microscopic organisms, like Aspergillus, Clostridium, Shigella, and Aeromonas, as well as non-commensal gatherings, like Burkholderia, Shigella, Vibrio, Campylobacter, Aeromonas and Salmonella. The activity and number of FMO3 as well as the equilibrium of dietary precursors, TMA-producing bacteria, and TMA-metabolizing bacteria all have an impact on blood TMAO concentrations [4].

The arterial wall's inflammatory response and TMAO

Cholesterol rich macrophages that invade the blood vessel wall add to the improvement of AS through oxidative pressure and irritation. Through researching miRNAs and their objective destinations connected with lipid digestion and cardiovascular articulation in TMAO digestion related macrophage and undifferentiated organism models, it was found that TMAO advances irritation and AS by upregulating miR-30c-5p and miR-21-5p and downregulating the objective quality of miRNAs, Period2 (PER2), which controls lipid digestion and the provocative reaction. In addition, a number of studies have demonstrated that TMAO stimulates CD36 and scavenger receptors on the surface of macrophages, facilitating the recognition and phagocytosis of oxidized LDL via the CD36/MAPK/JNK pathway, which results in the formation of foam cells and accelerates the development of AS. Raised plasma TMAO levels increment the declaration of favorable

to provocative cytokines, like IL-1β, IL-18, and TNF-α, while diminishing the outflow of mitigating cytokines, like IL-10. Human Umbilical Vein Endothelial Cells (HUVECs) oxidation and the ROS/TXNIP/NLRP3 inflammatory vesicle pathway regulate this process. By downregulating CXR4 expression, which affects the recovery of post-ischemic perfusion and angiogenesis, TMAO-treated hepatocytes (TMAO-Exos) significantly reduced cell migration and angiogenesis *in vitro* and impaired endothelial cell function [5].

Regulating blood pressure with SCFAs

SCFAs have been found to prevent the progression of AS by regulating hypertension, and it is well known that hypertension is one of the main risk factors for its development. Studies have shown that higher centralizations of SCFAs in human defecation are related with worse hypertension and that hypertensive people have a lower number of SCFA-creating microorganisms in their stomach microbiota contrasted with sound controls. G protein-coupled receptors, olfactory receptor 78, and short-chain fatty acid receptors like FFAR-2 and FFAR-3 are among the receptors that SCFAs target to control blood pressure. For example, SCFAs following up on FFAR-2 in the renal supply route cause blood vessel diastole and lower pulse, though SCFAs working on Olfr78 advance the arrival of renin and increment circulatory strain. In addition, SCFAs alter cardiac contractility and sympathetic tone. Mice injected with acetic acid showed a load-independent decrease in myocardial contractility as well as a simultaneous decrease in arterial pressure and heart rate. These impacts were offended by beta-1-adrenergic receptor adversaries like atenolol and tyramine. SCFAs and Fat Tissue SCFAs have likewise been found to straightforwardly or in a roundabout way take part in adipogenesis, catabolism, and provocative reaction, prompting restraint of the movement of AS . For instance, propionic corrosive advances leptin discharge from the more noteworthy omental fat tissue and subcutaneous fat tissue by enacting GPR41 and GPR43, coming about in altogether expanded leptin levels. Additionally, it has been demonstrated that by inhibiting lipolysis and regulating adipogenesis, SCFAs reduce blood triglyceride concentrations in humans. At long last, SCFAs have been displayed to restrain the provocative reaction in adipocytes and fat tissue, which further forestalls the advancement of cardiovascular sicknesses, including AS [6].

It has been demonstrated that secondary bile acids are potent signaling molecules that activate specific receptors, such as the Farnesoid X Receptor (FXR) and the Takeda G Protein-Coupled Receptor 5 (TGR5; GPBAR1). Sphingosine-1-Phosphate Receptor 2 (S1PR2), Pregnane X Receptor (PXR), Constitutive Androstane Receptor (CAR), Vitamin D Receptor (VDR), and Retinoic Acid-Related Receptor t (R O Rt) are additional receptors that are activated either directly or indirectly. The initiation of these receptors has been connected straightforwardly with the improvement of provocative inside illness, which has been related with an expanded gamble of atherosclerosis, cerebrovascular mishaps, and atrial fibrillation. Studies have additionally shown that TGR5 agonist INT-777 has immunosuppressive impacts that incorporate lessening macrophage creation of favorable to fiery cytokines, and deferring atherosclerotic plaque development in LD−/− mice . Investigates have shown that polyphenol-rich substances decrease plasma TMAO by managing digestive verdure, accordingly influencing the advancement of AS. Resveratrol (RSV), which has been shown to raise *Lactobacillus spp*. levels, was the first extract to be confirmed. Also, Bifidobacterium spp. through the remodeling of the flora in the intestine. It also increased Cholesterol 7a-Hydroxylase (CYP7A1) expression, promoted hepatic bile acid synthesis, inhibited the enterohepatic Foresaid X Receptor-Fibroblast Growth Factor 15 (FGF15) axis, and reduced ileal bile acid content. All of these reduced TMAO's ability to promote atherosclerosis [7].

Regulation of intestinal micro ecological disorders and prevention of atherosclerosis

A foundation for understanding the connection between gut microecology and AS and the development of appropriate control strategies is the assessment of the composition of gut microbials. Through 16S rRNA gene sequencing, the majority of intestinal flora are prokaryotes, so their 16S rRNA genes, which encode rRNA that is highly conserved and specific, are widely used to study the composition and distribution of

microbial communities. What's more, joining 16S rRNA quality sequencing with compound connected immunosorbent measure and lipid digestion appraisal further assesses the relationship between the provocative reactions brought about by gastrointestinal microecological messes, strange lipid digestion, and AS. The intestinal balance can be adjusted to prevent the onset of AS based on these tests' findings. As of now, a few procedures have been applied, including gastrointestinal greenery transplantation, probiotics, prebiotics, symbiotics, and transient anti-toxin applications, all of which can likewise assist with changing the microecology of digestive issues [8].

Discussion

In order to establish a new dynamic balance in the recipient's intestinal microecology, intestinal flora transplantation involves extracting and pretreating microbial communities from healthy feces stool before transplanting them into the recipient's colon. Intestinal bacterial infections, depression, and metabolic diseases like type 2 diabetes and obesity can all be effectively treated with Fecal Microbiota Transplantation (FMT). In the viable use of this strategy, there are still elements that lead to unsteady viability, like the security and solidness of the microbial organization of the giver's stomach, the level of readiness in the beneficiary's stomach, the technique and normalization of the transplantation activity, and so on. Accordingly, the utilization of creature models for significant adequacy evaluation is fundamental for the use of this strategy. Additionally, short chain fatty acids, which are prebiotics, probiotics, and postbiotics, have the ability to alter the composition of the gut microbiota and decrease LPS levels, thereby protecting against AS. In the beginning, probiotics were referred to as yogurt's beneficial flora; by stimulating intestinal flora, interfering with the immune response of the host, reducing cholesterol absorption, and other effects, they harm health. Prebiotics are defined as a specific fermentation component that aids in the development of probiotics in the human intestine and immune system function; consequently, lactulose is frequently utilized in common clinical preparations and prebiotics are frequently utilized in health foods. Synbiotics are a combination of probiotics and prebiotics, both of which have a greater impact on the adjustment of intestinal microecology and last longer [9, 10].

Conclusion

Changes in gastrointestinal microecology essentially allude to modifications in the piece of digestive microorganisms and the creation or retention limit of related metabolites, which influence the advancement of AS by applying comparing impacts on human resistance, digestion, and food breakdown. This audit subtleties the defensive or promotive impacts of microbial constituents LPS, microbial metabolites TMAO and SCFAs, microbial impedance with bile corrosive digestion, and organismal gastrointestinal hindrance interruption on AS. Clinical strategies for AS prevention and treatment can now take a new direction thanks to this information. Through a variety of means, the relevance of intestinal micro ecology to the development of AS has been demonstrated in numerous studies. However, the majority of research focuses on animal studies, and further investigation into their viability and generalizability to the population is required. In addition, the current therapeutic approaches such as intestinal flora transplantation, TMAO inhibitors, probiotics, and prebiotics still have drawbacks, such as their high price and unstable efficacy, which call for further development.

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